Antimicrobial Agents: Brief Study of Pyridazine Derivatives against Some Pathogenic Microorganisms

Mohammad Asif, Anita Singh, Lal Ratnakar

INTRODUCTION

Pyridazine is a six-membered heterocyclic diazine that containing two nitrogen atoms at adjacent position or replacing two carbon atoms to two nitrogen atoms in the benzene ring at adjacent position. Pyridazine derivatives represent an interesting class of compounds possessing a wide spectrum of biological activities such as antibacterial, antifungal, antiviral, antitubercular, analgesic, antiinflammatory, antidiabetic, anti-AIDS, antplatelet, anticancer, anticonvulsant, insecticide, herbicidal, antihypertensive, antidepressant, etc. In view of these facts we are discussing the biological properties of pyridazines, as potential antimicrobial agents against pathogenic bacteria and fungi (1-5). Therefore, recent efforts would be directed toward exploring antimicrobial activities of pyridazines with low toxicity profiles when compared with currently used antimicrobial agents (1-3).

Infectious diseases caused by microbes like bacteria or fungi or viruses are major diseases worldwide, have increased dramatically in recent years. Amongst those certain microbial infections are more common because of their tendency to develop new strains under any circumstances and developing resistance against the available drugs (1, 2). In spite of many significant advances in antibacterial therapy, the widespread use and misuse of antimicrobials have caused the emergence of bacterial resistance to antimicrobials, which is a serious threat to public health. In particular, the emergence of multidrug resistant gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), and vancomycin-resistant *Enterococcus* (VRE), has become a serious problem in the treatment of bacterial diseases (3).

Currently used antimicrobial agents

The term “antimicrobial drugs” can apply to compounds used to control a variety of microorganisms. The majority of currently used antimicrobials are directly related to one of three categories based on their mechanism of action: inhibition of bacterial cell wall synthesis, protein synthesis, or nucleic acid synthesis (6). Fungal infections are very widely, in such a high risk patients progress rapidly and are difficult to diagnose and treat (4). Deep mycoses are systemic infections, which are difficult to treat. Many of the antifungal compounds affect the physiological activities of pathogenic fungi. Like, numerous effect have been described on cell division, biosynthesis of DNA, RNA, protein, lipid metabolism and cell mat synthesis (7).

The biosynthesis of ergosterol and other membrane sterols is an important pathway in fungal growth. These sterols are required to maintain integrity and functioning of the cell membrane. Thus, this biosynthetic pathway presents an important cascade of events that can be blocked to achieve important therapeutic intervention for antifungal action (8). Mycobacterium tuberculosis is a contagious disease infecting one-third of the world’s population and killing between 2 and 3 million people each year. The increase in TB incidence during recent years is largely due to the AIDS epidemic and also the emergence of multidrug resistant (MDR) and extensively drug-resistant (XDR) strains. In particular, the appearance of MDR and XDR strains of *M. tuberculosis*, which exhibit in vitro resistance to at least two major antituberculous drugs (usually Isoniazide and Rifampicin) and cause intractable tuberculosis, has greatly contributed to the increased incidence of tuberculosis (9). Moreover, the development of drug-resistant strains of microbial species, has contributed to the inefficiency of the conventional antimicrobial therapy, thus, it is still necessary to search for new antimicrobial agents. This stimulated the scientists for development of novel molecules to combat these infectious diseases.

**Key words:** Pyridazine, antimicrobial, biological activities.

**Different mechanism of commonly used antimicrobial agents**

**Inhibition of bacterial cell wall synthesis:** Inhibiting the synthesis of the bacterial cell wall will include both groups of beta-lactam ring-based drugs (include penicillin, ampicillin, amoxicillin as well as cephalosporins like cefoxitin, ceftriaxone, and cefotidroit) as well as some non beta-lactam drugs (include glycopeptides such as, vancomycin) (10).

**Inhibition of protein synthesis:** Inhibition of protein synthesis is the mechanism of action for a wide variety of antimicrobial drugs including macrolides, tetracyclines, chloramphenicol, and aminoglycosides (11, 12).

**Inhibition of nucleic acid synthesis:** The third group of antimicrobial drugs affects either the synthesis of nucleic acids or their required precursors. Sulfonamides, compete with paraaminobenzoic acid for incorporation into folic acid (13, 14).

**Mechanisms of antimicrobial drug resistance:** Antimicrobial drug resistance or the ability of a bacterium to withstand the effects of an antimicrobial can be caused by a variety of mechanisms. Bacteria can also acquire resistance to an antimicrobial through a gradual process of genetic mutations or a sudden acquisition of genetic material. Bacteria can acquire genetic material through horizontal transfer accomplished by transduction, transformation, or conjugation. The mechanism by which the resistance is manifested often falls into one of four categories. These include:

1. reduced permeability of the cell to the antimicrobial agent,
2. active efflux or expulsion of the antimicrobial from the cell,
3. modification of the antimicrobial agent, or
4. modification of the target site associated with the bacterial cell.

Reduced cell permeability:

Reduced permeability of the cell can prevent the antimicrobial agent from ever penetrating the organism. An example of this type of resistance occurs in Klebsiella spp. which exhibits a reduced permeability to the antimicrobial, imipenem (15). Though not the most common of resistant mechanisms reduced permeability can help enable some bacteria to resist effectively.

Efflux pumps:

Efflux pumps have been associated with low-level multi-antibiotic resistance. Efflux pump associated with *P. aeruginosa*, a pathogen of concern in burn patients, which allowed for resistance to ciprofloxacin, nalidixic acid, tetracycline, chloramphenicol, and streptomycin (16). These pumps enable the bacteria to actively expel certain toxic compounds including antimicrobial drugs utilizing either the proton motive force or in some instances ATP hydrolysis as energy source (17). The genes encoding for efflux pumps are often found as part of an operon, and can be housed on chromosomal genetic material as well as plasmids (18).

**Modification of the antimicrobial agents:**

Modification of the antimicrobial as a resistance mechanism is utilized by a variety of bacterial species to avoid the detrimental effects of various antimicrobial drugs (6). One of the best gram-negative examples can be seen with *Enterobacteriaceae* resistance to cephalosporins. Certain bacteria use the production of enzymes known as *β*-lactamases to modify the drug rendering it nonfunctional. Specifically, these *β*-lactamases decrease *β*-lactam-based antibiotics through hydrolysis (19). *β*-lactamase genes have been found in many bacterial species including *E. coli*, *Salmonella*, and *S. aureus* (20, 21).

**Modification of the target site associated with the bacterial cell:**

The final mechanism of resistance involves modification of the bacterial target. Target site
Side effects of currently commonly used antimicrobial agents:

The currently used antimicrobial drugs show various severe adverse reactions. However, unpleasant side effects, relatively long duration of treatment and non-compliance to treatment regimen are drawbacks. Such non-adherence with the course of treatment leads to treatment failure and the development of drug resistance. Many microorganisms have acquired resistance to specific antimicrobial treatments. This has created immense clinical problem in the treatment of infectious diseases. In addition to this problem, antimicrobial agents some time associated with adverse effect on host, which include hypersensitivity, depletion of beneficial gut and mucosal microorganism, immunosuppression and allergic reactions. Although patients with AIDS manifest have higher frequency of hypersensitivity or other adverse effects (7, 9, 23).

The currently available medications are show serious side effects like severe damage to the eighth cranial nerve, (impairment of auditory function), e.g. streptomycin, potentially hepatoxicity, e.g. isoniazide, pyrazaminidate, rifampicin. Hypersensitivity reactions antikinase and kanamycin causes kidney damage as well as hearing loss, viomycin and capreomycin causes nephrotoxicity (Sulphonamides) and eighth cranial nerve toxicity, chloramphenicol causes gray baby syndrome, tetracycline causes pigmentation of bones. Mostly antimicrobials are increasing concomitantly for patients due to growing prevalence of antibiotic resistance. g.i.t. disorders (sore mouth, vagina, salivation, nausea, vomiting, abdominal pain, diarrhea, glossitis & stomatitis), diverse mental disturbances (such as depression, anxiety, psychosis, dizziness, drugresistance), hallucinations and headache) and hypersensitivity like urticaria, rash, desquamation, photosensitivity, fever, hepatotoxicity, jaundice, hepatocellular dysfunction, precipitate megaloblastosis, leukopenia, or thrombocytopenia, coagulation disorders, granulocytopenia, agranulocytosis, vitamin deficiency, seizures, leukopenia, eosinophilia. Betalactems causes bronchospasm, vomiting, Stevens-Johnson syndrome, anaphylaxis, angioedema, hypotension, asthma, skin eruptions, arthritis, purpura, myositis, bone marrow depression, kidney & liver disorders, hematopoietic disorders, impairment of platelet aggregation and change the composition of the microflora. Aminoglycosides causes reversible and reversible vestibular, cochlear, and renal toxicity, dysfunction of the optic nerve, neuritis, blood dyscrasias, angioedema, and anaphylactic shock.

Tetracycline causes gastrointestinal irritation, epigastric burning and distress, abdominal discomfort, should not be taken with dairy products or antacids, onycholysis, pigmentation of the nails, hepatic toxicity, renal toxicity, discoloration of the bone & teeth, which probably is due to its chelating property (tetracycline-calcium orthophosphate complex), vascular disorders, depress bone growth in premature infants, increased intracranial pressure, vestibular toxicity, angioedema, anaphylaxis, burning of the eyes, asthma, development of superinfections caused by strains of bacteria or fungi resistant to these agents, hematopoietic disorders, bone marrow depression, blurring of vision. Erythromycin causes hepatitis, jaundice, epigastric distress, abdominal disorder, arthralgias, tachycardia, auditory impairment. Telithromycin causes visual disturbances, hepatic dysfunction, risk of arrhythmia, melaena, pancytopenia and vascular dysfunctions. Vancomycin causes anaphylaxis, phlebitis and pain, chill, flushing, tachycardia, hypotension, extreme flushing syndrome, auditory impairment, nephrotoxicity, hypersensitivity. Amifungins like amphotericin B causes chills, respiratory disorders, anaphylaxis, nephrotoxicity, hepatic toxicity, bone marrow depression, hematologic disorders. Fluconazole causes enterocolitis, congestive heart failure (CHF), edema, hypertension, anorexia, hepatic failure have been reported. Fluconazole and Voriconazole cause skeletal and cardiac deformities, teratogenic, visual effects, flushing. Griseofulvin causes peripheral neuritis, lethargy, mental confusion, impairment of performance, fatigue, vertigo, blurred vision, altered color perception, photophobia, flabbleness, dry mouth and erythema (24, 25).

Anti microbial activity of pyridazine derivates:

A series of 6-anthracenepyridazinones containing indolyl moieties (II), these compounds showed antibacterial activity. Chloropyridazinyl derivative with some aliphatic or aromatic amines and anilinylidene acid, methylamine derivates, trimethylammonium iodide derivatives, some of the new products showed antibacterial activity (5).

A series of 2-(4-(substituted phthalazine-1-yl)alkyl)-1H-isooisole-1,3(2H)-diones and 2-(2-(1,3-dioxo-1,3-dihydro-2H-isooisole-2-yl-alkyl)-1-oxophthalazine-2(1H)-yl)alkoxy -1H-isooisole-1,3(2H)-diones (III) showed significant antimicrobial activity (26).

Several 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylanino-1,3,4-thiadiazoles were exhibit high antifungal activity (27). A series of 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylanino-1,3,4-thiadiazoles (IV) showed in vivo fungicidally activity against wheat leaf rust. Puccinia recondite. The structure activity relationship of the compounds containing both pyridazinones substituted 1,3,4-thiadiazoles and pyridazino-substituted 1,3,4-oxadiazoles. The results are consistent with a common mode of action for the pyridazino-substituted 1,3,4-thiadiazoles and the pyridazino-substituted 1,3,4-oxadiazoles, which further confirms that the 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring (28). Pyridazino-derivatives were used to prepare the corresponding dithio, thio & chloro derivatives (V). Some of the new compounds showed antibacterial and antifungal activities (29).
The new various metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazin-3-one were evaluated for their antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi. The Cd(II) and Ni(II) complexes exhibited selective and effective activities against one Gram-positive bacterium (S. aureus), one Gram-negative bacterium (P. putida) and against two yeast (C. albicans and C. tropicalis) in contrast to poor activity observed against other microorganisms (30). Compounds that effective against methicillin resistant S. aureus (MRSA) by inhibit S. aureus sortase (SrtA) may function as potent anti-infective agents as this enzyme attaches virulence factors to the cell wall. Using high-throughput screening, several pyridazinone and pyrazolethione analogs that inhibit SrtA (31).

**Antimycobacterial activity of pyridazines:**

Some pyridazine derivatives showed antibacterial activity against various gram-positive and gram-negative strains of bacteria and their antimycobacterial activity against *M. tuberculosis* H37Rv. Some compounds bearing pyridazinone or phthalazinone rings (VI) have been reported to have antimicrobial activities (3).

A series of 6-substituted phenyl-2-(3'-substituted phenyl pyridazin-6'-yl)-2,3,4,5-tetrahydropyridazin-3-ones were investigated for their in vitro antimycobacterial, antifungal and antibacterial activities (VII). The results indicated these compounds have mild to potent activities with reference to their appropriate reference standards. A series of 5-(3'-oxo-6'-substituted aryl)-2,3,4,5-tetrahydropyridazin-2'-ylmethyl)-2-substituted 1,3,4-oxadiazole (VIII) showed antibacterial activity against *E. coli*, *S. aureus*, *Micrococcus luteus* and *Kleb*.

**DISCUSSION:**

Microbial diseases are the most common of the world’s deadly diseases; search for new drugs leads is an urgent need due to the emergence of drug-resistant strains of microbes. These pathogens are successfully overcomes the numerous challenges presented by the immune system of the host. An HIV infection significantly increases the risk of microbial infections. The problem of increasing drug–resistance has been a pressing force to develop new antimicrobial drugs. There is thus a vital need for the development of novel chemotherapeutic agents active against different microbial infections or multidrug resistant, with minimal or free from side effects and improved pharmacokinetic properties. More importantly, the newly developed drugs are required to reduce the overall duration of treatment. It is also important to development of new drugs based on inhibition of bacterial and fungal target; we need to understand host factors such as immune mechanisms, genetic susceptibility and disease relapse. Therefore, the newer compounds now need to be developed on the understanding of the molecular mechanisms of drug action and drug resistance. In recent years, efforts are being made to develop new molecules based on different drug targets with different structures. Further, the molecular mechanisms and biosynthetic pathways are being easily understood for the already known and newer compounds. Researchers will be interested to working on pyridazines due to their wide range of biological activities particularly against microbes. The different new pyridazines will be synthesized in the future to overcome resistance and find new molecules for the target based treatment of microbial infection (23).

**CONCLUSION:**

Resistance of pathogenic bacteria towards available antimicrobial is rapidly becoming a major
worldwide problem. The design of new compounds to deal with resistant microbes has become one of the most important areas of antibacterial research today. In addition, primary and opportunistic microbial infections continue to increase rapidly because of the increased number of immuno-compromised patients. To overcome the development of drug resistance it is necessary to synthesize new antibacterial compounds possessing different chemical properties as well as less toxic effect from those of used commonly.

REFERENCES


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