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A REVIEW ON MANNICH BASE DERIVATIVES SOME OF NATURAL COMPOUNDS : ANTIMICROBIAL ACTIVITIES

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ABSTRACT

This review explores the synthesis and antimicrobial potential of Mannich base derivatives derived from various natural compounds. The Mannich reaction, a versatile method in organic synthesis, enables structural modification of bioactive compounds to enhance their pharmacological properties, particularly antimicrobial activities. This study systematically reviews recent literature on the design, synthesis, and biological evaluation of these derivatives against bacterial and fungal pathogens. The findings demonstrate that Mannich base derivatives exhibit improved efficacy through multiple mechanisms of action, such as inhibition of cell wall synthesis, protein synthesis, and membrane disruption. The review highlights the relevance of Mannich-based structural optimization as a promising strategy in the development of novel antimicrobial agents.

KEYWORDS *mannich base, natural compound, antimicrobial*

INTRODUCTION

Antibacterial resistance has developed over several decades and has now surfaced as a potential public health emergency everywhere. Therefore, there is an urgent need for potent drug candidates that can help combat antibiotic resistance in both bacteria and fungi (Bishoyi et al., 2021). The utilization of natural compounds as a source of therapeutic materials has been practiced for thousands of years to treat various diseases (Romano & Tatonetti, 2019). The history of the discovery process of new drugs shows that until the early 20th century, the majority of medications originated from natural sources, such as plants and microorganisms (Huang & Zhang, 2022; Newman & Cragg, 2020). The utilization of natural compounds as a source of therapeutic materials has been carried out for thousands of years to treat various diseases (Meiyanto & Larasati, 2019). However, in the mid-20th century, medications not only originated from natural sources but also emerged from chemical synthesis known as synthetic drugs (Manjula et al., 2016; Rahmawati et al., 2020). Due to their unique physical and chemical properties,

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significant structural diversity, and a broad pharmacological activity spectrum, natural products and their derivatives contributed to 32% of all approved small molecule drugs from January 1981 to September 2019 (Lv et al., 2019). Until now, they are still considered promising molecular targets for drug development research due to the discovery of new therapeutic potentials (Popiołek et al., 2018). The influence of the molecular structure of natural products remains highly significant in drug discovery and development. Over 40% of FDA-approved drugs (1981-2019) were obtained by modifying or duplicating natural compound structures (Marinescu et al., 2020). Indonesia, with its abundant biodiversity, is a country with great potential as a source of lead compounds to be optimized into drug candidates (Nyantakyi et al., 2018). Among these natural products, many have suitable structures as substrates in mannich reactions, making them highly prospective for development into new bioactive compounds using Mannich reactions. Research on the utilization of Mannich reactions for the discovery of antimicrobial compounds has shown interesting results (Salimova et al., 2023). In recent years, dozens of antimicrobial research results have been published by medicinal chemistry researchers in various scientific journals. Some of them have identified potential drug candidate compounds, which will be discussed in this article.

RESEARCH METHODS

This article employs a qualitative descriptive approach using a literature review method. The data used in this review were collected from various scientific publications published in national and international journals. The authors systematically searched, selected, and analyzed literature discussing the synthesis and antimicrobial activity of Mannich base derivatives derived from natural compounds.

Sources were identified through reputable academic databases such as PubMed, ScienceDirect, Google Scholar, and Scopus, focusing on studies published in the last two decades (2000–2024). The selection criteria included articles that:

a. Discussed the synthesis of Mannich base derivatives
b. Reported antimicrobial (antibacterial and antifungal) activity
c. Included mechanisms of action or biological evaluations.

The articles were analyzed to identify trends in synthesis methods, structural modifications, and the spectrum of antimicrobial activities. This method allows for mapping the development of Mannich base derivatives in medicinal chemistry, especially as potential antimicrobial agents.

RESULT AND DISCUSSION

Mannich Base

The Mannich base is a chemical compound that possesses one active hydrogen atom and has been proven to enhance various biological activities. Mannich bases are known to play a crucial role in the development of synthetic pharmaceutical chemistry. The introduction of Mannich base groups is one method of modifying the structure of a compound by incorporating nitrogen into the

structure of the parent compound to enhance its biological activity (Bishoyi et al., 2021). Structural modification through Mannich base substitution is carried out with the aim of increasing the biological activity of the compound compared to the parent compound. Mannich bases are highly reactive and have a wide range of properties, such as anti-inflammatory, anti-cancer, antibacterial, antifungal, anticonvulsant, anthelmintic, antitubercular, analgesic, anti-HIV, antimalarial, antipsychotic, and others. Mannich bases, produced from the Mannich reaction, involve the formation of unsaturated ketones through the deamination of hydrogen atoms in the amine group, which is primarily responsible for their biological activity (Bangia et al., 2019). The principles of this reaction are utilized to modify compounds containing nitrogen, as found in many drugs and natural compounds. The potential flexibility of these compounds can lead to diversified development to enhance the biological activity of drug compounds (de Oliveira Santos et al., 2018). The Mannich reaction is recognized as the formation of the strongest carbon-carbon bond in organic chemical synthesis, comprising three components that contain at least one active hydrogen atom, an aldehyde group (usually R1-CHO), and a primary or secondary amine reagent as a guiding compound , and the general pathway is illustrated in Scheme 1 (Esmatabadi et al., 2017). All of these components undergo condensation to form the final product of the β-amino carbonyl compound known as the Mannich base. The synthesis of Mannich base and its derivatives also serves as an intermediate step for designing bioactive molecules from various compounds with potential clinical activity, especially those with alkyl amino chains. Mannich base derivatives can be formed from various compounds, one of which is phenolic compounds because they possess active functional groups and nucleophilic properties (Reygaert, 2018).

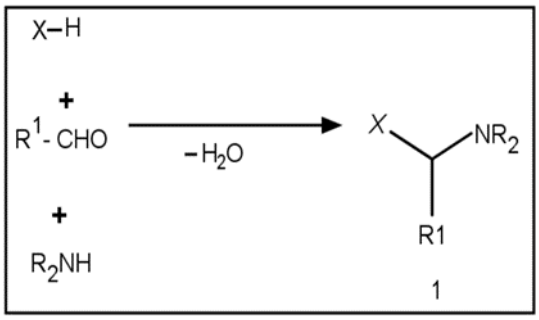


Figure 1. Mannich Reaction.

2. Mechanism of Action Antifungal

Antifungals work through various mechanisms to inhibit the growth and suppress the activity of fungal pathogens. Some identified mechanisms include the permeabilization of fungal cell membranes, inhibition of fungal cell wall synthesis, and inhibition of fungal cell adhesion Certain antifungal compounds have also been shown to exhibit antibiofilm activity, which is the ability to prevent the formation of biofilms by fungi and disrupt already formed biofilms.

While the exact mechanisms of some antifungal compounds are still not fully understood, ongoing research aims to further comprehend their modes of action and

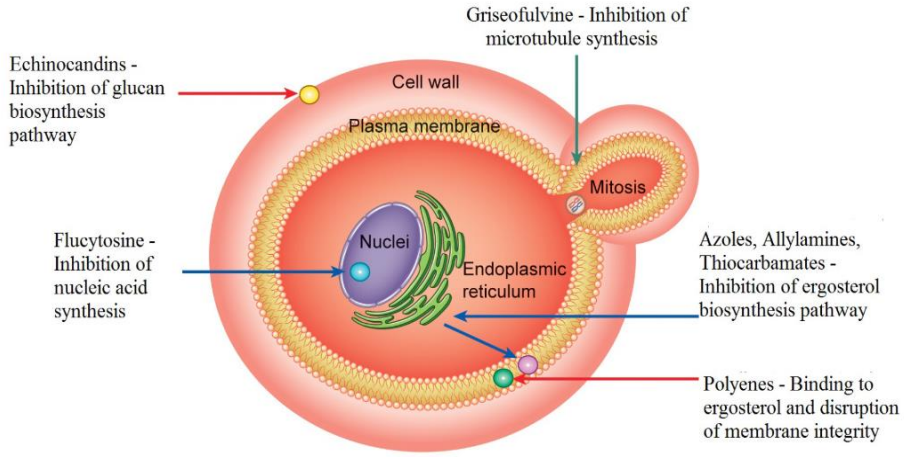
develop new strategies in the treatment of infections Certain antifungal compounds have also been shown to exhibit antibiofilm activity, which is the ability to prevent the formation of biofilms by fungi and disrupt already formed biofilms. While the exact mechanisms of some antifungal compounds are still not fully understood, ongoing research aims to further comprehend their modes of action and develop new strategies in the treatment of infections.

Antifungal resistance can occur through various mechanisms at the cellular and molecular levels. These mechanisms can be intrinsic or acquired, and they contribute to the reduced effectiveness of antifungal drugs in treating fungal infections. At the cellular level, one mechanism of resistance is the alteration of the fungal cell membrane. The cell membrane is a target for many antifungal drugs, and alterations in its composition or structure can reduce the drug's ability to bind to the membrane and exert its antifungal effects. This can be achieved through changes in the expression or activity of membrane transporters, which can pump out the drug from the cell, or through modifications in the composition of membrane lipids. Another cellular mechanism of resistance is the development of drug efflux pumps.

These pumps are proteins that actively transport antifungal drugs out of the fungal cell, reducing their intracellular concentration and effectiveness. Fungi can upregulate the expression of these pumps in response to antifungal drug exposure, leading to decreased drug accumulation and resistance. At the molecular level, one common mechanism of resistance is the alteration of the target site of the antifungal drug. Antifungal drugs often target specific enzymes or proteins involved in essential cellular processes, such as cell wall synthesis or DNA replication. Mutations or alterations in these target proteins can reduce the drug's binding affinity and inhibit its inhibitory effects on fungal growth. Another molecular mechanism of resistance is the production of enzymes that can modify or degrade the antifungal drug. For example, some fungi can produce enzymes called beta-lactamases that can break down beta-lactam antibiotics, rendering them ineffective. Similarly, some fungi can produce enzymes that modify the structure of antifungal drugs, preventing them from binding to their target sites.

Additionally, fungi can develop resistance through the acquisition of resistance genes through horizontal gene transfer. This can occur through the transfer of plasmids or other genetic elements containing resistance genes from one fungal strain to another. These resistance genes can confer resistance to specific antifungal drugs by producing enzymes that inactivate the drug or by altering the drug's target site. The mechanism of action of traditional antifungal agents (Picture 1) on cellular targets, such as Azoles, involves inhibiting ergosterol synthesis in the endoplasmic reticulum of fungal cells. They work by interfering with the enzyme lanosterol 14-α-demethylase, which is involved in transforming lanosterol into ergosterol. Polyenes act on the fungal membrane by binding to ergosterol, causing disruption of the membrane structure that promotes extravasation of intracellular constituents, and consequently, cell death. Flucytosine inhibits the enzyme thymidylate synthetase by interfering with DNA. Echinocandins inhibit (1,3) β-D-glucan synthase, thereby preventing the synthesis of glucan present in the fungal cell membrane. Allylamines and thiocarbamates inhibit the enzyme squalene

epoxidase, which participates in ergosterol synthesis. Griseofulvin works by disrupting spindle and cytoplasmic microtubule production, thereby inhibiting fungal mitosis.



Picture 2. Antifungal resistance can occur through various mechanisms at the cellular and molecular levels [25]

3. Mechanism of Action Antibacterial

An important quality for an antimicrobial drug is selective toxicity, meaning that it selectively kills or inhibits the growth of microbial targets while causing minimal or no harm to the host. Most antimicrobial drugs currently in clinical use are antibacterial because the prokaryotic cell provides a greater variety of unique targets for selective toxicity, in comparison to fungi, parasites, and viruses. Each class of antibacterial drugs has a unique mode of action , the way in which a drug affects microbes at the cellular level. Antimicrobial agents, such as antibiotics, work through various mechanisms to inhibit the growth and survival of microorganisms. The specific mechanism of action depends on the type of antimicrobial agent and the target organism. Here are some common mechanisms of action:

1. Inhibition of cell wall synthesis: Many antimicrobial agents, such as beta-lactam antibiotics (e.g., penicillins and cephalosporins), target the synthesis of bacterial cell walls. They do this by inhibiting the enzymes involved in the formation of peptidoglycan, a crucial component of the bacterial cell wall. Without a functional cell wall, bacteria become more susceptible to osmotic pressure and eventually lyse.
2. Inhibition of nucleic acid synthesis: Antimicrobial agents can interfere with the replication and transcription of microbial DNA or RNA. For example, fluoroquinolones inhibit the activity of bacterial DNA gyrase and topoisomerase IV, enzymes involved in DNA replication and repair. This disruption prevents the bacteria from replicating their genetic material and leads to cell death.
3. Inhibition of protein synthesis: Many antimicrobial agents target the ribosomes, the cellular machinery responsible for protein synthesis. They can bind to the

ribosomes and interfere with the translation process, preventing the synthesis of essential proteins. Examples of antimicrobial agents that inhibit protein synthesis include aminoglycosides, macrolides, and tetracyclines.

4. Disruption of membrane structure: Some antimicrobial agents, such as polymyxins and certain antifungal agents, disrupt the integrity of microbial cell membranes. They interact with the lipid components of the membrane, causing leakage of cellular contents and ultimately leading to cell death.

Antibacterial action generally falls within one out of four mechanisms, three of which involve the inhibition or regulation of enzymes involved in cell wall biosynthesis, nucleic acid metabolism and repair, or protein synthesis, respectively. The fourth mechanism involves the disruption of membrane structure. Many of these cellular functions targeted by antibiotics are most active in multiplying cells.

Antimicrobial resistance mechanisms in bacteria can be categorized into four main types:

1. Limiting drug uptake: Some bacteria have natural barriers that prevent the entry of certain antimicrobial agents. For example, gram-negative bacteria have an outer membrane called lipopolysaccharide (LPS) that acts as a barrier to large molecules, providing innate resistance to certain antimicrobial agents. Mycobacteria have a unique outer membrane that limits the uptake of drugs.
2. Modifying drug targets: Bacteria can modify the target sites of antimicrobial drugs, making them less susceptible to the drugs' effects. Gram-positive bacteria may alter the structure or function of their penicillin-binding proteins (PBPs), which are the targets of beta-lactam antibiotics. This modification reduces the binding affinity of the drugs to the target, rendering them less effective.
3. Inactivating drugs: Bacteria can produce enzymes that chemically modify antimicrobial drugs, rendering them inactive. For example, beta-lactamases are enzymes produced by bacteria that can break down beta-lactam antibiotics, such as penicillins and cephalosporins, making them ineffective.
4. Active drug efflux: Bacteria can possess efflux pumps that actively pump out antimicrobial drugs from within the cell, preventing them from reaching their target sites at effective concentrations. These efflux pumps can remove a wide range of drugs, including antibiotics from different classes

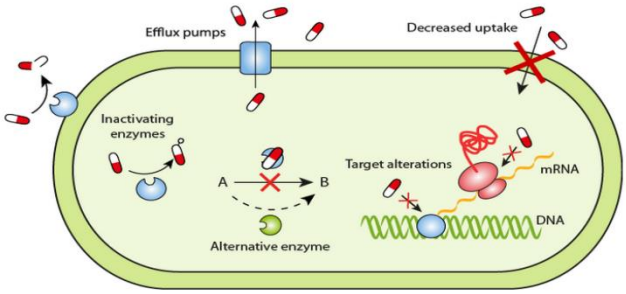


Figure 3. Antibiotic resistance strategies in bacteria. (Sources: Courtesy of E. Wistrand-Yuen)

CONCLUSION

The various mannich base derivatives increase the potensial of the antimicrobial activity, they can efficiently show their action on the target through various mechanisms to inhibit the growth and activity of microbial pathogens. Various synthesis of different mannich base derivatives of antimicrobial have been discussed such as, flavone compounds containing benzylamine groups through Mannich reaction , new pipemidic acid derivatives using the mannich reaction of 4,5-disubstituted 1,2,4-triazole-3-thione, tri-component synthesis of novel chiral benzimidazole mannich bases, azaspiroketal mannich base into anti-tuberculosis agents targeted at the membrane of 6-methoxy-1-n-octyl-1 H-indole, fusidane triterpenoid mannich base through the aminomethylation of propargyl fusidane ester reacted with secondary amines (morpholine, pyrrolidine, N-methylpiperazine, and piperidine) and formaldehyde, series of sulfonamides containing thymol, 4a-4l, through mannich condensation reactions of respective cycl1ic amines 3a-3g and N-heteroaryl-4-amino benzensulfonamides 3h-3l with thymol and formaldehyde, a morpholine-based mannich base of eugenol and the esters thereof , and pyrazolone corresponding mannich derivatives.

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