Recent Progress in the Chemistry of dihydropyrimidine Derivatives as Antibacterial Agents

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Abstract-Antibiotics are becoming increasingly ineffective due to drug resistance, leading to greater difficulty in the treatment of infectious diseases. Therefore, the development of new chemical entities with different mechanisms of action is essential .in the fight against resistant micro-organisms. Various studies have shown that dihydropyrimidine derivatives possess such as antimalarial, anticancer, anti-inflammatory, and antitubercular. Notable among these is antibacterial activity of dihydropyrimidine derivatives. The synthetic flexibility of the pyrimidine ring has led to the development of a wide range of structurally diverse dihydropyrimidine derivatives, which can act at various targets such as inhibit thymidylate synthase or dihydrofolate reductase, interfere with tubulin polymerization, DNA gyrase and topoisomerase IV. This review emphasizes the antibacterial potential of various reported dihydropyrimidine derivatives based on the substitution in the pyrimidine ring. The antibacterial activity is also discussed. This review aims to assemble and scrutinize the latest reports in the promising area of drug development.

Keyboards: Antibacterial resistance, Dihydropyrimidine derivatives, synthesis, mechanism of action, antibacterial activity.

I. INTRODUCTION

Infections caused by antimicrobial resistance can be particularly challenging and sometimes even impossible to treat. [1, 2]. This reduces the effectiveness of antimicrobial treatments, leading to higher rates of illness, increased mortality, and higher healthcare costs [3]. Antimicrobial resistance (AMR) occurs when microorganisms—such as bacteria, fungi, parasites, and viruses—adapt to the point that they no longer respond to the antimicrobial medications, like antibiotics, designed to treat these infections. Today, AMR is considered one of the most pressing global challenges of the 21st century, especially because infection rates are rising quickly and new antimicrobial drugs aren't being developed at a sufficient pace [4]. The widespread use and misuse of antibiotics in humans, agriculture, animal farming, industry, and the environment are major contributors to AMR [5,6]. Bacterial infections are a significant threat to human life due to how rapidly bacteria are becoming resistant to antibacterial drugs [7]. This has turned into a major global health concern, with around 5 million deaths linked to bacterial AMR reported in 2019 [8].Multi-drug-resistant (MDR) bacteria have emerged as a result of illness exposure in hospitals, overconsumption, and the use of inappropriate antibiotics. The World Health Organization (WHO) has identified antibiotic resistance as one of the key threats to global health. [9] Additionally, during the COVID-19 pandemic, increased antibiotic usage has further sped up the development of resistance among pathogens. [10]. To tackle bacterial resistance, discovering new antimicrobial compounds and utilizing antibacterial drugs with various structural types and mechanisms thoughtfully is crucial. Currently, pyrimidine-containing agents are leading the way in the search for new antibacterial drugs.

Pyrimidines are one of the organic heterocyclic compounds containing a 6-member unsaturated ring structure composed of two nitrogen atoms at positions 1 and 3 [11]. Pyrimidines are widely found in nature, as they are vital components of nucleic acids, i.e., DNA and RNA, in the form of N-substituted sugar derivatives (nucleosides) [12].

Pyrimidines are one of the three isomeric diazines, including important biological molecules such as uracil, thymine, and cytosine. These compounds are known as breakdown products of uric acid and are integral components of nucleic acids [13]. They help as coenzymes and can join with metal ions, which helps us to understand what metal ions do in the body [14]. Pyrimidines have diverse pharmacological properties such as effective bactericides, fungicides, insecticides, anticancer, and herbicidal agents [15]. The Pyrimidine skeleton is also present in vitamin B1 (thiamine), and many synthetic compounds, such as barbituric acid, which are used as hypnotics [16]. They play an energetic role in the field of synthetic heterocyclic chemistry and also play an important role in medicinal science[17].

Dihydropyrimidines are heterocycles with a pyrimidine moiety in the ring nucleus[18]. These are a class of organic compounds with a broad spectrum of biological activity and are widely used in medicine. The biological investigations of these various molecules via molecular manipulation showed activities such as antifungal [19], antimicrobial [20, 21, 22], antitumor [23], anticancer [24], antihypertensive [25], anti-HIV [26], anti-malarial [27], anti-inflammatory [28, 29], antioxidant, anti-leishmanial [30], antibacterial [31, 32]anti-parasitic, anti-thyroid [33] human lactate dehydrogenase inhibitors [34].

Recent advances in dihydropyrimidine research have uncovered an impressive range of biological activities that go well beyond what was initially known. Early studies mainly looked at their cardiovascular effects linked with calcium channel modulation. However, today's research has discovered that these compounds possess strong antibacterial properties that work through various innovative mechanisms. The ability to easily modify the dihydropyrimidine structure has allowed for a thorough exploration of how different features affect antibacterial strength, selectivity, and the way these compounds work. [35] .

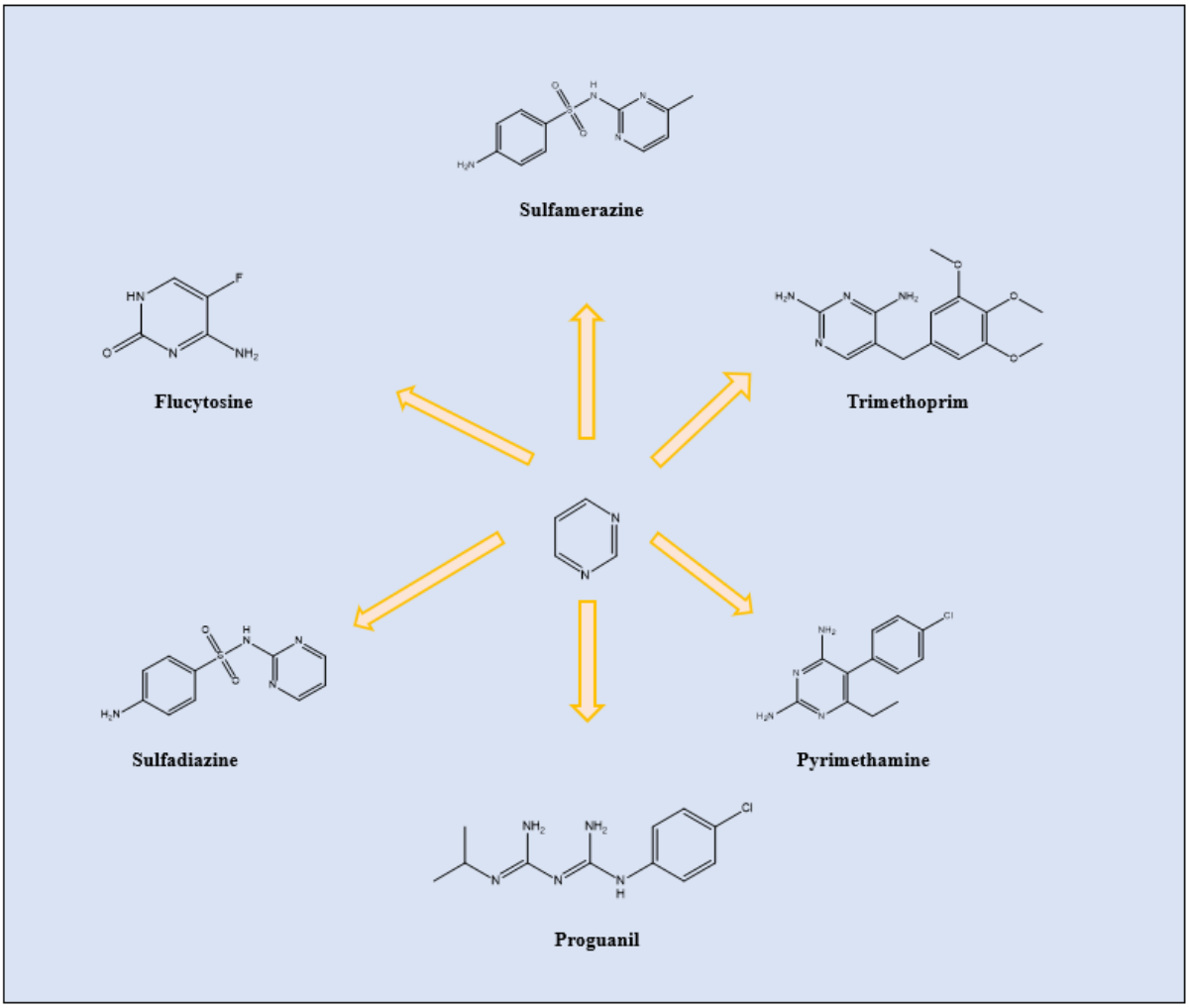

Fig. 1: Chemical structure of pyrimidine-containing antimicrobial drugs

II. SYNTHETIC METHODOLOGIES AND CATALYTIC ADVANCES

In recent years, there has been great progress in developing new protocols for synthesizing dihydropyrimidine derivatives [36]. To improve their chemical and biological characteristics, several research teams have been working on creating pyrimidine derivatives with altered molecular structures. [37, 38]. The foundation of dihydropyrimidine chemistry was established by Pietro Biginelli's seminal work in 1893. The synthesis of these derivatives mainly hinges on the adaptable Biginelli multicomponent reaction, which involves the acid-catalyzed combination of aromatic aldehydes, β-keto esters (usually ethyl acetoacetate), and urea or thiourea in an acidic environment (as shown in Fig. 2) [39].

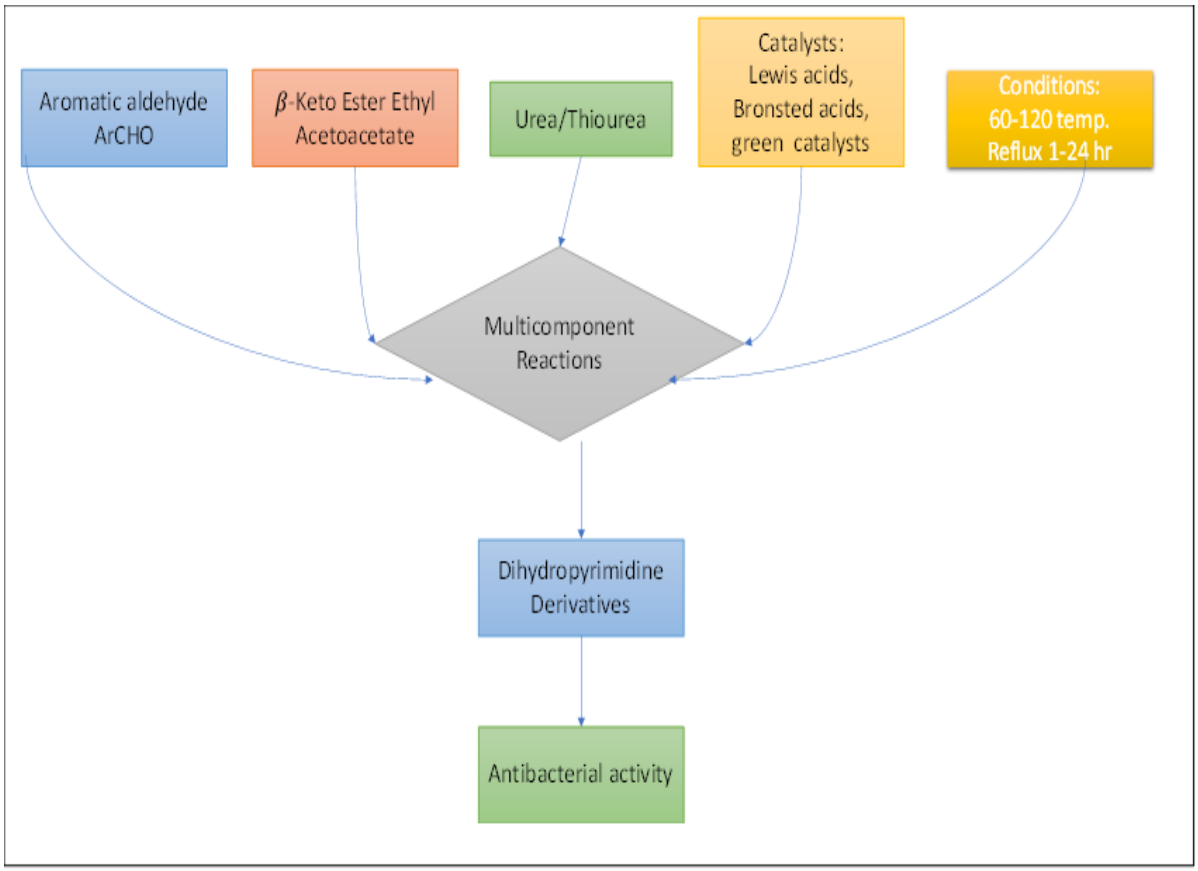

Fig. 2: Synthetic Methodologies and Catalytic Advances for the synthesis of dihydropyrimidine derivative

This one-pot three-component synthesis offers significant advantages in terms of atom economy, operational simplicity, and structural diversity, making it particularly attractive for combinatorial chemistry approaches and library generation (depicted in Scheme 1) [40, 41]. The reaction proceeds through a well-established mechanism involving the formation of an N-acyliminium ion intermediate from the aldehyde and urea, followed by nucleophilic attack by the enol tautomer of the β-keto ester, ultimately yielding the characteristic dihydropyrimidine scaffold (depicted in Scheme 2) [42]. In 2000, Kappe had developed an alternative synthetic strategy for the synthesis of DHPMs apart from the traditional Biginelli condensation. The reaction proceeds through the initial formation of an N-acyliminium ion intermediate from the condensation of aldehyde and urea, followed by nucleophilic attack by the enol tautomer of the β-keto ester, ultimately yielding the dihydropyrimidine product through cyclization and dehydration steps. This mechanistic insight has proven crucial for the development of improved catalytic systems and the rational design of structural modifications that enhance both synthetic efficiency and biological activity (depicted in Scheme 3) [43].

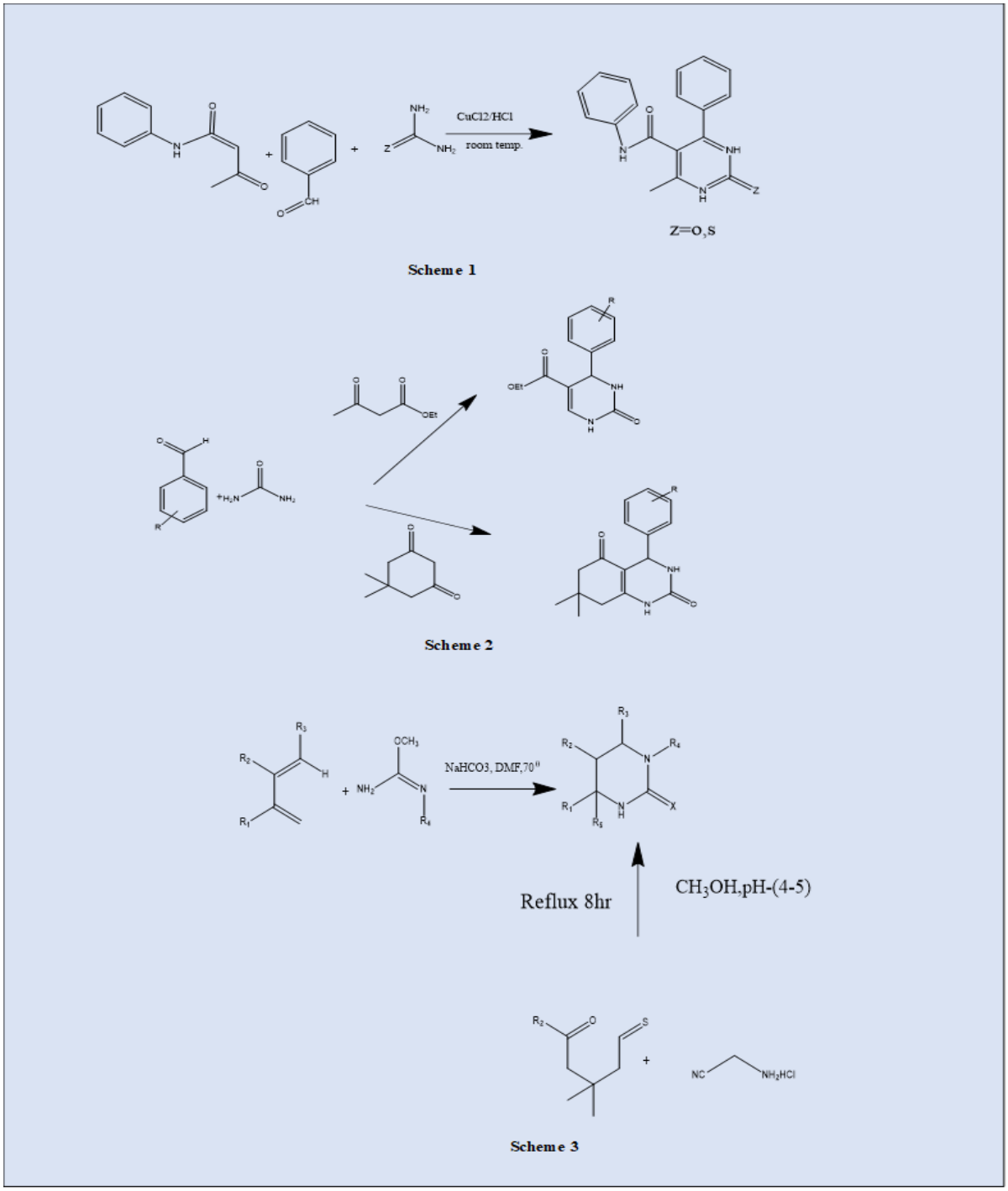

Fig.2: Schemes for the synthesis of dihydropyrimidine derivatives

Microwave-Assisted and Solvent-Free Protocols have revolutionized dihydropyrimidine synthesis, enabling dramatic reductions in reaction times from hours to minutes while maintaining or improving product yields. Microwave-enhanced protocols capitalize on the unique heating mechanism of polar molecules, providing rapid and uniform energy distribution that accelerates reaction rates and improves selectivity. Lanthanum oxide (La_2O_3) has proven exceptionally effective as a microwave-compatible catalyst, enabling complete conversion to dihydropyrimidines within 20-60 seconds at 320 W microwave power. The combination of microwave irradiation with solvent-free conditions offers multiple advantages, including reduced environmental impact, simplified workup procedures, enhanced product purity, and compatibility with a broad range of substrates, including acid-sensitive aldehydes that typically undergo decomposition under traditional conditions (depicted in scheme 4) [44].

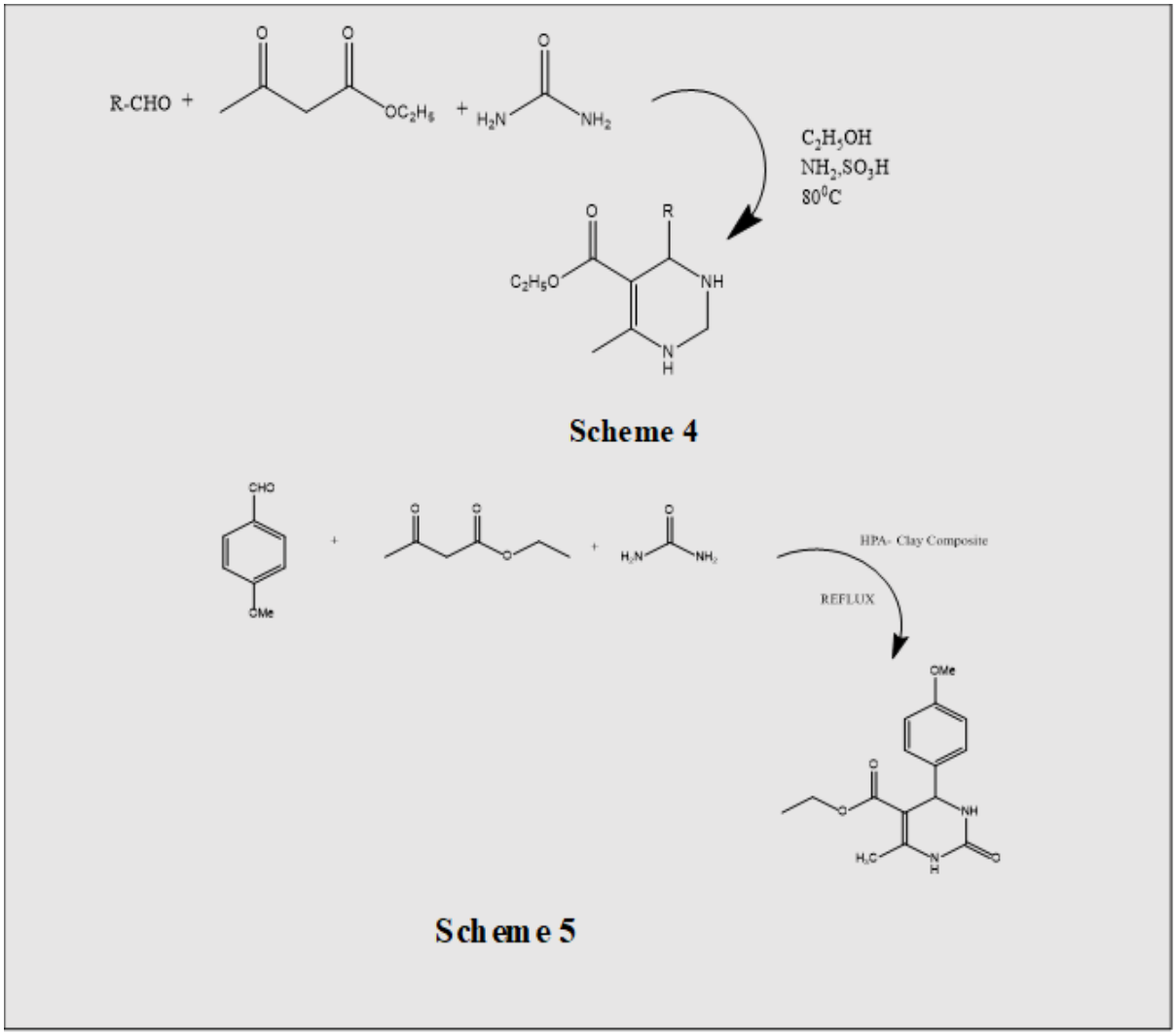

Fig.4: Scheme for the synthesis of dihydropyrimidine derivatives

The way of synthesize dihydropyrimidines today has really evolved, thanks to the principles of green chemistry and sustainable development. This shift addresses important concerns about the environmental impact and resource use in pharmaceutical production. We've seen a major change from traditional acid-catalyzed methods to eco-friendly catalytic systems, with exciting new techniques like biocatalysis, heterogeneous catalysis, and solvent-free processes, all achieving impressive results while reducing waste and energy consumption. One standout in this area is glutamic acid, which has become a popular bio-based catalyst. This amino acid catalyst works through a dual activation mechanism, activating both the aldehyde component with hydrogen bonding and promoting enol formation from the β-keto ester via general base catalysis (depicted in scheme 5) [45]. Exciting developments in green chemistry have transformed. This progress highlights the importance of using renewable catalysts, working without solvents, and adopting process intensification technologies. The effective use of bio-organic catalysts like taurine, along with renewable reaction media such as citrus fruit juices, marks a significant change towards more sustainable pharmaceutical production. These advancements show that we can prioritize both environmental stewardship and synthetic efficiency (depicted in scheme 6) [46].

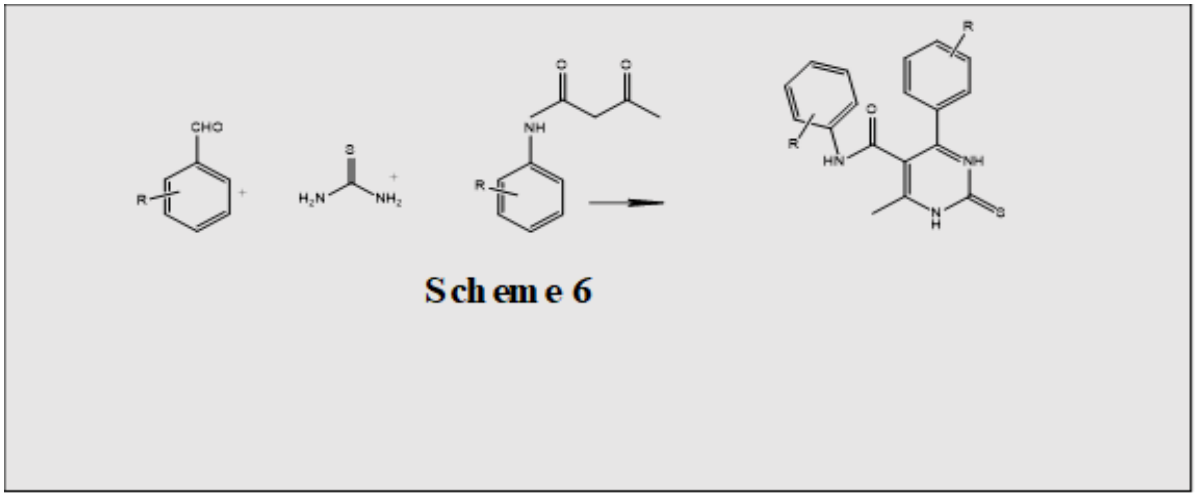

Fig. 5: Scheme for the synthesis of dihydropyrimidine derivatives

III. MECHANISMS OF ANTIBACTERIAL ACTION

3.1 Inhibition of DNA Gyrase and Topoisomerase

Dihydropyrimidine derivatives have been shown in recent molecular target identification studies to exhibit antibacterial properties through a variety of mechanisms, with inhibition of DNA gyrase (topoisomerase II) being one of the main mechanisms. Comparing these chemicals to known inhibitors, molecular docking experiments show that they have a higher binding affinity to the bacterial DNA gyrase active site, with binding scores indicating significant molecular interactions. Bacterial cell death results from the disruption of transcription and DNA replication processes caused by DNA gyrase inhibition. Because it is an underutilized antibacterial target, this mechanism is especially important because it may lessen the chance of cross-resistance with current antibiotic classes [47].

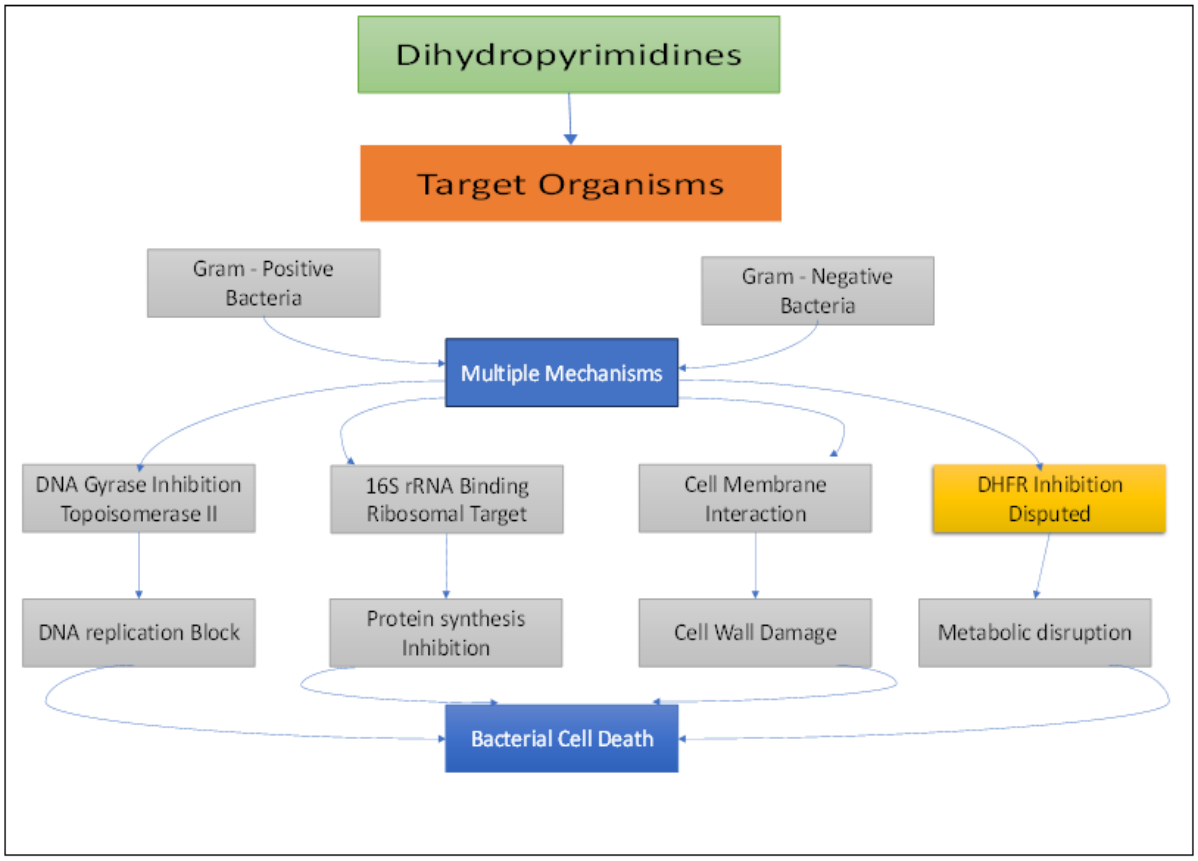

Fig. 6: Mechanisms of antibacterial action shown by dihydropyrimidine derivatives

3.2 Disruption of Protein Synthesis and Ribosomal RNA Binding

Dihydropyrimidine derivatives have been found to selectively attach to bacterial ribosomes while exhibiting negligible interaction with mammalian 40S rRNA, indicating that ribosomal 16S rRNA is an additional molecular target. Achieving antimicrobial efficacy while reducing host damage requires this specificity. By interfering with the machinery involved in protein synthesis, the binding to ribosomal RNA contributes to the overall antibacterial impact in a synergistic manner. The strong action shown against strains that are resistant to many drugs may be explained by the dual targeting of DNA replication and protein synthesis, which may also prevent the emergence of resistance [48].

3.3 Metabolic Target Consideration

Dihydropyrimidine derivatives share structural similarities with well-known DHFR inhibitors like trimethoprim, preliminary research indicated that they might have antibacterial effects by inhibiting dihydrofolate reductase (DHFR) [49]. However, thorough in vitro enzyme kinetics investigations have repeatedly shown that even at doses as high as 64 μg/mL, strong antibacterial dihydropyrimidines do not significantly block DHFR. It's interesting to note that dihydropyrimidines completely lose their antibacterial action when they oxidize to their equivalent pyrimidines, rejecting DHFR as the main culprit and demonstrating that the reduced dihydropyrimidine structure is necessary for biological activity [50].

IV. CLINICAL CONSIDERATIONS AND SAFETY PROFILE

Studies on safety have uncovered crucial factors to take into account while developing dihydropyrimidine-based antibacterial drugs for clinical use. Despite the fact that several derivatives have strong antibacterial activity, thorough cytotoxicity tests against mammalian cell lines have revealed selectivity issues that need to be resolved for therapeutic use. There are limited therapeutic windows as a result of recent research showing that a number of promising drugs have notable mammalian cytotoxicity at concentrations near their antibacterial minimum inhibitory concentrations. Nonetheless, promising outcomes have been achieved with particular structural alterations; certain derivatives exhibit strong antibacterial activity at concentrations as high as 80 μg/mL without exhibiting any appreciable cytotoxicity against mouse fibroblast cell lines [51]. The creation of photoaffinity probes with trifluoromethyl diazirine groups has made it possible to conduct mechanistic research while preserving antibacterial activity; optimized probes have been shown to have MIC values of 2 μg/mL against strains of S. aureus. Crucially, at pertinent concentrations, these drugs show no haemolytic action, suggesting that nonspecific membrane disruption is not a part of the antibacterial process. According to this selectivity profile, additional structural optimization may produce therapeutically feasible candidates with better therapeutic indices [52].

Resistance Factors and Prospects for the Future

Antibiotics with unique modes of action that can get beyond current resistance mechanisms are desperately needed in light of the rise of multidrug-resistant bacterial infections. Because of their special dual-targeting strategy that influences both the DNA replication and protein synthesis pathways, dihydropyrimidine derivatives provide notable benefits in this situation. The substances show sustained efficacy against bacteria that are resistant to several types of antibiotics, such as aminoglycosides, fluoroquinolones, and β-lactams. Dihydropyrimidines may not be susceptible to common resistance mechanisms that affect traditional antibiotics, such as efflux pump overexpression, enzymatic degradation, or target change, based on their broad-spectrum effectiveness against resistant organisms [53, 54]. The potential of dihydropyrimidine derivatives in combination therapies has been investigated recently, especially in relation to well-known antibiotics or as adjuvants to improve the effectiveness of currently used treatments [55]. Through the suppression of resistance mechanisms or the augmentation of antibiotic absorption, several dihydropyrimidine compounds have been shown in synergistic investigations to restore sensitivity to standard antibiotics in resistant bacteria. These drugs' multiple mechanisms of action make them appealing candidates for combination strategies that could maximize treatment efficacy while lowering the risk of resistance development The ongoing development of ecologically sustainable synthetic techniques remains a top objective for the practical application of dihydropyrimidine-based therapies. Recent breakthroughs in catalyst design, such as the

creation of recyclable heterogeneous catalysts and biomimetic systems, promise to lessen the environmental impact of large-scale production while maintaining high efficiency and selectivity. The use of continuous flow chemistry and automated synthesis platforms may improve the scalability of these synthetic techniques, making them economically viable for pharmaceutical production [56,57].

V.CONCLUSION

The synthesis and development of dihydropyrimidine derivatives as antibacterial agents represents a promising frontier in the fight against antimicrobial resistance, offering unique mechanisms of action and broad-spectrum activity against multidrug-resistant pathogens. The versatile Biginelli multicomponent reaction provides an efficient and sustainable synthetic platform for generating structurally diverse compound libraries, while green chemistry approaches ensure environmental compatibility and economic viability. Structure-activity relationship studies have identified key molecular features governing antibacterial potency, enabling rational design approaches for next-generation therapeutics with enhanced efficacy and selectivity profiles. The elucidation of dual mechanisms involving DNA gyrase and ribosomal RNA targeting positions dihydropyrimidines as innovative antibacterial agents capable of circumventing existing resistance mechanisms. While current challenges related to mammalian cytotoxicity and pharmacokinetic optimization require continued research efforts, the significant therapeutic potential demonstrated by these compounds justifies sustained investment in their development. The integration of advanced computational approaches, sustainable synthetic methodologies, and comprehensive preclinical evaluation programs provides a clear pathway for translating these promising research findings into clinically viable antibacterial therapeutics capable of addressing the growing global threat of antimicrobial resistance.

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