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Synthetic Antibacterial Agents of Various Chemical Structures. Representatives of the New Generation of Cephalosporin Antibiotics

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Abstract: Antibiotics are substances that inhibit the growth of bacteria without endangering the eukaryotic host that is afflicted. When it comes to treating diseased humans and animals, beta-lactams are one of the most important therapeutic drugs. To battle a variety of present and potential multi-resistant bacterial diseases, the pharmaceutical industry is being forced to look for new antibacterial medications due to the growing problem of antibiotic resistance. With an emphasis on semi-synthetic cephalosporins, we present an overview of the evolution, novelty, and present state of beta-lactam therapeutic uses in this study. A naturally occurring secondary metabolite of the filamentous fungus Acremonium chrysogenum, cephalosporin C (CPC) is essential to the synthesis of contemporary antibiotics as well as the creation of novel ones. Semi-synthetic cephalosporins that can manage infections with various resistance mechanisms are made using CPC as a core component. Thus, we provide an overview of the most recent information we have on the fungal host's regulation of the CPC biosynthesis pathway. Lastly, we outline how CPC is a major source of leads for the in vitro and, more importantly, in vivo synthesis of 7-aminocephalosporanic acid (7-ACA), which is the primary building block for the pharmaceutical synthesis of semi-synthetic cephalosporins, both present and future.

Keywods: Siderophores, antibiotics, resistance, antimicrobial agents, nanoparticles, antimicrobial peptides.

Introduction. Alexander Fleming's 1928 discovery of penicillin in London, a major turning point that prevented countless deaths from infectious infections, essentially ushered in the modern era of medicine. The pharmaceutical corporation Eli Lilly in the United States was able to produce penicillin on a big scale in the 1940s, and it was quickly used as the first beta-lactam antibiotic in clinical medicine. The beta-lactam ring of the fundamental molecular structure of this class of antibiotics facilitates the disruption of bacterial cell wall building, which is the basis for the collective group of pharmaceutical compounds with antibacterial action [1-5]. Over the past century, three further major families of beta-lactam antibiotics based on naturally occurring secondary metabolites have been discovered after the successful discovery of penicillin. These included the 1948 and 1976 discovery of cephalosporins and carbapenems, which have a bicyclic nucleus that resembles the fundamental chemical structure of penicillin, and the 1981 discovery of monobactam antibiotics, a distinct class of beta-lactam antibiotics distinguished by a monocyclic system. Their varied range of bactericidal activity, pharmacological characteristics, and specific level of tolerance to antibiotic resistance are determined by their unique core structure and different side chain alterations [6-11]. Alternative beta-lactam antibiotics, known as cephalosporins, are frequently used to treat mild to severe infectious illnesses because of their great effectiveness. According to the healthcare database from 2004 to 2014 cited above, the number of prescriptions for cephalosporins (47.5% of all antibiotics) in the USA recently surpassed the number of narrow- and wide-spectrum penicillins (39.7% of all antibiotics). Semi-synthetic cephalosporins, which are based on the bicyclic nucleus of a beta-lactam ring joined to a six-membered dihydrothiazine ring, are broadly active against both Gram-positive and Gram-negative bacteria. The cephalosporin scaffold's C3 and C7 carbons offer a great deal of potential for adding different side chains that would greatly increase the antibacterial activity and improve the

structural stability against beta-lactamases [12-17]. At first, it was thought that widespread resistance to antibiotics was unlikely. However, the overuse of antibiotics caused beta-lactam and other antimicrobial resistances to proliferate, which posed a serious risk to human health (Aslam et al. 2018). The over use of antibiotics in health care, animal feed, and direct or indirect interaction with contaminated environments are the main causes of developing antimicrobial resistances. Therefore, to create new antibiotics that might offer efficient ways to treat emerging resistances, advancements in a variety of pharmaceutical research fields, such as genetic engineering and synthetic chemistry, are required. In order to combat the growing antimicrobial resistance in clinical settings, we highlight the significance and high applicability of cephalosporins as essential lead generation beta-lactam antibiotics in this review. We also go over the present status of biotechnological approaches for the synthesis of semi-synthetic cephalosporins [18-24].

The main purpose of this presented analytical manuscript is synthetic antibacterial agents of various chemical structures. It consists of a brief commentary on the representatives of the new generation of cephalosporin antibiotics.

Cephalosporin antibiotics. The filamentous fungal species Acremonium chrysogenum is the source of cephalosporin antibiotics. The first cephalosporin antibiotic chemical to be identified was Cephalosporin C (CPC). Giuseppe Brotzu of Italy made the discovery in 1945, and shortly after, its chemical structure was determined. Both Gram-positive and Gram-negative bacteria are susceptible to the wide antibacterial action of CPC and its derivatives. They are crucial for hospital patients to prevent and cure upper respiratory and urinary tract infections, as well as infectious disorders that affect the skin, ears, and bones. Numerous extremely potent semi-synthetic cephalosporins have been created and are now often prescribed all over the world in recent decades. The characteristics of each class of cephalosporins, how they circumvent mechanisms of antibiotic resistance, and the most recent developments in cephalosporin use and development are discussed in the sections that follow. Furthermore, the creation of cephalosporin antibiotic derivatives is the main topic of this paper, which presents CPC as a key lead generation molecule for industrial production techniques and biosynthesis of semi-synthetic cephalosporin building blocks [1-7]. By interfering with the peptidoglycan chains of bacterial cell walls, cephalosporins, which are bactericidal drugs, prevent growth. Penicillin-binding proteins (PBP) catalyze the last stage of peptidoglycan layer construction by cross-linking the linear glycopeptides to create a three-dimensional structure. Cephalosporins, a class of beta-lactam antibiotics, attach to PBPs by imitating the structure of glycopeptides, hence permanently preventing the formation of bacterial cell walls. Based on their range of antibiotic activity and the time of discovery, cephalosporin antibiotics have been evolved into five key generations thus far [8-12].

Cephalosporin antibiotic classification. First-generation cephalosporins are very effective against methicillin-sensitive *Staphylococcus aureus* (MSSA) and other Gram-positive cocci, including streptococci, such as *Streptococcus pneumoniae*, which causes the majority of community-acquired pneumonia infections. With the exception of middle ear fluid and cerebrospinal fluid (CSF), the majority of tissues absorb and distribute first-generation oral cephalosporins well. First-generation cephalosporins, on the other hand, are not very effective against Gram-negative bacteria like *Enterobacter* or *Pseudomonas aeruginosa*. When a pathogen is resistant to at least three separate types of antimicrobials, it is said to be multidrug-resistant. By bringing second-generation cephalosporins to the market, the drawbacks of first-generation cephalosporins were addressed. These cephalosporins shown greater stability against beta-lactamases made by certain Gram-negative bacteria, including several Enterobacteriaceae species and Haemophilus influenza, which is linked to respiratory illnesses. The prolonged half-life and lower dosage of second-generation cephalosporins are two important features that help the patients receiving these antibiotics [1,2,4,7,11, 14]. With the number of multidrug-resistant organisms growing dramatically, there was an urgent need for stronger antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the germs that the fifth-generation cephalosporins, which were created to treat multidrug-resistant bacterial strains, have an exceptionally broad antibiotic spectrum. After *E. coli,* the most common pathogen linked to mortality, MRSA was the second most common pathogen responsible for drug-resistant deaths in 2019. Necrotizing

pneumonia and severe skin and soft tissue infections acquired in the community are caused by MRSA. The regular exchange of resistant genetic material encoding mutant PBPs led to the development of MRSA's broad resistance. These mutations interfere with the target binding functions of all other beta-lactam antibiotics by attaching to their beta-lactam rings [12-17].

Conventional antibiotics are widely used and effective in treating bacterial infections, but they have a number of serious drawbacks. The quick emergence of bacterial resistance is one of the main problems, as it may eventually make these medications useless. Due to expensive prices, protracted development periods, and strict regulatory restrictions, the discovery and development of new antibiotics has slowed down considerably, making it challenging to keep up with the emergence of resistance strains. AMPs are a promising substitute for small-molecule antibiotics in the fight against bacterial infections and antibiotic resistance. Their broad-spectrum action, which enables them to target a variety of pathogens such as bacteria, fungus, and viruses, is one of their main advantages. The development of resistance is less likely while using AMPs because they usually work quickly and have a less specific mechanism of action than conventional antibiotics. Additionally, they have the ability to break down biofilms, which are defense mechanisms produced by bacterial communities that are frequently impervious to the effects of traditional antibiotics [4,5,7,8,9,11]. However, AMPs also have certain disadvantages, including poor pharmacokinetic properties, cytotoxicity towards human cells at higher concentrations, and susceptibility to proteolytic degradation by human body enzymes. These require frequent dosing or alternative administration routes, which may be less convenient for patients. Combination therapy, which overcomes the majority of the disadvantages associated with the use of single components, represents a promising frontier in the fight against AMR. This novel treatment increases antimicrobial efficacy by fusing the focused effectiveness of conventional antibiotics with the strong, broad-spectrum activity of AMPs. The type of infection, the particular microorganisms involved, the patient's characteristics, and the resources available all influence the decision between coadministration and antibiotic–AMP conjugates. Although coadministration offers ease and flexibility, it must be carefully managed to prevent problems with medication resistance and interactions. Conjugates have the potential to provide highly targeted, efficient treatment with less development of resistance, but they also present complexity and expense issues. Antibiotic–AMP conjugates provide more precise targeting of bacterial cells over host cells while also improving antibiotic penetration and intracellular concentration by utilizing the membrane-active characteristics of AMPs [7-11]. In addition to increasing the treatment's efficacy, this dual-action strategy permits lower dosages, which lowers the possibility of adverse effects and resistance development. Even though no antibiotic–AMP conjugates have made it to market yet, research is still being conducted, and with new developments in peptide synthesis, delivery systems, and conjugation technologies, as well as a better understanding of bacterial biology and the mechanisms by which AMPs and small-molecule antibiotics work, antibiotic–AMP conjugates are becoming a more effective and adaptable approach to the global problem of antimicrobial resistance. The development and application of antibiotic–AMP conjugates must be heavily influenced by financial and regulatory incentives. In order to speed up the discovery of novel antimicrobial agents, governments and health organizations are offering financing, tax breaks, and faster regulatory processes in recognition of the pressing need to tackle AMR. For pharmaceutical corporations to participate in this high-risk, high-reward field of research and development, these incentives are essential. Conclusion: Antibiotic–AMP conjugates are becoming a key component in the fight against antimicrobial resistance (AMR) thanks to the combination of state-of-the-art technologies, a growing understanding of bacterial biology, and supportive economic and regulatory frameworks. In order to protect public health for coming generations, these conjugates have the potential to restore the effectiveness of already available antibiotics and introduce fresh, powerful antimicrobial treatments [11-24].

Discussion. A increasing global public health concern is the lack of new medications that are effective against germs that are resistant to antibiotics1. The chemical alteration of natural products (semisynthesis) has been a major part of the quest for novel antibiotics for more than 50 years, but this approach is not well-suited to address the continually changing risks of resistance. In polyfunctional

antibiotics, semisynthetic changes are usually restricted in scope, typically result in an increase in molecular weight, and infrequently allow for modifications to the underlying scaffold. Fully synthetic methods can readily overcome these drawbacks when they are appropriately designed. Here, we describe the structure-guided design and component-based synthesis of a rigid oxepanoproline scaffold that, when attached to the clindamycin aminooctose residue, yields an antibiotic with a remarkable range of activity and potency that we call iboxamycin [1-5]. Without endangering the eukaryotic host that is infected, antibiotics are antibacterial substances that prevent bacteria from growing. Beta-lactams are one of the most important therapeutic drugs used to treat sick humans and animals. However, the pharmaceutical industry is being forced to look for new antibacterial medications to fight a variety of present and potential multi-resistant bacterial diseases due to the growing antibiotic resistance dilemma. We give a summary of the evolution, novelty, and present state of beta-lactam therapeutic applications in this review, with an emphasis on semi-synthetic cephalosporins. The filamentous fungus Acremonium chrysogenum naturally produces cephalosporin C (CPC), a secondary metabolite that is essential to the synthesis of contemporary antibiotics as well as the creation of novel ones. Many bacterial illnesses in the population and, more significantly, serious infectious disorders in hospitals brought on by germs resistant to antibiotics are treated using cephalosporin drugs. The majority of semi-synthetic cephalosporins are produced by chemically altering side chains from the main building block 7-ACA. Since A. chrysogenum is the industrial manufacturer of CPC, the substrate for the enzymatic synthesis of 7-ACA, it is essential in this case [9-15]. Thus, for industrial and financial reasons, it is very appealing to look into the fungus A. chrysogenum, which produces CPC, and new 7-ACA manufacturing techniques. Future pharmaceutical processes would surely benefit from the discovery of sustainable and ecologically safe manufacturing techniques. The industry has been looking for ways to reduce manufacturing costs all the time. Industrial businesses have achieved this by regularly doing A. chrysogenum strain upgrades, which maximize CPC output from fungal fermentation. In the meantime, decreasing the enzymatic processes following the fermentation steps is another strategy to lower manufacturing expenses. On an industrial scale, one-step direct conversion from CPC to 7-ACA has been accomplished in vitro utilizing CCA [16-20]. In order to create semi-synthetic cephalosporins that can manage infections with various resistance mechanisms, CPC is a necessary building block. Thus, we provide a summary of our most recent findings about the process of CPC biosynthesis and its control in the fungal host. Finally, we explain how CPC is a major source of leads for the in vitro and, more importantly, in vivo synthesis of 7-aminocephalosporanic acid (7-ACA), which is a critical core chemical for the pharmaceutical synthesis of semi-synthetic cephalosporins that are currently on the market and will be in the future. ESKAPE pathogens that express Erm and Cfr ribosomal RNA methyltransferase enzymes, which are gene products that confer resistance to all clinically relevant antibiotics that target the large ribosomal subunit, such as macrolides, lincosamides, phenicols, oxazolidinones, pleuromutilins, and streptogramins, are susceptible to the effects of Iboxamycin. Iboxamycin's structural foundation for this increased activity, which includes a nucleotide displacement upon antibiotic binding, is shown by X-ray crystallographic investigations of the antibiotic in association with both the native bacterial ribosome and the Erm-methylated ribosome. In an era of growing antibiotic resistance, the ability of chemical synthesis to produce new antibiotics is demonstrated by the fact that it is safe, efficacious, and orally accessible for treating both Gram-positive and Gram-negative bacterial infections in mice [16-24].

Conclusions. Antibiotic resistance is a serious global public health issue that contributes to 4.95 million deaths worldwide. Bacteria can quickly decrease their susceptibility to drugs through acquired or naturally occurring resistance that is produced by DNA mutation or horizontal gene transfer. It is necessary to find new antibacterial agents to fight bacterial infections. New approaches to rational design and screening-based approaches, including nanotechnology, computational techniques (in silico and FBDD), drug repurposing (ticagrelor, mi-tomycin C, auranofin, pentamidine, and zidovudine), antibiotic alternatives (antimicrobial peptides, essential oils, anti-Quorum sensing, darobactins, vitamin B6, bacteriophages, odilorhabdins, 18β-glycyrrhetinic acid, and cannabinoids), and the synthesis of novel antibacterial agents (lactones, piperidinol, sugar-based bactericide, isoxazole, carbazole, pyrimidines, and prodrugs).

Cephalosporin antibiotics are frequently administered for a variety of bacterial illnesses in the general population and, more significantly, for serious infectious disorders brought on by germs that are resistant to antibiotics in hospitals. By chemically altering side chains, the majority of semi-synthetic cephalosporins are produced from the fundamental building block 7-ACA. As the industrial manufacturer of CPC, the substrate for the enzymatic synthesis of 7-ACA, A. chrysogenum is essential in this case. Consequently, for industrial and financial reasons, it is very appealing to look into the CPC-producing fungus A. chrysogenum and innovative 7-ACA manufacturing techniques.

It is appealing to enhance further novel production by introducing such a one-step bioconversion system into the fungus that produces CPC. CPC can be instantly transformed into 7-ACA once the CCA enzyme is produced and activated close to the site of substrate biosynthesis. This eliminates entire enzyme-related downstream steps and drastically lowers production costs.

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