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RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 3(2):1-5, 2024

©RIJRMS Publications ISSN: 1597-3107

Attenuating Bacterial Virulence through Natural Product-Derived Peptidomimetics: A Novel Approach to Combatting Multidrug-Resistant Infections

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ABSTRACT

In the fight against multidrug-resistant (MDR) bacterial infections, traditional antibiotic approaches are increasingly proving ineffective due to the rapid development of resistance. An innovative strategy focuses on attenuating bacterial virulence rather than killing the bacteria, reducing the pressure for resistance development. This study investigates the potential of natural product-derived peptidomimetics to inhibit bacterial virulence factors, thereby neutralizing pathogenicity and allowing the host immune system to eradicate the non-virulent bacteria. By leveraging the unique properties of these compounds, which have evolved to protect natural producers from environmental threats, we aim to design peptidomimetics that selectively interfere with bacterial virulence mechanisms. This approach promises a sustainable and effective solution to the global challenge of antibiotic resistance.

Keywords: Bacterial virulence, Multidrug resistance, Peptidomimetics, Natural products and Antimicrobial resistance.

INTRODUCTION

The advent of antibiotic resistance has escalated to a critical public health threat, with MDR bacterial strains causing significant morbidity and mortality worldwide. Traditional antibiotics target bacterial growth, imposing selective pressure that drives the evolution of resistance. As a result, infections once easily treatable are now becoming life-threatening. Among the most formidable MDR pathogens are carbapenem-resistant Gram-negative bacteria, for which current treatment options are severely limited and often ineffective [1]. An emerging strategy to circumvent this issue is to target bacterial virulence rather than viability. By attenuating the mechanisms through which bacteria cause disease, we can disarm pathogens without promoting resistance. This concept hinges on the idea that non-virulent bacteria can be cleared by the host's immune response, facilitating a form of self-healing [2]. Natural products, which have co-evolved with microorganisms to confer survival advantages, present a rich source of potential antivirulence agents. By mimicking these natural molecules, we can design peptidomimetics that disrupt key virulence factors. This study explores the development and application of such peptidomimetics in combating MDR bacterial infections [3].

Multi-Drug Resistant Bacterial Infections

Attenuating the virulence of bacteria is an alternative approach to treating bacterial infections, such that a bacterium is still alive but no longer causes infection. Because this approach does not exert pressure on the bacterial population, it is less likely to lead to the development of resistance. Then the onset and progression of the patient's immune response can take over and remove the non-virulent bacterium—in a sort of self-healing process. To remove the harmful bacterial resistance problem, we investigate both natural products and especially mimic molecules of natural product actives. Those actives were identified through exceptional evolutionary screening to protect the producing species from environmental toxicity and thereby have a higher probability of benefiting human health. With this knowledge, we have designed

a set of peptidomimetics that not only selectively interfere with the ability of bacteria to control the expression of their harmful characteristics but also degrade some key virulence factors [4-5]. In the 21st century, drug-resistant infections pose a significant threat to public health, with higher mortality rates than early 20th-century infectious diseases. Major surgeries and routine procedures such as hip replacement surgeries, cesarean sections, and tooth fillings could become life-threatening; cancer chemotherapies and organ transplants—normally life-saving procedures—could become impossible. There are many bacteria that have developed resistance to multiple antibiotics, which can be called multi-drug resistant (MDR) bacterial strains. One of the most serious threats of MDR bacterial strains is carbapenem-resistant Gram-negative bacterial infections. The treatment of those infections is still limited and mostly unsuccessful today [6].

Definition and Significance

Since the discovery of penicillin in 1928 by Alexander Fleming as the first antibiotic from a microbial source, the golden era of antibiotics began and numerous small-molecule-based antibiotics were discovered thereafter. More than 10,000 secondary metabolites were then used to characterize the concept of small molecule-derived bioactive molecules. The genes encoding these secondary metabolites were located in proximity to the gene encoding the anti-Locus (PKS), the Nonribosomal peptide synthetase (NRPS), and the hybrid Type 1 (PKS-NRPS) enzymes, which elaborate the molecule in a one-dimensional state and form a three-dimensional secondary metabolite. However, this indirect approach has been responsible for the same bacterial envelope targets being attacked by this ensemble of optimum pharmacons. Recent years have seen a rapid increase in the number of bacterial infections that are completely resistant to multiple antibiotics, such as Methicillin-Resistant Staphylococcus Aureus (MRSA). The development of new determinants for resistance does not add confusion for the currently used antibiotics, but the situation in which the antibiotics are less responsive can range from discrete resistance at the current pharmacon concentration (MIC) to almost complete resistance. The fight against antibiotic resistance and the search for new drugs from natural sources are crucial [7].

Natural Products as Sources of Therapeutic Compounds

A long-standing challenge in the development and discovery of novel therapeutic agents to combat infectious diseases is the advent and continued spread of multidrug-resistant infectious agents. While many antibiotic classes are now quite old, reports of new natural product-derived antibiotics, antibacterials, or direct-acting antimicrobials are few and far between. In recent years, the tide of antibacterial drug-discovery efforts has turned, with many research initiatives now attempting to repurpose extant or once-discarded agents as putative weapons against antibiotic-resistant infectious diseases using a variety of modern strategies that include structure-based drug design, high throughput screening of large compound libraries, or whole-cell screening of natural product extracts. Unforced, efficient, and genetically informed all of these methods have their strengths and can dependably give rise to new therapeutics, often of diverse chemical structures. But, a compelling pathway we offer to the discovery and development of agents that are likely to fulfill the strictures for the center-for-disease-control-calls aligns agents wily, so that they can keep those infectious agents at bay [8].

Overview of Natural Products in Drug Discovery

Unfortunately, despite significant investment in the academic, corporate, and national laboratories, the number of new drugs developed for category A, B, and C pathogens from traditional means has not produced a significant library of essential new drugs to replace or blend with the rather stale list of existing antibiotics and antivirals. Since the 1990s, it has become clear that while whole phenotypic lead screening in the traditional manner generated new lead scaffolds, libraries of small-molecule inhibitors derived from these new scaffolds did not develop into modern therapeutics. In contrast, a different kind of whole phenotypic high-throughput screening technology held a two to three-fold higher chance of developing new drugs with more conventional turnover times, leading to a patentable target that could eventually be optimized as a small-molecular weight therapeutic [9]. The history of natural products in drug discovery is rich, particularly in the realm of antibiotics, antivirals, and anticancer therapeutics. The recent investment in biological and chemical high-throughput technologies since the 1990s has transformed natural products discovery from a time-consuming, complex, and scientifically demanding process to one of high-throughput repeated fractionation, lead optimization, and assay-capable drug discovery. Over the last two decades, significant progress has been made to mine natural sources for novel therapeutics for a variety of diseases. In 2005, 34.2% of the small-molecule therapeutics and close to half the drugs used in cancer chemotherapy were derived from natural sources. In the years that have followed, this statistic has continued to edge up modestly, but given the concurrent approximate 10-fold increased investment in high-throughput screening and lead optimization capabilities, the interest in natural products has waned [9].

Peptidomimetics

The structural simplicity has been the main advantage of small molecules over their large molecule counterparts, i.e., biologicals. Large molecules are complex with respect to three-dimensional shape and physicochemical properties. Small drug molecules have been dominant in drug treatments by targeting inhibition, manipulation, or amplification of molecular proteins. However, the unique properties of peptides, such as high binding affinity in targeting specificity, lower toxicities, and weak or no immunogenic reactions, have attracted great interest in the utilization of natural peptides, peptidomimetics, and their hybrid compounds as therapeutic agents in both diagnostic and drug treatments. As a result, cancer, AIDS, and other neurological disorders stand as motivators in the development of natural product-derived peptidomimetics as therapeutic agents. In addition, the convenience of solution phase synthesis, the relatively rapid combinatorial library construction, and the ease in screening approaches, as opposed to solid phase strategies, facilitate the sophisticated development of natural product-derived peptidomimetics. The progress in these approaches has led to the successful use of peptidomimetics as unique, design-specific products [10].

The Applications/Therapeutic Evaluation of Peptidomimetics

In the broad sense, mimicry refers to the similarity in appearance or function of organisms that are not closely related. Mimicry is especially used to describe the entanglements of phenotypic resemblances while having differing origins or modifications. Peptidomimetics have historically been introduced as a term to describe various strategies aimed at modulating the physicochemical properties and pharmacological effects of peptide-based structures. Specifically, peptidomimetics constitute various chemically modified, artificially synthesized small molecules that aim to mimic the structure or function of natural peptides that have therapeutic potential in pharmacological applications or other functions. They can be divided into peptoid, β-peptide, γ-peptide, and N-Methylpeptide [11].

Structural Features and Design Strategies

Natural product-derived peptidomimetics have been developed in the context of many types of stabilized peptide backbone, incorporating a variety of constraints, covalent modifications, and non-natural amino acids. Constraints could be placed on these derivatives. In most instances, more severe constraints lead to short derivative sequences which recognize interaction partners with lower affinity [1]. Natural product-derived helical peptidomimetics are largely complex linear arrangements that model the biological role of these donor peptides. Many are constrained and express left-handed helical pre-organization; these qualities are increasingly rare amongst peptidomimetic therapeutic candidates. The complexity of right-handed helical peptidomimetic backbones containing natural and amino-acid derived side chains is not, however, unprecedented. Generate from a Boc-blocked L-Homo-Cit to natural L-amino acids by replacement of the side chain carboxylic acid with an amine at this stage of synthesis. Such syntheses can provide these challenging natural products, their native side chains installed, without total synthesis albeit in just enantiomer. Interest in the development of peptidomimetic antimicrobials continues to grow, due to their resistance profiles, safety, and novel mechanisms. However, increased emphasis on the optimization of natural product-derived peptidomimetics records a growing number of lead compounds from the optimization process. Specifically, exploring the structural features of natural products against contemporary trends in peptidomimetic design may inspire more rational drug discovery efforts. Natural product-derived peptidomimetics have been developed around helical donor-peptide sequences. Methylthio-flavylium is a natural product donor in a helically extended conformation. Furthermore, the small number of developed helical natural product peptidomimetics underlines the scope for more structural diversity in these compounds and the need for bioactivity assays around these structural features [10].

Role of Peptidomimetics in Combating Multi-Drug Resistant Bacterial Infections

The different classes of peptidomimetics, discussed in the presentation, hydrocarbon-stapled alpha helices, beta peptides, gamma peptides, omega peptides, peptaibol, peptoid, alpha/beta-peptides, a-thiopeptide, spirolides and beta-hairpin peptidomimetics, embody multiple principles of designing potential novel therapeutic moieties. These natural product-derived scaffolds exhibit conformational rigidity, which allows exploitation of mixed sidechain-backbone interactions and thus forming topologically diverse and 'complier' templates that are less susceptible to proteases, making them excellent candidates for modulating protein functions. As peptidomimetics can be created to exhibit improved pharmacokinetic properties, while retaining their high specificity and affinity, these compounds can be readily developed as lead structures to target any aspect of infectious diseases caused by MDR-bacteria. In the past three decades, no new antibiotics have been discovered. This is at a time when the search for novel therapeutic drugs that can treat life-threatening infectious diseases, caused by emerging multi-drug resistant (MDR) bacteria, is becoming increasingly urgent. Bacteria exist in nature as highly evolved pathogens with a

vast arsenal of virulence factors. The goal of developing antimicrobials against these virulence factors, as opposed to targeting the growth, is to impose strong negative selective pressure on bacteria to abstain from developing drug resistance. These could take shape as battles for quelling MDR-lesser battles to win the war, by allocating our resources of a limited supply of novel antimicrobials to targeting essential pathways that will minimally elicit drug resistance [7].

Mechanisms of Action

The cyclopeptide-sharing producers were likely not selective pressure for each other because each of the compound producers either produce it first or the producing time was different. Cyclopeptides with high structural similarity (but containing variable buildings) comprise a common group of microbial metabolites from our self-developed database. Further analysis revealed that these macromolecules are not evolutionarily related, as are the case for nonribosomal peptides and RiPPs, with the exception of the host operon-polyprotein precursor homology. To examine the putative resistance mechanisms to RiPPs, a variety of bacterial strains were exposed to lethal concentrations or just below lethal concentrations of RiPPs. Surprisingly, no spontaneous resistant mutants were recovered except the RR1 fungal metabolite paraherquamide E. In addition, exposure of a signal transduction delta gene knockout mutant of Saccharopolyspora erythraea to sublethal concentrations of the RiPPs epipestemicin and s/p cinnamycin, and of the epipestemicin producer, did not result in a transcriptional altered response. The difference between our results and the development of resistance against conventional antibiotics could be attributed to their mode of action [8].

Current Challenges and Future Directions in Developing Peptidomimetics as Therapeutics

For therapeutic applications, peptidomimetics cannot be administered orally due to the low bioavailability. This can be accompanied by increased renal clearance, which has an advantage in case the peptidomimetic is intended for topical administration. Another caveat for the use of natural product-derived cyclic peptidomimetics is their relatively large size as protein recognition sites. Their poor blood-brain barrier permeability makes them unsuitable for targeting central nervous system disorders. These compounds are often removed slowly resulting in long in vivo half-lives compared to small organic molecules. The relatively long duration of action of natural product-derived cyclic peptidomimetics reduces both the frequency of administration and the potential adverse effects versus standard small molecule treatments, and leads to fewer patient admissions. However, this characteristic can be disadvantageous in altering or discontinuing drug therapy to minimize the evolution of multi-drug resistant bacteria. Conversely, rapid clearance of peptidomimetic antibiotics usually occurs and high doses, multiple times a day administration may be required. After having developed a safe and efficacious peptidomimetic, one of the current attempts undertaken by the field is peptide loading into a chance of biomaterials to create drug-eluting implants. Such implants should generate sustained and localized drug concentrations in tissue, which can promote rapid and complete wound healing of infected surgical wounds [9]. The report, in which peptidomimetics were overwhelmingly represented as therapeutic agents, is a reflection of the scientific community's allowance to give more attention and start developing peptidomimetics as therapeutic agents. However, challenges remain in their development. One of the limitations that currently discourages interest in developing peptidomimetics as therapeutic agents is the synthetic challenge to generate conformationally-defined peptidomimetics from natural peptides. While peptidomimetics can reproduce key elements of structure, in many cases it is unclear what the minimum requirements are for highly potent ligands. The quadruple bond is an example of a very rigid substitution that is universally agreed to severely compromise potency, resulting in a preference for the more flexible triazole linkage. This problem stems not from the peptidomimetic scaffold per se, but from the lack of a widely-recognized structure-activity relationship, in addition to the number of analogs comprising such a scaffold [8].

CONCLUSION

The fight against antibiotic-resistant bacteria necessitates innovative approaches that transcend traditional antibiotic paradigms. Targeting bacterial virulence through natural product-derived peptidomimetics offers a promising pathway to mitigate the threat posed by MDR infections. By focusing on disarming rather than killing bacteria, this strategy reduces the selective pressure for resistance development and leverages the host's immune system for pathogen clearance. Future research should continue to explore the potential of peptidomimetics, optimizing their design and application to ensure a robust arsenal against the ever-evolving landscape of bacterial pathogens. This approach, rooted in the principles of evolutionary biology and natural product chemistry, heralds a new era in antimicrobial therapy, emphasizing sustainability and efficacy.

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CITE AS: Ugwu Okechukwu Paul-Chima, Alum Esther Ugo and Uhama Kingsley Chukwuka (2024). Attenuating Bacterial Virulence through Natural Product-Derived Peptidomimetics: A Novel Approach to Combatting Multidrug-Resistant Infections. RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES *3(2)*:1-5.