The Significance of Functionalized Polyanilines: The Resistance Mechanisms Against Global Health Threat.

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ABSTRACT

Polyanilines (PANI) have garnered significant attention in recent years due to their unique properties and versatile applications, particularly in the realm of combating global health threats. This review highlights the importance of functionalized polyanilines in addressing various challenges posed by emerging infectious diseases, antimicrobial resistance, and environmental pollutants. Functionalized polyanilines exhibit remarkable properties such as diverse biomedical applications. In the context of global health threats, functionalized polyanilines have demonstrated efficacy as antimicrobial agents, drug delivery vehicles, biosensors, and environmental remediation agents.

This review provides an overview of the synthesis methods and properties of functionalized polyanilines, emphasizing their specific applications in combating global health threats. We explore their role in antimicrobial resistance, highlighting their ability to inhibit bacterial growth and overcome antibiotic resistance mechanisms. Additionally, we discuss their utility in drug delivery systems, enabling targeted and controlled release of therapeutic agents to combat infectious diseases. The synthesis of functionalized polyanilines with tailored properties offers a platform for innovation in the development of novel solutions to address evolving global health challenges. Integrating interdisciplinary approaches is crucial for harnessing the full potential of functionalized polyanilines in combating global health threats.

In conclusion, functionalized polyanilines represent a promising class of materials with multifaceted applications in addressing global health threats. ultimately contributing to the enhancement of global health security.

INTRODUCTION

The rapid emergence and spread of antibiotic-resistant bacteria has become a global healthcare crisis, posing a significant threat to public health. Bacterial resistance has rendered many once-effective antibiotics ineffective, making it increasingly difficult to treat infections caused by resistant strains[1]. The World Health Organization (WHO) has declared antibiotic resistance a “global health emergency,” emphasizing the urgent need for novel antimicrobial strategies to combat this growing menace (WHO, 2019). The development of new antimicrobial agents that can effectively target resistant bacteria without contributing to the further development of resistance is crucial to address this challenge[2].

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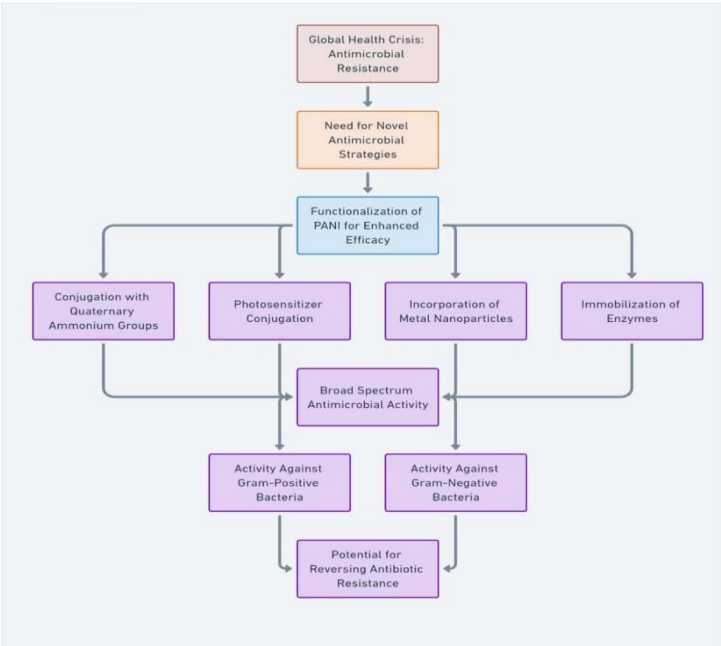
In the search for novel antimicrobial agents, researchers have explored various materials, including polymers, peptides, and nanomaterials[3]. Among these, polyanilines (PANI), a class of conducting polymers, have emerged as promising candidates due to their unique antimicrobial properties[4]. PANI is composed of repeating units of aniline monomers, which can exist in various oxidation states, resulting in different chemical and physical properties[5]. The structure of PANI allows for electron transfer and conductivity, making it an attractive material for electronic and electrochemical applications[6]. However, recent studies have revealed the potential of PANI in biomedical applications, particularly as antimicrobial agents [7].

The antimicrobial activity of PANI is attributed to multiple mechanisms, including the generation of reactive oxygen species (ROS) and the disruption of bacterial cell membranes [4]. When PANI interacts with bacteria, it can produce ROS such as superoxide anions and hydrogen peroxide, which can damage bacterial DNA, proteins, and lipids, leading to cell death [8]. Additionally, the positively charged backbone of PANI can interact with the negatively charged bacterial cell membrane, causing membrane destabilization and permeabilization[9]. This multifaceted mechanism of action makes PANI a potent antimicrobial agent with the potential to overcome bacterial resistance.

To further enhance the antimicrobial efficacy and broaden the spectrum of action of PANI, researchers have explored functionalization strategies[7]. Functionalization involves the modification of the chemical structure of PANI by introducing new functional groups, such as quaternary ammonium compounds, metal nanoparticles, or photosensitizers[10]. These modifications can improve the solubility, biocompatibility, and antimicrobial potency of PANI, making it a versatile platform for developing targeted antimicrobial agents[11]. Functionalized polyanilines (fPANI) have demonstrated broad-spectrum activity against a wide range of pathogens, including Gram-positive and Gram-negative bacteria, as well as multi-drug resistant strains[12]. The ability to tailor the properties of fPANI through functionalization offers a promising approach to combat bacterial resistance and address the growing need for effective antimicrobial agents.

This review will explore the recent advancements in the development of functionalized polyanilines as broad-spectrum antimicrobial agents against bacterial resistance. We will discuss the mechanisms of antimicrobial action, functionalization strategies, and the potential applications of fPANI in combating antibiotic-resistant bacteria. By highlighting the progress and challenges in this field, we aim to provide insights into the role of fPANI in addressing the global health threat of bacterial resistance.



Figs 1 showing the flow chat of Functional PANI

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FUNCTIONALISATION STRATEGIES FOR POLYANILINES

The functionalization of polyanilines (PANI) has emerged as a powerful strategy to enhance their antimicrobial properties and expand their potential applications in combating bacterial infections. By introducing various functional groups or conjugating PANI with other molecules, researchers can tailor the physical, chemical, and biological properties of the polymer to optimize its antimicrobial efficacy and selectivity[3].

Conjugation with Quaternary Ammonium Groups

One of the most widely explored functionalization strategies for PANI involves the conjugation with quaternary ammonium compounds (QACs). QACs are well-known for their antimicrobial properties, which stem from their ability to disrupt bacterial cell membranes through electrostatic interactions[13]. By incorporating QACs into the PANI structure, researchers can create powerful antimicrobial agents that combine the inherent properties of PANI with the membrane-targeting action of QACs[10].

The mechanism of action of PANI-QAC conjugates involves a multi-step process. First, the positively charged QAC groups interact with the negatively charged bacterial cell surface, facilitating the binding and attachment of the conjugate to the cell membrane[13]. According to [10], the authors established the that this interaction destabilizes the membrane structure, increasing its permeability and allowing the PANI-QAC conjugate to penetrate the cell and can further disrupt cellular processes, leading to cell lysis and death[10]. They also discovered that the antimicrobial efficacy of PANI-QAC conjugates has been demonstrated in numerous studies. For example, they developed a series of polyhexamethylene guanidine (PHMG) conjugates functionalized with QACs, which exhibited potent broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria. The authors attributed this enhanced efficacy to the synergistic effect of the PHMG backbone and the QAC groups, which facilitated the rapid and efficient killing of bacterial cells[10].

Photosensitizer Conjugation

Another promising approach to functionalizing PANI involves conjugation with photosensitizers, which are molecules that generate reactive oxygen species (ROS) upon exposure to light[14]. The author strategy combines the antimicrobial properties of PANI with the principles of photodynamic therapy (PDT), a light-activated antimicrobial approach that has gained increasing attention in recent years.

In PDT, the photosensitizer absorbs light energy and undergoes a series of photochemical reactions, leading to the generation of ROS, such as singlet oxygen and superoxide radicals[14]. The author confirmed these highly reactive species can oxidize various cellular components, including proteins, lipids, and DNA, causing irreversible damage to bacterial cells and ultimately leading to cell death.

The conjugation of photosensitizers to PANI offers several advantages over traditional PDT agents. First, the polymeric nature of PANI allows for the incorporation of a high density of photosensitizer molecules, enhancing the overall ROS generation capacity of the conjugate[11]. Second, the conductive properties of PANI can facilitate electron transfer processes, further increasing the efficiency of ROS production andfinally, the ability to functionalize PANI with targeting moieties, such as antibodies or aptamers, can improve the selectivity of the conjugate towards specific bacterial strains[11].

Several studies have demonstrated the potential of PANI-photosensitizer conjugates as antimicrobial agents. For instance, [11]developed a PANI-based nanoplatform functionalized with the photosensitizer rose bengal, which exhibited potent antibacterial activity against both Gram-positive and Gram-negative bacteria upon light irradiation. The authors attributed this enhanced efficacy to the efficient generation of ROS by the

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conjugate, as well as its ability to target and disrupt bacterial cell membranes.

Other Functionalization Approaches

In addition to the conjugation with QACs and photosensitizers, several other functionalization strategies have been explored to enhance the antimicrobial properties of PANI. One such approach involves the incorporation of metal nanoparticles, such as silver or gold, into the PANI matrix[15]. The authors discovered that metal nanoparticles have been shown to exhibit potent antimicrobial activity, which is attributed to their ability to release metal ions that can disrupt bacterial cellular processes. By combining the antimicrobial properties of metal nanoparticles with those of PANI, researchers can create highly effective antimicrobial materials with multiple modes of action[15].

Another promising functionalization strategy involves the immobilization of enzymes on the PANI surface. Enzymes, such as lysozyme and lactoferrin, are known for their antimicrobial properties, which are mediated through the hydrolysis of bacterial cell wall components or the sequestration of essential nutrients [16]. By immobilizing these enzymes on PANI, researchers can create antimicrobial materials that combine the inherent properties of PANI with the specific targeting capabilities of enzymes[16].

MECHANISMS OF ANTIMICROBIAL ACTION

Functionalized polyanilines (fPANI) exhibit potent antimicrobial activity through multiple mechanisms, including the production of reactive oxygen species (ROS), disruption of bacterial membrane integrity, and interference with bacterial metabolic and respiratory processes. These multifaceted mechanisms of action contribute to the broad-spectrum efficacy of fPANI against various bacterial pathogens, including antibiotic-resistant strains[4,7].

Production of Reactive Oxygen Species (ROS)

One of the primary mechanisms by which fPANI exerts its antimicrobial effects is through the generation of reactive oxygen species (ROS). ROS, such as superoxide anions (O2•?), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH), are highly reactive molecules that can cause significant damage to various bacterial cell components, including DNA, proteins, and lipids[17]. The production of ROS by fPANI leads to oxidative stress within bacterial cells, compromising their viability and ultimately leading to cell death[7].

The role of ROS in bacterial cell damage and death has been well-established. ROS can oxidize DNA bases, resulting in mutations and DNA strand breaks, which can impair bacterial replication and survival[18]. Additionally, ROS can oxidize proteins, causing structural changes and loss of function, thereby disrupting essential cellular processes[19]. Lipid peroxidation by ROS can also compromise the integrity of bacterial cell membranes, leading to increased permeability and cell lysis[20].

Evidence of ROS generation by functionalized PANI has been reported in[7]. In their study, the authors investigated the antimicrobial mechanism of polyaniline (PANI) and its functionalized derivatives, finding that the antimicrobial action of PANI likely involves the production of hydrogen peroxide (H_2O_2). This suggests that the antimicrobial activity of PANI and fPANI may, in part, be attributed to their ability to catalyze the formation of ROS, thereby inducing oxidative damage, and impairing bacterial cell function.

Disruption of Bacterial Membrane Integrity

Another key mechanism of fPANI's antimicrobial action is the disruption of bacterial membrane integrity. The bacterial cell membrane plays a crucial role in maintaining cellular homeostasis, regulating the transport of nutrients and waste products, and protecting the cell from external stressors[21]. Maintaining membrane

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stability is essential for bacterial survival, and any disruption to the membrane can lead to cell death[22].

Studies have demonstrated the ability of functionalized PANI to cause membrane damage in bacteria. The effectiveness of polyprodrug antimicrobials has been investigated[4], which employ a strategy like fPANI's mode of action, by causing serious membrane damage to bacteria. These materials can compromise the integrity of bacterial cell membranes, increasing their permeability and leading to the leakage of intracellular contents, ultimately resulting in cell death[4].

The mechanism by which fPANI disrupts bacterial membranes is thought to involve electrostatic interactions between the positively charged fPANI and the negatively charged bacterial cell surface[8]. The interaction of fPANI with the bacterial membrane can lead to the formation of pores or channels, allowing the influx of extracellular molecules and the efflux of intracellular contents, thereby disrupting membrane integrity, and causing cell death[8,9].

Interference with Bacterial Metabolic and Respiratory Processes

In addition to ROS production and membrane disruption, fPANI can also interfere with bacterial metabolic and respiratory processes. Bacterial metabolism and respiration are essential for energy production, growth, and survival[23]. Disrupting these processes can have detrimental effects on bacterial viability and proliferation.

The authors in[7]explored how fPANI derivatives disrupt the metabolic and respiratory machinery of bacteria. Specifically, they found that a homopolymer poly(3-aminobenzoic acid), used as an example of a fPANI, directly targets ATP synthase. ATP synthase is a critical enzyme involved in the synthesis of adenosine triphosphate (ATP), the primary energy currency of the cell[24]. By disrupting ATP synthase, fPANI impairs the bacteria's energy production and induces acid stress, further compromising bacterial viability[7].

The exact mechanisms by which fPANI interferes with bacterial metabolic and respiratory processes are still under investigation. However, it has been proposed that fPANI may act as an electron acceptor, competing with the natural electron transport chain and disrupting the proton gradient required for ATP synthesis[8]. The authors added that fPANI may interact with other enzymes and proteins involved in bacterial metabolism and respiration, leading to their inhibition or inactivation.

These mechanisms work synergistically to combat a wide range of bacterial pathogens, including antibiotic-resistant strains. The ability of fPANI to target multiple bacterial cell components and processes reduces the likelihood of resistance development, making it a promising candidate for novel antimicrobial strategies. Further research into the specific mechanisms of action and structure-activity relationships of fPANI will aid in the design and development of more effective antimicrobial agents to address the growing threat of bacterial resistance.

BROAD SPECTRUM ANTIMICROBIAL ACTIVITY AND EFFICACY

Functionalized polyanilines (fPANI) have emerged as a promising class of antimicrobial agents, exhibiting potent broad-spectrum activity against a wide range of bacterial pathogens. The ability of fPANI to combat both Gram-positive and Gram-negative bacteria, including antibiotic-resistant strains, highlights their potential as a versatile solution to the growing challenge of bacterial resistance[12].

Activity Against Gram-Positive Bacteria

Gram-positive bacteria, characterized by their thick peptidoglycan cell wall, are a major target for antimicrobial agents. Functionalized polyanilines have demonstrated impressive efficacy against various

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Gram-positive strains, offering a promising alternative to conventional antibiotics[8]. For instance, the authors [25] reported the synthesis of a novel fPANI derivative, polyaniline-graft-chitosan (PANI-g-CS), which exhibited strong antimicrobial activity against Gram-positive bacteria such as Staphylococcus aureus and Bacillus subtilis. The authors attributed this activity to the synergistic effect of the cationic chitosan and the conductive PANI, which facilitated bacterial membrane disruption and oxidative stress[25].

Compared to conventional antibiotics, fPANI offers several advantages in targeting Gram-positive bacteria. First, the multiple mechanisms of action of fPANI, including membrane disruption, ROS generation, and metabolic interference, reduce the likelihood of resistance development[9]. Second, the broad-spectrum activity of fPANI allows them to be effective against a wider range of Gram-positive strains, unlike some antibiotics that have a narrow spectrum of activity[3]. Finally, the ability to functionalize PANI with various groups enables the fine-tuning of their antimicrobial properties, allowing for the development of targeted antimicrobial agents[11].

Activity Against Gram-Negative Bacteria

Gram-negative bacteria, with their outer membrane and lipopolysaccharide layer, present a significant challenge for antimicrobial agents. The outer membrane acts as a barrier, limiting the entry of antimicrobial compounds into the cell[26]. Despite these challenges, functionalized polyanilines have shown remarkable success in combating Gram-negative bacteria[4].

One successful strategy involves the functionalization of PANI with quaternary ammonium compounds (QACs), which are known for their antimicrobial properties. The authors[10] reported the synthesis of a PANI-QAC conjugate that demonstrated potent activity against Gram-negative bacteria such as Escherichia coli and Pseudomonas aeruginosa. The positively charged QAC groups facilitated the interaction with the negatively charged bacterial membrane, leading to membrane disruption and cell death[10].

Another approach exploits the photodynamic properties of fPANI to enhance their antimicrobial activity against Gram-negative bacteria. The authors[12] designed a red fluorescent fPANI bearing quaternary ammonium groups, which exhibited outstanding broad-spectrum antimicrobial activity against Gram-negative bacteria under light irradiation. They also proposed that the light-activated generation of ROS by the fPANI contributed to its enhanced efficacy against Gram-negative strains.

The versatility of fPANI, coupled with their multiple mechanisms of action and the potential for targeted functionalization, makes them an attractive candidate for the development of novel antimicrobial strategies. As the threat of antibiotic resistance continues to grow, further research into the antimicrobial properties and clinical applications of fPANI is crucial to harness their full potential in combating resistant infections and safeguarding public health.

POTENTIAL FOR REVERSING ANTIBIOTIC RESISTANCE

The alarming rise of antibiotic-resistant bacteria poses a severe threat to global health, rendering many once-effective antibiotics ineffective and leading to increased morbidity and mortality rates[27]. As traditional antimicrobial agents lose their potency, the development of innovative strategies to combat resistant pathogens has become a top priority. In this context, functionalized polyanilines (fPANI) have emerged as a promising class of antimicrobial agents with the potential to not only effectively combat antibiotic-resistant bacteria but also possibly reverse the very mechanisms that confer resistance [9,12].

Mechanisms of Antibiotic Resistance in Bacteria

To appreciate the potential of fPANI in reversing antibiotic resistance, it is essential to understand the mechanisms by which bacteria acquire and maintain resistance. Antibiotic resistance can be intrinsic or

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acquired, with the latter occurring through genetic mutations or horizontal gene transfer[28]. The main mechanisms of resistance include:

1. Enzymatic inactivation of antibiotics: Bacteria produce enzymes that modify or degrade antibiotics, rendering them ineffective[28].
2. Alteration of antibiotic targets: Mutations in bacterial genes encoding antibiotic targets can reduce the affinity of the antibiotic for its target, diminishing its effectiveness[28].
3. Reduced permeability and efflux pumps: Modifications in bacterial cell membranes can limit the entry of antibiotics, while efflux pumps actively remove antibiotics from the cell[28].

These mechanisms, often working in concert, enable bacteria to survive and proliferate in the presence of antibiotics, leading to the development and spread of resistant strains[29].

Hypotheses on How Functionalized PANI Could Overcome Resistance Mechanisms

The unique properties and diverse functionalization strategies of polyanilines offer several potential avenues for overcoming antibiotic resistance mechanisms. One hypothesis is that fPANI could bypass traditional resistance mechanisms by targeting bacterial cells through alternative pathways, such as membrane disruption and reactive oxygen species (ROS) generation[12]. By inducing membrane permeability changes and oxidative stress, fPANI could potentially circumvent the resistance mechanisms that bacteria have developed against conventional antibiotics, which often target specific enzymes or pathways[8].

Another promising hypothesis is that fPANI could enhance the effectiveness of existing antibiotics by facilitating their entry into resistant bacterial cells. By compromising the integrity of bacterial cell membranes or inhibiting efflux pumps, fPANI could increase the intracellular concentration of antibiotics, overcoming resistance mechanisms[10]. This synergistic approach could potentially restore the efficacy of antibiotics that have become less effective due to resistance development.

Furthermore, the ability to functionalize PANI with various antimicrobial moieties, such as quaternary ammonium compounds (QACs) or metal nanoparticles, could provide additional mechanisms for targeting resistant bacteria[3]. These functionalized PANI derivatives could exploit the antimicrobial properties of the conjugated moieties while benefiting from the intrinsic properties of PANI, resulting in a multi-pronged attack on resistant pathogens[11].

Preliminary Evidence and Future Research Directions

Preliminary evidence supporting the potential of fPANI in reversing antibiotic resistance is emerging. For instance, the authors[12] reported on a red fluorescent fPANI bearing quaternary ammonium groups that demonstrated potent antimicrobial activity against ampicillin-resistant Escherichia coli. The polymer's ability to kill 100% of the resistant bacteria at low concentrations upon light irradiation highlights its potential in combating resistant strains[12].

Similarly, the authors[9] investigated the antimicrobial activity of polyaniline-coated silver nanoparticles (PANI-AgNPs) against multidrug-resistant bacteria. The PANI-AgNPs exhibited potent activity against resistant strains of Staphylococcus aureus and Pseudomonas aeruginosa, demonstrating their potential as an alternative to conventional antibiotics in the fight against resistant infections[9].

The efficacy of fPANI against antibiotic-resistant bacteria can be attributed to their multiple mechanisms of action, which differ from those of conventional antibiotics. By targeting bacterial membranes, generating ROS, and interfering with metabolic processes, fPANI can overcome the resistance mechanisms that render antibiotics ineffective[8]. Moreover, the ability to functionalize PANI with various antimicrobial moieties provides an opportunity to develop tailored strategies to combat specific resistant strains[11].

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While these studies provide promising preliminary evidence, further research is needed to fully understand the mechanisms by which fPANI overcome antibiotic resistance and to optimize their application in clinical settings. Future research should focus on:

1. Elucidating the precise mechanisms of action of fPANI against resistant bacteria, including their effects on membrane permeability, efflux pumps, and other resistance determinants.
2. Investigating the synergistic effects of fPANI with existing antibiotics and identifying optimal combinations for targeting specific resistant strains.
3. Evaluating the safety, efficacy, and potential side effects of fPANI in vivo, particularly when used in combination with other antimicrobial agents.
4. Developing targeted delivery systems for fPANI to minimize potential cytotoxicity and maximize their antimicrobial action against resistant bacteria.

By addressing these research gaps, scientists can harness the full potential of fPANI in reversing antibiotic resistance and developing novel antimicrobial strategies to combat the growing threat of resistant infections.

CONCLUSION

In conclusion, functionalized polyanilines (fPANI) have emerged as a promising class of broad-spectrum antimicrobial agents with the potential to revolutionize the fight against bacterial resistance. The unique properties of PANI, combined with the diverse functionalization strategies available, enable the development of tailored antimicrobial materials that can effectively combat a wide range of bacterial pathogens, including antibiotic-resistant strains. By targeting bacteria through multiple mechanisms of action, such as membrane disruption, reactive oxygen species generation, and interference with metabolic processes, fPANI offers a versatile and potent alternative to conventional antibiotics. Moreover, the ability of fPANI to overcome traditional resistance mechanisms and potentially reverse antibiotic resistance highlights their significance in addressing the global health crisis posed by resistant infections.

The urgency of developing new strategies against bacterial resistance cannot be overstated. As the prevalence of antibiotic-resistant bacteria continues to rise, the effectiveness of our current antimicrobial arsenal is rapidly diminishing. This alarming trend not only jeopardizes the treatment of common infections but also threatens the success of modern medical procedures that rely on effective antibiotics, such as surgeries, chemotherapy, and organ transplantation. The consequences of failing to address this crisis are dire, with projections estimating that by 2050, antibiotic resistance could cause 10 million deaths annually and cost the global economy up to $100 trillion[30]. In light of these sobering statistics, the development of innovative antimicrobial strategies, such as those based on fPANI, is not merely an academic pursuit but an urgent necessity to safeguard public health and ensure the continued progress of modern medicine.

To accelerate the development and translation of fPANI-based antimicrobial strategies, a multidisciplinary approach is essential. The complexity of bacterial resistance and the challenges associated with designing effective antimicrobial materials require the combined expertise of researchers from various fields, including materials science, chemistry, microbiology, and medicine. By fostering collaborations across these disciplines, we can leverage the unique insights and methodologies of each field to drive innovation and accelerate the discovery of novel fPANI-based antimicrobial agents. Moreover, close partnerships between academia and industry are crucial to ensure the rapid translation of promising research findings into clinically relevant applications. Only through such concerted efforts can we hope to keep pace with the evolving threat of bacterial resistance and develop the next generation of antimicrobial therapies that will secure the health and well-being of future generations.

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