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Review

Structural Innovations in Vancomycin: Overcoming Resistance and Expanding the Antibacterial Spectrum

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Abstract

Vancomycin, a cornerstone antibiotic against severe Gram-positive infections, is increasingly challenged by resistance in Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin *Enterococcus* spp. (VRE), necessitating the development of novel therapeutic strategies. This review examines how structural modifications to vancomycin can enhance its antibacterial activity and explores the critical role of computational approaches in designing the next generation of analogs. By analyzing the existing literature, we highlight how strategic alterations, such as the introduction of lipophilic side chains, substitutions on the sugar moieties, and modifications to the aglycone core, have yielded derivatives with improved antibacterial potency. Notably, certain analogs (e.g., Vanc-83, Dipi-Van-Zn) have demonstrated expanded activity against Gram-negative bacteria and exhibited enhanced pharmacokinetic profiles, including prolonged half-lives and improved tissue penetration, crucial for effective treatment. Semisynthetic glycopeptides like telavancin, dalbavancin, and oritavancin exemplify successful translation of structural modifications, offering sustained plasma concentrations and simplified dosing regimens that improve patient compliance. Complementing these experimental efforts, computational methods, including molecular docking and molecular dynamics simulations, provide valuable insights into drug–target interactions, guiding the rational design of more effective analogs. Furthermore, physiologically based pharmacokinetic modeling aids in predicting the in vivo behavior and optimizing the pharmacokinetic properties of these novel compounds. This review highlights a critical path forward in the fight against multidrug-resistant infections. By meticulously examining the previously carried out structural refinement of vancomycin, guided by computational predictions and validated through rigorous experimental testing, we underscore its immense potential.

Keywords: vancomycin analogs; multidrug resistance; structural modifications; computational drug design; pharmacokinetics

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1. Introduction

Antimicrobial resistance (AMR) represents a critical global health challenge [1], exacerbated by the increasing prevalence of multidrug-resistant (MDR) pathogens. These

pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococcus (VRE), and others such as carbapenem-resistant Enterobacteriaceae (CRE), pose significant threats to effective clinical management of infectious diseases [2]. The World Health Organization (WHO) has highlighted MDR organisms as high-priority pathogens requiring urgent action [3], emphasizing the pressing need for innovative antibiotic solutions to combat these emerging threats [4]. The annual global mortality attributed to AMR is projected to rise from the current estimate of 700,000 deaths to 10 million by 2050 if unaddressed [5,6].

Vancomycin, the first-generation glycopeptide antibiotic discovered in the 1950s [7], has historically served as a critical treatment option for severe infections caused by Gram-positive bacteria [8]. Initially derived from *Amycolatopsis orientalis* [7], vancomycin targets bacterial cell wall synthesis by binding to the D-Ala-D-Ala termini of peptidoglycan precursors, thereby disrupting transglycosylation and transpeptidation processes [8]. This mechanism renders it particularly effective against pathogens with robust cell wall structures [9,10]. Despite its efficacy and widespread use [8], the emergence of resistance in enterococci in the late 1980s and subsequently in *Staphylococcus aureus* [11] has significantly diminished its clinical utility [9,12].

Resistance to vancomycin is primarily mediated through genetic adaptations, such as the VanA and VanB phenotypes, which involve the modification of the D-Ala-D-Ala target site to D-Ala-D-Lac [11]. This single-atom substitution reduces vancomycin's binding affinity by approximately 1000-fold [13]. Additionally, the VanC phenotype, associated with *Enterococcus gallinarum* and *E. casseliflavus*, employs intrinsic resistance mechanisms [13]. These adaptations [11,13], coupled with bacterial strategies like biofilm formation and intracellular persistence, underscore the complexity of addressing vancomycin-resistant infections [10,14].

Recognizing these resistance mechanisms, significant research efforts have focused on modifying vancomycin's molecular structure to enhance its activity against resistant strains [15]. Semisynthetic derivatives, second-generation lipoglycopeptides, such as telavancin (2009), dalbavancin (semisynthetic derivative of teicoplanin, 2014), and oritavancin (2014), have introduced novel mechanisms, including improved membrane interaction and disruption. These compounds are created by chemically modifying the naturally produced vancomycin molecule, leveraging its existing antibacterial scaffold while introducing new functionalities. This approach allows researchers to precisely engineer improvements such as enhanced membrane interaction and disruption, which are crucial for overcoming bacterial defense mechanisms [16]. These modifications extend vancomycin's spectrum of activity and provide alternative therapeutic options for resistant infections [15,16]. Moreover, synthetic efforts targeting dual-binding analogs capable of recognizing both D-Ala-D-Ala and D-Ala-D-Lac termini have shown promise in restoring efficacy against resistant strains [6,10].

Another promising approach involves conjugating vancomycin with lipophilic or polycationic moieties to improve membrane permeability and biofilm penetration [6,14]. Studies on vancomycin–fatty acid conjugates and polyarginine derivatives demonstrate significant antimicrobial potential, particularly against biofilm-associated infections and persistent bacterial populations [6,14,15]. Advances in linker technology, such as the use of heterobifunctional linkers, have further optimized the pharmacokinetic and pharmacodynamic profiles of vancomycin derivatives, enhancing their clinical applicability [12].

Synthetic advancements have also addressed the limitations of traditional production methods: recent innovations in total synthesis techniques have reduced step counts and improved yields, enabling scalable production of vancomycin derivatives [12]. This has facilitated preclinical evaluation and accelerated the development of next-generation

glycopeptide antibiotics [12,16,17]. These efforts exemplify the synergy between chemical innovation and clinical need [18], providing a robust framework for addressing the escalating AMR crisis [4].

This concise review offers a timely and comprehensive consolidation of the most recent and impactful advancements in these vancomycin modification strategies, meticulously examining their structural underpinnings, functional consequences at the molecular and cellular levels, and potential therapeutic implications in combating MDR infections. By systematically exploring these innovations, we aim to provide crucial insights into the ongoing renaissance of glycopeptide antibiotics, showcasing their remarkable versatility and adaptability as essential tools in our armamentarium against the ever-growing threat of AMR, ultimately informing future research directions and clinical applications in this critical area.

2. From Discovery to the Challenge of Resistance

Vancomycin was initially isolated from the microorganism *Amycolatopsis orientalis*, which was originally found in a soil sample referred to as "Mississippi mud" [7,19]. The molecule, approved by the FDA in 1958 [19], is a rigid tricyclic heptapeptide with three macrocyclic ring systems embedded in its framework, featuring axial chirality in the biaryl axis of one and planar chirality in two others [20]. The central phenol of the aglycon is attached to a disaccharide consisting of glucose and vancosamine [20]. The remarkable structural complexity of vancomycin, boasting numerous stereocenters, a highly constrained three-dimensional architecture, and intricate glycosidic linkages, presented a monumental challenge for chemical synthesis, captivating the attention of leading organic chemists for decades [9,20,21].

The pursuit of vancomycin's total synthesis was driven by the desire to confirm its structure, develop methods for producing analogs, and advance the field of synthetic organic chemistry. The successful total syntheses reported by the Evans group in 1998 [22] and the Nicolaou group in 1999 [23] each employed distinct and elegant strategies to tackle the synthetic hurdles. These included sophisticated protecting group manipulations to ensure regioselectivity, intricate coupling reactions to form the peptide backbone, and carefully designed macrocyclization steps to construct the complex ring systems. For example, the Evans synthesis utilized a convergent approach involving the coupling of three main fragments, while the Nicolaou synthesis featured a cascade of reactions to form the macrocycles [22,23].

Given the lengthy and often low-yielding nature of total synthesis, semisynthetic approaches have become the mainstay for producing vancomycin and generating structural analogs for drug development [16]. These methods leverage the complex molecular framework produced by microbial fermentation and selectively modify specific sites on the molecule [20]. Common modification points include the amino acid side chains, the sugar residues (particularly the vancosamine sugar), and the aglycone core [24]. Semi-synthesis offers advantages in terms of scalability and efficiency, allowing for the generation of a diverse library of vancomycin derivatives with altered pharmacological properties [25].

The clinical contribution of vancomycin in managing infections caused by resistant pathogens has been immense [8]. For instance, it has been crucial in treating infections caused by MRSA, where resistance to beta-lactam antibiotics like cloxacillin is prevalent [26], as well as ampicillin-resistant *Enterococcus faecalis* [27], Streptococcus spp. exhibiting decreased susceptibility to third-generation cephalosporins [28], and *Clostridioides difficile* [29]. Consequently, vancomycin is one of the few antibiotics whose dosage is routinely adjusted based on plasma levels and pharmacokinetic simulations, as recommended by relevant scientific societies such as the American Society of Health-System Pharmacists (ASHP),

the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) [30].

However, the emergence of vancomycin-resistant enterococci in 1987 [11], vancomycin-intermediate resistant *Staphylococcus aureus* (VISA) [11], and vancomycin-resistant *Staphylococcus aureus* (VRSA) in 2002 [31] underscores the urgent need to continue exploring the synthesis and development of next-generation antimicrobials capable of overcoming these resistance mechanisms [21]. A deep understanding of the structural intricacies of vancomycin, coupled with the knowledge gained from both total and semisynthetic endeavors, forms a critical foundation for the rational design, synthesis, and evaluation of novel analogs with improved efficacy and expanded activity against MDR pathogens.

3. Structure–Activity Relationship Considerations

This section lays the groundwork by first describing the bacterial cell wall structure and the precise mechanism by which vancomycin inhibits its synthesis through binding to the D-Ala-D-Ala terminus. It then details the primary resistance mechanism—the D-Ala-D-Lac substitution—which significantly weakens vancomycin's binding affinity. By outlining these fundamental principles, this section establishes the critical context for understanding why and where structural modifications are needed. Crucially, it then demonstrates how various structural alterations to vancomycin, ranging from aglycone modifications and sugar derivations to dimerization and lipidation, have been designed to counteract resistance and even expand the antibacterial spectrum. This comprehensive overview implicitly highlights the pivotal role of computational approaches in rationally designing these next-generation analogs by predicting how specific changes will impact the binding affinity and drug efficacy against resistant strains.

The cell wall of Gram-positive bacteria is a complex structure primarily composed of repeating units of the disaccharide N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc), with a pentapeptide (typically L-Ala-D-iso-Glu-L-Lys-D-Ala-D-Ala) attached to the MurNAc residue [32]. In many species, a pentaglycine bridge further extends from the ε-amino group of L-Lys, facilitating cross-linking between adjacent peptidoglycan strands [32]. The biosynthesis of this crucial cell wall component involves two key enzymatic processes: transglycosylation, responsible for the polymerization of GlcNAc-MurNAc units into long glycan chains, and transpeptidation, which catalyzes the formation of cross-links that provide structural rigidity to the cell wall [32]. Vancomycin exerts its bactericidal effect by disrupting peptidoglycan synthesis through a mechanism distinct from that of beta-lactam antibiotics, which target the transpeptidases. Instead, vancomycin binds with high affinity to the D-Ala-D-Ala terminus of the peptidoglycan precursor, specifically, lipid II, thereby sterically hindering the transglycosylase enzyme and preventing the necessary elongation of the glycan chains and the subsequent transpeptidation reactions [20,32]. This sequestration of lipid II also prevents the recycling of the C55 lipid carrier, which is essential for the transport of peptidoglycan precursors across the bacterial membrane [20,32].

The interaction between vancomycin and the D-Ala-D-Ala dipeptide is primarily mediated by the heptapeptide aglycone of vancomycin and is stabilized by a network of five key hydrogen bonds [32,33]. Three of these hydrogen bonds occur between the amide residues at positions 1, 2, and 3 of the aglycone and the carbonyl and amide groups of the terminal D-Ala residue. A fourth hydrogen bond is formed between the carbonyl of the fourth amino acid residue of vancomycin and the amide proton of the terminal D-Ala. The fifth crucial hydrogen bond is established between the amide proton of the seventh amino acid residue of the aglycone and the carbonyl of the penultimate D-Ala residue [32].

In addition to the aglycone, the two pharmacologically active sugars of vancomycin, D-glucose and L-vancosamine, play a significant role in enhancing its antibacterial activity [5,20,34]. These sugars interact with the phenolic group of the 4-hydroxyphenylglycine side chain at the fourth amino acid position of the aglycone, contributing to the overall binding affinity and potentially influencing the molecule's conformation [5,20,34]. The core structure of vancomycin is highly cross-linked, contributing to its rigidity, with the exception of positions 1 (*N*-methyl-leucine) and 3 (asparagine), whose side chains do not directly interact with the D-Ala-D-Ala dipeptide but are nonetheless crucial for maintaining the molecule's overall conformation and activity [5,20,34].

The primary mechanism of bacterial resistance to vancomycin involves the genetic modification of the peptidoglycan precursor, leading to the replacement of the terminal D-Ala-D-Ala dipeptide with D-Ala-D-Lac [10,20,32,34,35]. This seemingly minor substitution, replacing a crucial amide bond with an ester linkage and a terminal amine group with an oxygen atom, results in a significant reduction in binding affinity for vancomycin, often by up to 1000-fold [10,20].

To overcome this resistance, a wide array of modifications to the vancomycin structure have been explored, targeting various parts of the molecule, including alterations to the N- or C-terminus of the heptapeptide aglycone, the creation of homo- and heterodimers, modifications of the sugar residues, and alterations to the aglycone core [20,35]. For instance, the semisynthetic derivative Vanc-83, characterized by a complex functional group C80H87Cl2N11O24 at the C-terminus, has demonstrated complete in vitro activity against VRE strains [35]. Another notable analog, Vanc-42, has shown high in vitro activity against VanA, VanB, and VanC resistance phenotypes, exhibiting a low propensity for inducing further resistance and improved therapeutic indices against a broad range of resistant pathogens, including MRSA and *C. difficile* [35]. Figure 1 shows the structures of vancomycin and its most extensively studied analogues.

Hydrophobic adduct alkylation, such as the lipidation of the sugar moieties, has emerged as a powerful strategy for enhancing vancomycin's activity, potentially by improving its penetration through the bacterial cell wall and membrane [17]. Another approach involves conjugating vancomycin with antimicrobial peptides (AMPs) like nisin and cathelicidins. This strategy can lead to synergistic effects, with the vancomycin targeting cell wall synthesis and the AMPs disrupting the bacterial membrane, resulting in improved activity against both Gram-positive and Gram-negative bacteria [16]. Further strategies focus on modifying the C-terminus of vancomycin, such as the addition of lipophilic quaternary ammonium groups, which has been shown to yield substantial increases in activity against VRE, likely due to enhanced interactions with the bacterial membrane [37].

Modifications to the aglycone core have also been crucial in the development of resistance-overcoming analogs. For example, replacing the carbonyl oxygen at the fourth amino acid residue with a protonated amidino nitrogen has been shown to restore the molecule's affinity for the D-Ala-D-Lac depsipeptide, leading to a significant increase in activity (up to 600-fold) against VanA-type VRE [20,32]. This structural change introduces a positive charge that can interact favorably with the altered binding site in resistant strains.

Finally, the conjugation of vancomycin with zinc(II) chelators, such as in the case of Dipi-Van, represents an innovative approach to combatting antimicrobial resistance [36]. This strategy has demonstrated enhanced antibacterial activity, improved eradication of biofilms, and the promising ability to re-sensitize NDM-producing Gram-negative bacteria to carbapenems, highlighting the potential of vancomycin derivatives to address a wider spectrum of resistant infections [36].

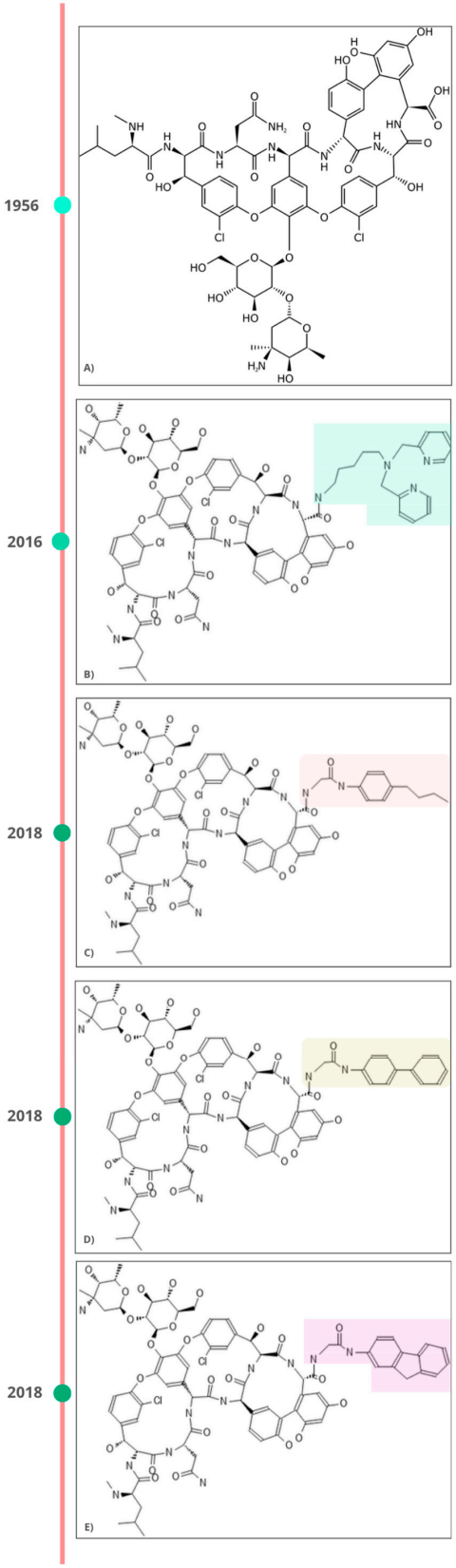

Figure 1. Representative structures of vancomycin and its most extensively studied analogues. The figure illustrates the chemical structures of vancomycin and four of its key structural analogues developed to overcome antimicrobial resistance and/or improve pharmacokinetic properties. (**A**) Baseline vancomycin structure (reference compound); (**B**) Analogue Dipi-Vanc. (**C**) Analogue Vanc-39; (**D**) Analogue Vanc-83; and (**E**) Analogue Vanc-42. Image adapted from Sarkar et al. [36] and Mishra et al. [35].

4. Analogs: Definition and in Silico Development

This section delves into how structural modifications of vancomycin are rationally designed to boost its antibacterial power and overcome resistance. We will explore various analog strategies, from tweaking its core structure to creating dimers, showcasing clinically successful examples. Crucially, we then highlight the transformative role of computational approaches—like virtual screening, molecular docking, and dynamics simulations—in predicting drug–target interactions and pharmacokinetic properties, thereby accelerating the discovery and design of the next generation of vancomycin analogs.

Vancomycin derivatives, or analogs, are defined as molecules that retain the core structural framework of vancomycin but feature modifications, such as alterations to the N- or C-terminus of the heptapeptide aglycone, homo- and heterodimerization, sugar substitutions, and changes to the aglycone region [20,35,38]. These modifications are strategically designed to enhance the drug's interaction with its target, overcome resistance mechanisms, or improve its pharmacokinetic properties. Clinically approved semisynthetic lipoglycopeptides illustrate the success of these strategies: telavancin (2009) incorporates a lipophilic tail that anchors into the bacterial membrane, enhancing its mechanism of action; dalbavancin (2014), exhibits an exceptionally long half-life, allowing for less frequent dosing; and oritavancin (2015) displays a multifaceted mechanism, including inhibition of transpeptidation and transglycosylation, as well as disruption of the bacterial membrane [38]. The ongoing need to combat evolving resistance has fueled extensive research into a plethora of other vancomycin analogs, many of which are showing promising results in preclinical studies; demonstrating improved efficacy against VRE, VISA, and VRSA strains; or exhibiting more favorable pharmacokinetic profiles [5,38].

In silico studies have revolutionized the field of drug discovery [39–41], and the development of vancomycin analogs is no exception [42]. The in silico drug development process typically begins with the identification and structural characterization of the target molecule, in this case, the bacterial peptidoglycan precursor, including both the D-Ala-D-Ala and the D-Ala-D-Lac variants. Virtual screening is then often employed to sift through vast libraries of chemical compounds, predicting their potential to bind to the target based on computational models [43,44]. Molecules exhibiting promising binding scores are then subjected to more rigorous analyses, such as molecular docking, which predicts the precise orientation and affinity of the ligand (the vancomycin analog) within the binding pocket of the receptor (the peptidoglycan precursor) [32,45]. For example, after successfully modifying vancomycin's binding pocket to achieve dual D-Ala-D-Ala/D-Ala-D-Lac binding, researchers further enhanced the antimicrobial potency by introducing peripheral structural changes, such as a C-terminal quaternary ammonium salt, which imparts a second, independent mechanism of action (cell wall permeabilization) that synergistically improves activity against VRE by up to 200-fold and can be combined with other modifications (e.g., 4-chlorobiphenylmethyl addition) to yield highly potent agents with multiple, durable mechanisms of action, making resistance acquisition less likely [46].

Following molecular docking, molecular dynamics (MD) simulations provide a more dynamic and realistic representation of the drug–target interaction [32,47,48]. By simulating the movement of atoms over time, MD simulations can reveal critical information about the stability of the complex, the conformational changes that occur upon binding, and the specific intermolecular interactions, such as hydrogen bonds and hydrophobic interactions, that contribute to the overall affinity. For example, MD simulations have been crucial in understanding how the D-Ala-D-Lac substitution in resistant strains disrupts the crucial hydrogen bonding network with vancomycin [32].

The pharmacokinetic properties of vancomycin analogs are also extensively studied using in silico methods, particularly physiologically based pharmacokinetic modeling [45].

These models integrate a wealth of information, including the physiological characteristics of the organism, the physicochemical properties of the drug, and its potential metabolic pathways, to predict how the drug will be absorbed, distributed, metabolized, and excreted by the body [49–51]. This is particularly important for vancomycin analogs, where subtle structural changes can significantly impact their pharmacokinetic profiles, affecting their efficacy and safety [45].

Several specific examples illustrate the power of in silico methods in guiding the design of vancomycin analogs. Computational studies have been used to explore the impact of attaching various lipophilic groups to the vancomycin structure, mimicking the approach used in telavancin and dalbavancin, predicting the effect on membrane binding and overall antibacterial activity [52]. In the realm of dimerization, in silico modeling has aided in the design of both homo- and heterodimers of vancomycin, predicting their potential for enhanced avidity and improved binding to resistant targets by simultaneously engaging two peptidoglycan precursors [53]. Furthermore, the rational design of aglycone modifications, such as the introduction of the protonated amidino group that restores binding to D-Ala-D-Lac, was significantly informed by computational studies that allowed researchers to visualize and quantify the energetic benefits of these specific interactions [20,32]. The optimization of conjugates with Zn(II) chelators, like Dipi-Van, also relied on in silico modeling to ensure proper presentation of the chelating moiety for metal binding while maintaining the vancomycin's ability to interact with its primary target [36].

Despite their significant contributions, in silico methods are not without limitations. The accuracy of the predictions is highly dependent on the quality of the computational models, the force fields used to describe interatomic interactions, and the availability of high-resolution structural data [43]. For complex molecules like glycopeptides, accurately modeling their behavior and interactions can be particularly challenging. Therefore, it is crucial to emphasize that in silico findings serve as valuable guides for experimental research and must be rigorously validated through in vitro and in vivo studies to confirm their accuracy and translational potential [54–56]. Looking towards the future, the integration of cutting-edge artificial intelligence (AI) and machine learning (ML) algorithms with traditional in silico methods holds transformative promise for accelerating the discovery and optimization of novel vancomycin analogs. These advanced computational approaches can rapidly explore vast chemical spaces, enabling high-throughput virtual screening of billions of potential molecules, and even facilitating the de novo design of entirely new chemical entities tailored for specific resistance targets or improved properties. AI/ML models can predict complex drug–target interactions with unprecedented accuracy, rapidly assess ADME-Tox (absorption, distribution, metabolism, excretion, and toxicity) profiles, and more efficiently guide the lead optimization process by identifying optimal structural modifications. For vancomycin analogs, this means AI could rapidly screen for novel modifications that restore binding affinity to D-Ala-D-Lac, predict the impact of complex dimerizations on membrane permeability, or even design entirely new scaffolds that overcome current resistance mechanisms while maintaining favorable pharmacokinetic and safety profiles [57]. This synergistic combination of AI/ML with established computational chemistry techniques is poised to significantly shorten the drug discovery pipeline, bringing more effective and safer glycopeptide therapies to patients battling multidrug-resistant infections more quickly.

5. Spectrum of Action, Pharmacokinetic and Safety Implications

This section is crucial for understanding how strategic structural modifications are enhancing vancomycin's fight against increasingly resistant bacteria. It delves into specific

examples of vancomycin analogs, like vancomycin–peptide conjugates (VPCs), demonstrating how alterations can not only improve activity against resistant Gram-positive strains but, remarkably, even enable activity against Gram-negative bacteria, which were previously impervious. Furthermore, the section explores how these modifications optimize pharmacokinetic profiles for better patient outcomes and critically assesses the safety implications of these novel compounds. This deep dive into design principles and experimental validation directly sets the stage for appreciating the indispensable role of computational approaches in rationally designing the next generation of these vital antibacterial agents. Table 1 shows a comparative overview of vancomycin analogues, structural modifications, antimicrobial activity, and safety profiles.

Table 1. Comparative overview of vancomycin analogues, structural modifications, antimicrobial activity, and safety profiles.

Analog/Group	Structural Modification	Spectrum of Activity	Pharmacokinetic Properties	Safety Profile	Reference(s)
Vancomycin	Parent compound	Gram-positive cocci; MRSA; some Enterococci	t½: 4–6 h; Vd: ~0.4–1 L/kg; Cmax: 20–40 µg/mL	Nephrotoxicity, ototoxicity at high doses	[34]
Vancomycin–peptide conjugates (VPCs)	Peptide conjugation at C-/N-terminus, vancosamine, resorcinol	VRE (↑ activity; MIC 2 µM); VISA (MIC 2–10 µM); partial activity vs. *E. coli*, *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*	Not reported	Improved safety at C-terminal; some derivatives show low toxicity	[57–60]
Oritavancin	Lipoglycopeptide	MRSA; VRE	t½: 245 h; Vd: 87 L (~1.24 L/kg); Cmax: 138 µg/mL	Not detailed	[34,37]
Telavancin	Lipoglycopeptide	Resistant Gram-positives	t½: 7.5–9 h; Vd: 0.11 L/kg; Cmax: 87 µg/mL	Not detailed	[61,62]
Dalbavancin	Semisynthetic teicoplanin derivative	MRSA; Streptococci; some VRE	t½: 271 h; Vd: 0.52 L/kg; Cmax: 84.8–106.0 µg/mL	Generally well tolerated	[58]
Vanc-83	C-terminal biphenyl substitution	VRE; MRSA; VISA; *C. difficile* (↑ activity)	t½: ~12 h; bactericidal against MRSA	TI > 200; no cytotoxicity	[35]
Vanc-42	Fluorene C-terminal substitution	VRE (VanA, VanB, VanC1); MRSA; VISA; *C. difficile*	Bactericidal vs. MRSA; bacteriostatic vs. VRE	TI up to 865; low risk of resistance development	[35]
Vanc-39	Butyl-benzene C-terminal substitution	VRE; MRSA; VISA	Stable MICs; no cytotoxicity	Bactericidal vs. MRSA; low resistance emergence	[35]
Amidine-van	Substitution of carbonyl oxygen with amidino nitrogen	VanA-VRE (↑ activity ×600)	Not reported	Not reported	[20,32,61]
Dipi-Van	Dipicolyl moiety binds Zn^{2+} and pyrophosphate of lipid carriers	VRE (VanA, VanB); VISA (↑ activity ~375-fold)	↑ in vivo efficacy; enhances cell wall precursor accumulation	Non-toxic in RBCs and models; no resistance development	[37]
Lipophilic analogs (e.g., decyl, biphenyl)	Insertion of lipophilic moieties	VRE; VISA	Enhanced membrane interaction	Hydrophilic substitutions improve renal/auditory safety	[58]
QAV-a1	Quaternary ammonium moiety + triazole group	MRSA (↑ up to ×32); partial VRE activity	t½: 5.2 h; Cmax: 7.47 µg/mL	No toxicity at 45 mg/kg; LD_{50}: 60.5 mg/kg in mice	[63]

Abbreviations: *A. baumannii* = *Acinetobacter baumannii*; Cmax = maximum plasma concentration; *C. difficile* = *Clostridioides difficile*; ED_{50} = median effective dose; *E. coli* = *Escherichia coli*; h = hours; LD_{50} = median lethal dose; L/kg = liters per kilogram; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa* = *Pseudomonas aeruginosa*; RBCs = red blood cells; t½ = elimination half-life; TI = therapeutic index; Vd = volume of distribution; VISA = vancomycin-intermediate *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococcus* spp.; Zn^{2+} = zinc ion. Preclinical entries (e.g., QAV-a1, VPCs) are included for comparative purposes only and are not currently approved for clinical use. Pharmacokinetic values for these analogs were derived from animal models or in vitro studies and may not directly translate to human pharmacology.

The development of vancomycin analogs has aimed to broaden the spectrum of activity, improve pharmacokinetic properties, and enhance the safety profile compared to the parent molecule. Studies on vancomycin–peptide conjugates (VPCs) have demonstrated a notable expansion of the antibacterial spectrum. For instance, Guan et al. [59] and Shi et al. [60] reported the synthesis and evaluation of 72 VPCs, where peptides with affinity for lipopolysaccharide (LPS), a key component of the outer membrane of Gram-negative bacteria, were attached to vancomycin at four distinct sites: the resorcinol group, the C-terminal, vancosamine, and the N-terminal.

The antibacterial activity assessment of these VPCs revealed significant enhancements, particularly against resistant Gram-positive pathogens. Against VRE, where vancomycin typically exhibits a minimum inhibitory concentration (MIC) > 88 μM, certain VPCs, such as VPC-59, demonstrated a remarkable 40-fold increase in activity, achieving an MIC of 2 μM [60]. Similarly, against vancomycin-intermediate VISA, VPCs showed MIC values ranging from 2 to 10 μM, surpassing the activity of vancomycin against these strains [59,60]. These improvements are attributed to structural modifications that enhance the interaction of the conjugates with the bacterial cell wall, potentially through increased binding affinity or altered mechanisms of cell wall disruption [59].

A particularly noteworthy finding was the activity of VPCs against Gram-negative bacteria, which are intrinsically resistant to vancomycin due to the presence of an outer membrane composed primarily of LPS that hinders the penetration of glycopeptides. VPCs like VPC-45 and VPC-67 exhibited some level of activity against pathogens such as *Escherichia coli* and *Acinetobacter baumannii* [60]. Activity was also observed against Pseudomonas aeruginosa and *Klebsiella pneumoniae*, with MIC values of 33 μM and 16 μM, respectively [59]. This expanded spectrum of action is likely due to the attached peptides facilitating the transport of the vancomycin moiety across the Gram-negative outer membrane by interacting with LPS or utilizing specific bacterial uptake mechanisms [61]. Structure–activity relationship analysis indicated that peptide conjugation at the C-terminal of vancomycin often yielded superior antibacterial activity compared to conjugates at other sites, suggesting that this position is optimal for maintaining vancomycin's binding to its target while allowing the peptide to interact effectively with the Gram-negative outer membrane [60]. The incorporation of lipophilic chains, such as decyl or biphenyl groups, also enhanced activity against VRE and VISA, potentially by increasing membrane interactions and disrupting membrane integrity [60].

The pharmacokinetic profiles of vancomycin analogs have been tailored to improve treatment efficacy and convenience. Oritavancin, a lipoglycopeptide, exhibits a significantly prolonged elimination half-life (approximately 245 h), enabling single-dose or less frequent dosing regimens, which can improve patient adherence [34,36]. Its large volume of distribution (around 87 L) suggests excellent tissue penetration, which is crucial for treating deep-seated infections. Following a single 1200 mg dose, oritavancin achieves a mean maximum plasma concentration (Cmax) of 138 μg/mL and demonstrates efficacy against MRSA and VRE [34,36]. Televancin, another lipoglycopeptide, has a shorter half-life (approximately 8 h) and a smaller volume of distribution (0.11 L/kg), indicating a more restricted distribution, yet sufficient for treating infections in specific tissues [62]. Vanc-83 also shows an improved half-life (approximately 12 h) compared to vancomycin, maintaining effective plasma concentrations for extended periods and demonstrating bactericidal activity against severe VRE infections. The Dipi-Van-Zn complex exhibits up to a 375-fold increase in antibacterial activity against resistant Enterococci and metallo-beta-lactamase-producing bacteria and shows an improved volume of distribution, potentially enhancing its ability to eradicate bacterial biofilms [36]. The conjugation with Zn(II) chelators is thought to facilitate interaction with critical bacterial structures, such as membrane-bound lipid

pyrophosphate [36]. Modifications to the aglycone, such as the replacement of a carbonyl oxygen with a protonated amidino nitrogen, have been shown to restore affinity for altered peptidoglycan (D-Ala-D-Lac), resulting in a 600-fold increase in activity against VanA-type VRE [63]. While specific pharmacokinetic data for this analog is pending, its enhanced in vitro activity suggests potential for managing severe VRE infections. The incorporation of lipophilic structures and additional sugars in many of these analogs often contributes to the observed changes in pharmacokinetic parameters, influencing their distribution, metabolism, and elimination.

The safety profiles of vancomycin analogs are also a critical consideration. Studies on QAV-a1 in murine models indicated acute toxicity at higher doses (100% lethality at 75 mg/kg) but no mortality at 45 mg/kg [64]. However, some modifications, particularly substitutions in the sugar moieties where lipophilic fractions are replaced with more hydrophilic components, appear to lead to improved safety profiles compared to vancomycin, potentially reducing nephrotoxicity and ototoxicity [59]. In vitro toxicity evaluations of the VanHdipi derivative in HEK cells and human red blood cells showed no hemolytic activity or significant cellular toxicity, suggesting a favorable safety profile for further development [36].

While many of these vancomycin analogs show promising results in preclinical studies, further research, including comprehensive pharmacokinetic and pharmacodynamic evaluations in animal models and rigorous clinical trials, is necessary to fully understand their potential clinical utility and safety implications in humans. The development of resistance to these newer analogs also remains a concern that requires ongoing monitoring and investigation.

6. Discussion

The AMR crisis represents a formidable global health challenge, with pathogens such as MRSA and VRE posing significant clinical threats. Vancomycin has been a crucial antibiotic for treating Gram-positive bacterial infections since the 1950s. However, the emergence and spread of resistance mechanisms, notably, the modification of the D-Ala-D-Ala dipeptide to D-Ala-D-Lac in the bacterial cell wall, which reduces vancomycin's binding affinity by up to 1000-fold [10], have severely compromised its efficacy. This critical situation has spurred extensive research and development efforts focused on creating structural analogs of vancomycin capable of overcoming these limitations.

Structural modifications of vancomycin have proven to be a successful strategy for expanding its activity spectrum and optimizing its pharmacokinetic properties. Key clinically relevant analogs include oritavancin and televancin, alongside promising experimental compounds like Vanc-83 and Dipi-Van-Zn. Each of these represents a targeted approach to address specific resistance challenges. Oritavancin, a lipoglycopeptide approved in 2014, features a chlorophenylbenzyl group on the vancosamine sugar, which enhances its activity against MRSA, VRE, and biofilm-forming bacteria [34]. Its exceptionally long half-life ($T_{1/2} \approx 245$ h) allows for convenient single-dose regimens, significantly improving patient adherence to treatment [34]. Televancin, another lipoglycopeptide, incorporates modifications in both the vancosamine sugar and the peptidic core, leading to improved efficacy against a range of Gram-positive bacteria. However, its pharmacokinetic profile, characterized by a shorter half-life (T _{1/2} $\approx$ 8 h) and a more limited volume of distribution ($V_d \approx 0.11$ L/kg) [34], may make it less suitable for certain types of infections compared to oritavancin.

Experimental analogs like Vanc-83 and Dipi-Van-Zn highlight the potential of innovative structural design. Vanc-83, which features the addition of a complex functional group ($C_{80H87C12N11O24}$) at the C-terminal end, demonstrates significantly improved bac-

tericidal efficacy against VRE strains and exhibits longer-lasting plasma concentrations, reducing the need for frequent dosing [59]. Dipi-Van-Zn, designed to inhibit metallo-beta-lactamases such as NDM-1, showcases remarkable antibacterial activity, up to 375 times greater than standard vancomycin, and effectively eradicates biofilms while restoring susceptibility to carbapenems in NDM-producing bacteria [36]. This targeted interaction with specific resistance mechanisms demonstrates a promising strategy for combating multidrug-resistant infections.

While vancomycin traditionally exhibits activity primarily against Gram-positive bacteria, recent analogs, particularly VPCs, have shown promising activity against Gram-negative pathogens, which are historically resistant due to their LPS outer membrane barrier. For example, compounds like VPC-45 and VPC-67 have demonstrated activity against Escherichia coli and *Acinetobacter baumannii*, achieving MIC values of 33 μM and 16 μM, respectively [60]. These findings underscore the significant impact of structural modifications, such as the addition of lipophilic chains and peptide conjugates with affinity for LPS, in enhancing the permeability of these molecules across the Gram-negative outer membrane and improving target specificity [59,60]. This expansion of the antibacterial spectrum is a crucial advancement in addressing infections caused by Gram-negative bacteria with limited treatment options.

The optimization of pharmacokinetic properties has been central to enhancing the clinical utility of vancomycin analogs. The success of oritavancin, with its extended half-life allowing for single-dose administration, and the tailored pharmacokinetic profiles of other analogs demonstrate how structural adjustments can lead to better therapeutic outcomes and improved patient convenience. Compounds like Dipi-Van-Zn further exemplify this by exhibiting an improved volume of distribution, potentially leading to better penetration into infected tissues and biofilms [36]. The structure–activity relationship studies discussed in Section 3 and the in silico development strategies outlined in Section 4 have played a crucial role in guiding these modifications. For instance, computational modeling likely assisted in predicting how lipophilic modifications in oritavancin would affect its pharmacokinetic parameters and membrane interactions.

Balancing efficacy and safety remains a paramount challenge in the development of these analogs. While compounds like VanHdipi have shown minimal toxicity in vitro [36], animal studies have revealed potential dose-dependent toxicity in some compounds, such as QAV-a1 [59]. Addressing this requires ongoing efforts to refine structural designs, minimizing adverse effects while preserving the desired therapeutic efficacy. The trend towards replacing lipophilic fractions in sugar moieties with more hydrophilic components in some analogs suggests a strategy to improve safety profiles [59].

Despite the significant progress made in the development of vancomycin analogs, several challenges persist. The emergence of new resistance mechanisms, including those mediated by horizontal gene transfer, poses an ongoing threat to the long-term effectiveness of these solutions [20]. The complex and often costly synthesis of glycopeptides and the regulatory hurdles involved in bringing new antibiotics to market further limit the scalability and accessibility of these advancements, particularly in resource-limited settings [20]. To address these challenges, innovative therapeutic strategies, such as combining vancomycin analogs with synergistic agents or developing bifunctional hybrid molecules that target multiple bacterial pathways, offer promising avenues for combating multidrug-resistant pathogens [60]. Continued research into novel delivery systems that can improve drug penetration and target specificity is also crucial. Furthermore, international collaborations and policy reforms are needed to address the economic and accessibility barriers to ensure that these life-saving medications reach the patients who need them most.

The continuous evolution of vancomycin analogs underscores the dynamic and essential interplay between scientific innovation and clinical necessity in the face of the escalating AMR crisis. By expanding the drug's utility beyond traditional Gram-positive targets and leveraging advanced synthetic and computational approaches, these developments are paving the way for more robust and effective solutions to combat resistant bacterial infections. Continued investment in fundamental research, streamlined regulatory pathways, and global access strategies will be essential for translating these scientific breakthroughs into impactful therapies that can safeguard public health.

7. Conclusions

The urgent threat of multidrug-resistant pathogens like MRSA and VRE demands new therapies. While vancomycin remains crucial, resistance, especially the D-Ala-D-Lac substitution, has severely hampered its effectiveness. Our review shows how strategic structural modifications and advanced computational methods have created promising vancomycin analogs, restoring efficacy, broadening activity to include Gram-negative bacteria, and improving pharmacokinetic properties. From a synthetic standpoint, the success of existing semisynthetic derivatives and experimental analogs proves the huge potential of ongoing chemical innovation. The synthesis of novel vancomycin analogues is vital. This involves exploring new modifications to the glycopeptide backbone and adding new functional groups to overcome current and future resistance, as well as tackle complex issues like biofilm infections. Despite progress, challenges like emerging resistance, high synthesis costs, and safety persist. Future research should prioritize the computational design and synthesis of dual-targeting glycopeptides that hit multiple bacterial vulnerabilities. We also need to develop cost-effective and scalable synthesis routes to make these advanced drugs accessible, ensuring a new generation of effective therapies against antimicrobial resistance.

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