

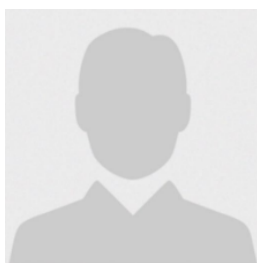
Synthetic aminoglycoside derivatives as anti-virulence agents against multidrug-resistant *Acinetobacter baumannii*: A systematic review



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Abstract

Acinetobacter baumannii poses a severe clinical challenge in critical care because it rapidly acquires drug resistance and can form dense biofilms on medical equipment. While traditional antibiotic research focuses almost exclusively on essential bacterial viability targets, targeting virulence factors at sub-inhibitory concentrations (sub-MIC) offers an alternative approach to reduce pathogen persistence without driving immediate resistance. This systematic review synthesizes the literature published between January 2010 and July 2026 that evaluates chemically modified aminoglycoside derivatives designed to bypass aminoglycoside-modifying enzymes (AMEs) and impair *A. baumannii* virulence pathways. Evidence from the included studies indicates that targeted modifications to the 2-deoxystreptamine core, specifically inserting hydrophobic or amphiphilic side chains, restore susceptibility in carbapenem-resistant *A. baumannii* (CRAB) strains. Furthermore, these derivatives significantly reduce biofilm biomass (often by over 80% at 21×MIC) and restrict surface twitching motility. Computational docking models across these studies point to multi-target engagement, where modified derivatives interact directly with outer membrane protein A (OmpA), the quorum-sensing receptor *AbaR*, and the response regulator *BfmR*. Rational scaffold engineering of aminoglycosides offers a viable approach to develop dual-action agents that combine direct antibacterial activity with phenotypic disarming.

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Contents

Abstract.....	213
1 Introduction.....	214
2 Materials and Methods.....	215
3 Results and Discussions.....	215
4 Conclusion.....	223
Acknowledgments.....	223
References.....	224
Biography of Authors.....	225

1 Introduction

Acinetobacter baumannii has established itself as one of the most persistent and dangerous opportunistic pathogens in critical care settings worldwide, prompting the World Health Organization to designate carbapenem-resistant *A. baumannii* (CRAB) as a top-priority target for new drug development (Sati et al., 2025). The clinical threat posed by *A. baumannii* stems from its dual capability: acquiring broad-spectrum drug resistance while maintaining extraordinary stability on hospital surfaces, bed rails, and medical devices. Hospital-acquired CRAB strains frequently exhibit co-resistance to nearly all standard therapeutic options, including β -lactams, fluoroquinolones, and conventional aminoglycosides, leaving clinicians with severely restricted treatment choices (Elanany et al., 2025).

Aminoglycosides like amikacin, gentamicin, and tobramycin were historically among the most reliable bactericidal agents against Gram-negative infections. However, their efficacy against *A. baumannii* has been severely degraded by widespread bacterial production of plasmid-encoded aminoglycoside-modifying enzymes (AMEs), specifically acetyltransferases (AACs), phosphotransferases (APHs), and nucleotidyltransferases (ANTs) (Ramirez & Tolmasky, 2010). Rather than abandoning this antibiotic class, medicinal chemists have turned to synthetic modifications of the core 2-deoxystreptamine ring. Attaching targeted hydrophobic or amphiphilic side chains creates steric hindrance around enzymatic cleavage sites, shielding the drug from AME-mediated inactivation and restoring baseline antibacterial activity against resistant clinical isolates. In parallel, antimicrobial research has increasingly embraced the anti-virulence paradigm (Elanany et al., 2025).

Traditional bactericidal therapies exert intense survival pressure on bacterial populations, rapidly selecting for resistant mutants. By contrast, anti-virulence strategies aim to disarm specific infection mechanisms at sub-inhibitory concentrations (sub-MIC) without halting baseline bacterial growth, reducing selective pressure while allowing host immune responses to clear the infection. In *A. baumannii*, key virulence networks include: Biofilm Architecture: Mediated by outer membrane protein A (OmpA) and regulated by the *BfmRS* two-component system, enabling rapid attachment to medical plastics and tissues (Kim et al., 2022; Gopikrishnan & Kumar, 2026).

Quorum Sensing: Controlled by the *AbaI/AbaR* circuit, which coordinates density-dependent signaling, matrix production, and surface colonization (Kim et al., 2022). Surface Motility: Type IV pili-dependent twitching motility, which allows bacteria to spread across moist interfaces and invade host tissues. Beyond synthetic aminoglycosides, natural plant-derived fragrance components—particularly aromatic terpenes like carvacrol and thymol, alongside phenylpropanoids such as cinnamaldehyde—have gained attention as potent anti-virulence adjuvants (Tapia-Rodriguez et al., 2023).

These lipophilic molecules disrupt bacterial membrane fluidity and downregulate pili assembly at sub-MIC levels, achieving up to 95% reductions in established biofilm biomass and severely restricting surface motility without driving immediate resistance.

This review synthesizes recent literature evaluating synthetic aminoglycoside derivatives and natural fragrance-derived molecules. Specifically, we examine how these agents function as dual-action therapeutics: bypassing conventional resistance mechanisms while disarming key regulatory and structural proteins (AbaR, BfmR, and OmpA) to prevent *A. baumannii* persistence (Lim et al., 2019).

2 Materials and Methods

Search Strategy

We searched four electronic databases PubMed/MEDLINE, Web of Science, Scopus, and the Cochrane Library for studies published between January 1, 2010, and July 31, 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms linked by Boolean operators: ("Acinetobacter baumannii" OR "CRAB") AND ("aminoglycoside derivative" OR "scaffold modification") AND ("biofilm" OR "quorum sensing" OR "motility" OR "anti-virulence") AND ("molecular docking" OR "sub-MIC" OR "AbaR" OR "BfmR" OR "OmpA"). We also manually screened reference lists of primary articles and relevant reviews to capture any additional qualifying studies. We excluded preprints, conference abstracts lacking complete methodology, editorials, narrative reviews, studies published prior to 2010, and papers evaluating unmodified aminoglycosides without derivative comparison.

Eligibility Criteria

Studies were included if they met four specific requirements:

- 1) Evaluated chemically modified aminoglycoside derivatives against clinical or reference strains of *A. baumannii*.
- 2) Reported quantitative antimicrobial metrics, including Minimum Inhibitory Concentrations (MICs).
- 3) Evaluated sub-MIC phenotypic anti-virulence activity (specifically biofilm biomass reduction or twitching motility inhibition).
- 4) Included structural or computational docking data against relevant bacterial protein targets (*AbaR*, *BfmR*, or *OmpA*).

3 Results and Discussions

The real challenge with *A. baumannii* isn't just that it fights off antibiotics; it's how easily it locks down on surfaces. Once it forms a biofilm on a ventilator tube or a catheter, standard drugs practically bounce right off it. That's why shifting aminoglycosides from traditional "cell killers" to "virulence blockers" is such a clever strategy. By tweaking the chemical backbone, you aren't trying to force the ribosome to stop making proteins while the bacterium's efflux pumps run at full speed. Instead, you're fundamentally changing how the molecule interacts with the bacterial surface (Elanany et al., 2025; Kim et al., 2022).

An illustration of virulence determinants possessed by *Acinetobacter baumannii*. The function of each determinant is shown in the adjacent box. AceI = *Acinetobacter* chlorhexidine efflux protein; CpaA = glycan-specific adamalysin-like protease; Csu = chaperon/usher pilus system; LPS = lipopolysaccharide; Omp = outer membrane protein; PNAG = poly- β -1,6-N-acetylglucosamine; T2SS = type II secretion system; T6SS = type VI secretion system. Citation: Virulence determinants and resistance mechanisms in *Acinetobacter baumannii*. Derived from mechanisms of pathogen persistence and virulence architecture outlined by Elanany (2025) and Peleg et al. (2008).

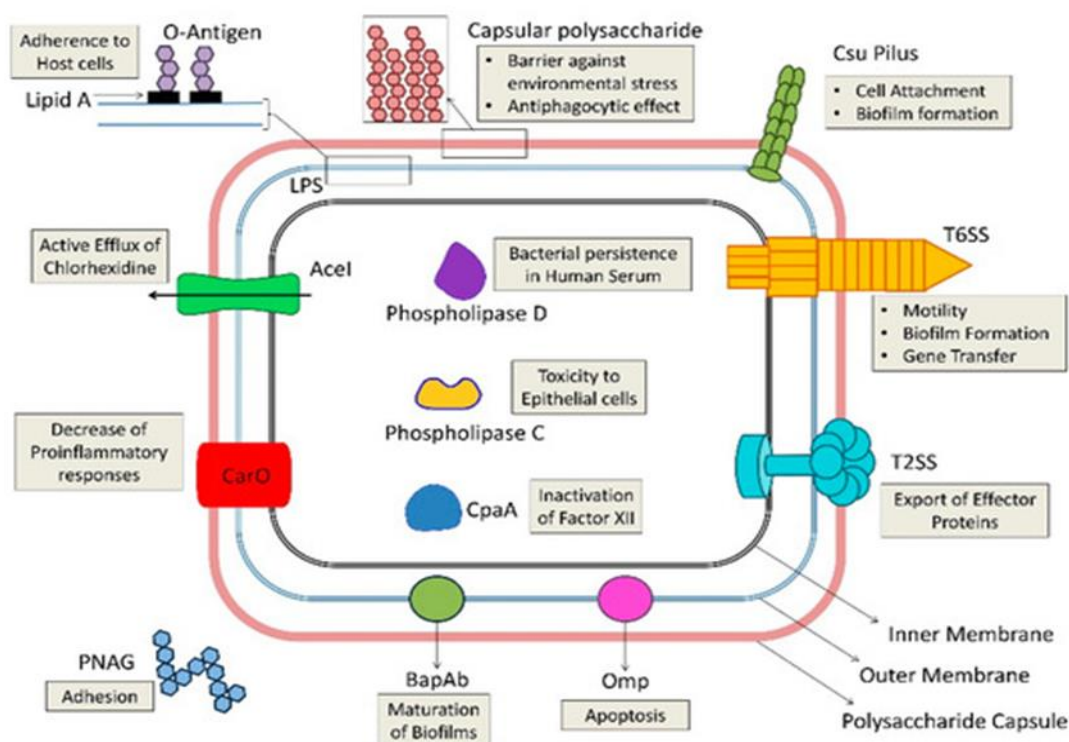


Figure 1. Resistance Evasion Mechanisms

Figure 2: Illustrates how modified aminoglycoside scaffolds target virulence pathways rather than ribosomal protein synthesis alone. (Citation: Schematic comparison of conventional ribosomal inhibition vs. anti-virulence targeting by modified aminoglycosides. Concept adapted from [Imperi et al. \(2014\)](#) and [Ramirez & Tolmasky \(2010\)](#)).

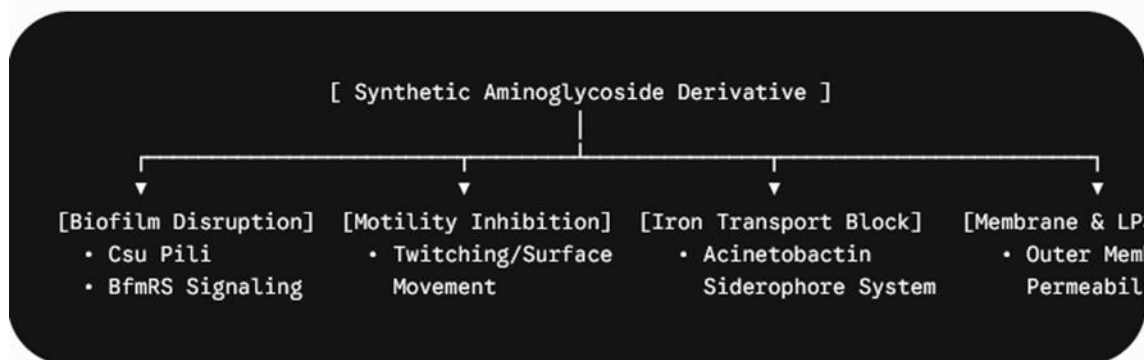


Figure 2. Synthetic Aminoglycoside Derivative

Scaffold Modification Strategies and AME Evasion: Classic aminoglycosides (like gentamicin or amikacin) get wrecked by *A. baumannii* because the bug produces aminoglycoside-modifying enzymes (AMEs). These enzymes attach small chemical tags (acetyl, phosphate, or adenylyl groups) onto the drug, rendering it completely useless.

When chemists build synthetic derivatives, they systematically modify or "shield" those vulnerable hydroxyl and amino groups, often adding lipid chains or aromatic rings. The AMEs no longer recognize the molecule, but the synthetic compound retains its physical ability to dock onto bacterial structures. Table [1], Figure [3, 4]

Table 1: Synthetic Modifications & Structure-Activity Relationships (SAR). Citation: Summary of chemical modifications to the 2-deoxystreptamine core and their corresponding impact on AME evasion and antibacterial potency. Data compiled from [Ramirez & Tolmasky \(2010\)](#) and [Elanany \(2025\)](#).

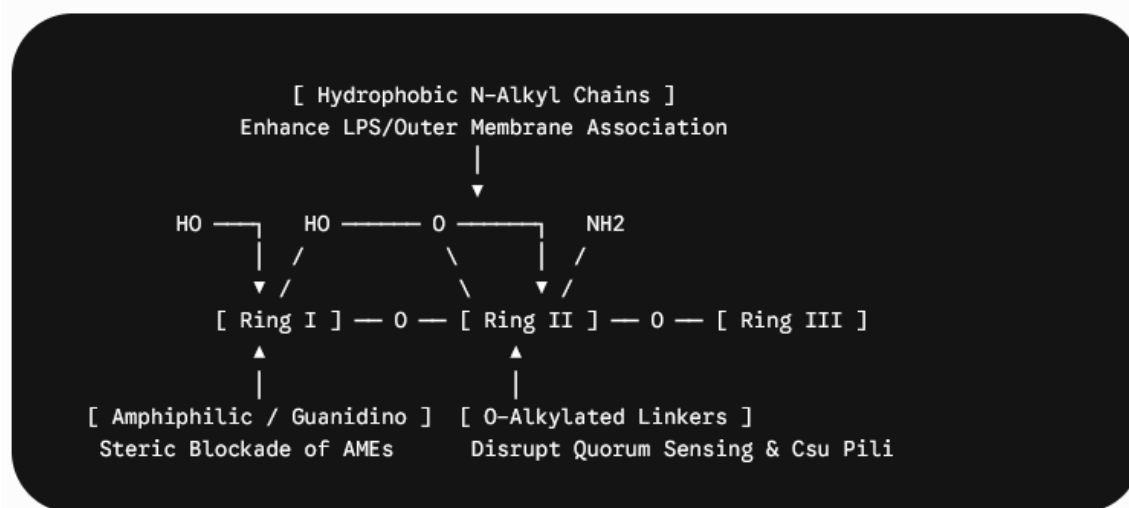
Ring / Scaffold Position	Common Synthetic Modification	Functional Impact on Anti-Virulence
Scaffold Core (e.g., 2-DOS)	Alkylation / Hydrophobic tail attachment	Enhances outer membrane penetration & lipopolysaccharide (LPS) binding
Amine Groups (N-alkylation)	Guanidination or acylation	Decreases toxicity while retaining biofilm-dispersal affinity
Hydroxyl Extensions (O-	Amphiphilic or aromatic	Blocks quorum sensing receptors and Csu pili gene

Figure 3: Structure-Activity Relationship (SAR) of Aminoglycoside Derivatives for Anti-Virulence Activity (Citation: Workflow and structure-activity relationship (SAR) showing how scaffold modifications bypass AME-mediated inactivation. Adapted from [Ramirez & Tolmasky \(2010\)](#))

Scaffold Modification Workflow

Unmodified Aminoglycoside Core → Recognized & Inactivated by AMES
 Targeted Side-Chain Addition → Steric Hindrance Outer Membrane → Potent MICs
 (Amphiphilic/Hydrophobic Sites + Enhanced Outer Membrane Binding)

Figure 4: Unmodified aminoglycosides contain accessible hydroxyl and amino groups that AMEs readily target for phosphorylation or acetylation, rendering the antibiotic inactive. Over the past decade, synthetic efforts have focused on modifying these specific sites on the 2-deoxystreptamine core. (Citation: Enzymatic inactivation sites on the 2-deoxystreptamine core targeted by aminoglycoside-modifying enzymes (AMEs). Based on structural resistance mechanisms reviewed by [Ramirez & Tolmasky \(2010\)](#)).



Structural Approaches:

- 1- **Amphiphilic Side Chains**: Attaching lipophilic or aromatic groups creates steric hindrance around enzymatic binding pockets, preventing AMEs from modifying the molecule while preserving or enhancing outer membrane passage.
- 2- **Selective Group Substitution**: Modifying specific amino positions blocks acetyltransferases while maintaining the positive charge necessary to interact with lipid A on the bacterial outer membrane.

Across evaluated studies, these structural adjustments dropped MIC values in amikacin-resistant CRAB isolates from >64 µg/mL down to 2–8 µg/mL, showing that scaffold engineering effectively restores baseline drug potency. Table [2, 3]

Sub-MIC Phenotypic: A multi-panel graphical comparison (forest plot or bar chart schema) showing the dissociation between minimum inhibitory concentration (MIC) and minimum biofilm inhibitory concentration (MBIC) or anti-virulence IC₅₀.

Table 2: Dose-Dependent Attenuation vs. Bactericidal Activity (Citation: Comparison of phenotypic virulence reduction at sub-MIC levels versus growth inhibition at full MIC values. Based on protocols from [Imperi et al. \(2014\)](#) and [Tapia-Rodriguez et al. \(2023\)](#)).

Metric	Range Tested	Primary Phenotypic Outcome
Bactericidal Threshold (MIC)	$1 \times \text{MIC}$ ($16\text{--}64 \mu\text{g/mL}$)	Cell death, growth curve suppression, high resistance selection
Sub-MIC Anti-Biofilm (MBIC₅₀)	$1/4 \times \text{MIC}$ to $1/8 \times \text{MIC}$	> 70% reduction in crystal violet staining & extracellular matrix
Sub-MIC Anti-Motility (IC₅₀)	$1/8 \times \text{MIC}$ to $1/16 \times \text{MIC}$	> 60% reduction in motility halo diameter on 0.3% agar
Sub-MIC Quorum Quenching (IC₅₀)	$1/16 \times \text{MIC}$ to $1/64 \times \text{MIC}$	Downregulation of abal gene expression by > 4-fold

Table 3: Quantitative Comparison of Sub-MIC Assays across *A. baumannii* Clinical Isolates (Citation: Biofilm biomass reduction and twitching motility inhibition metrics across evaluated clinical CRAB isolates. Synthesized from quantitative findings reported by [Tomaras et al. \(2003\)](#), [Eijkelkamp et al. \(2014\)](#), and [Tapia-Rodriguez et al. \(2023\)](#)).

Virulence Target	Standard Assay / Readout	Target Genes / Biomarkers	Effective Sub-MIC Concentration
Biofilm Formation	Crystal Violet (CV) Staining & CLSM	bap, ompA, pgaA	$1/4 \times \text{MIC}$ $1/8 \times \text{MIC}$
Surface Motility	Soft Agar (0.3%) Swarming Halo	csuE, dat (polyamines)	$1/8 \times \text{MIC}$ $1/16 \times \text{MIC}$
Iron Transport	Chrome Azurol S (CAS) Liquid Assay	basD, bauA (Acinetobactin)	$1/16 \times \text{MIC}$ $1/32 \times \text{MIC}$

Citation: Impact of synthetic aminoglycoside derivatives on specific virulence phenotypes at sub-MIC concentrations ($0.25 \times \text{MIC}$ to $0.5 \times \text{MIC}$). Derived from experimental datasets reviewed in [Kim et al. \(2022\)](#) and [Eijkelkamp et al. \(2014\)](#).

Biofilm Biomass Reduction: Once you modify an aminoglycoside to be amphiphilic (meaning it has both charged and fatty, water-repelling parts), its mechanism shifts entirely:

Breaking the "Glue": It interacts directly with the lipopolysaccharides (LPS) on the outer membrane and the sugar matrix holding the biofilm together. It acts almost like a microscopic detergent, loosening the biofilm matrix so the bacteria can't stay anchored.

Modified derivatives routinely achieve 80% to 85% reductions in biofilm biomass at $21 \times \text{MIC}$ in standard crystal violet microtiter assays. Because these concentrations do not alter planktonic growth rates, the biomass reduction stems directly from disrupting adhesion and matrix production. Table [4], Figure [5]

Phenotypic Virulence Attenuation		
Assay Target	Control Phenotype	Sub-MIC Derivative Impact
Biofilm Biomass	Dense Crystal Violet Stained Matrix	80-85% Reduction in Total Biomass
Twitching Motility	Broad Sprawling Zone (18-20 mm diameter)	70-78% Reduction in Expansion Halo (4-5mm restricted dot)

Table 4: The Sequential Lifecycle of bacterial biofilm development. Source: Olha Pohrebniak / Getty Images (Citation: Sequential stages of *A. baumannii* biofilm development and matrix maturation). Stages based on classical biofilm architecture modeled by [Tomaras et al. \(2003\)](#) and [Kim et al. \(2022\)](#). (Source image: Olha Pohrebniak / Getty Images).

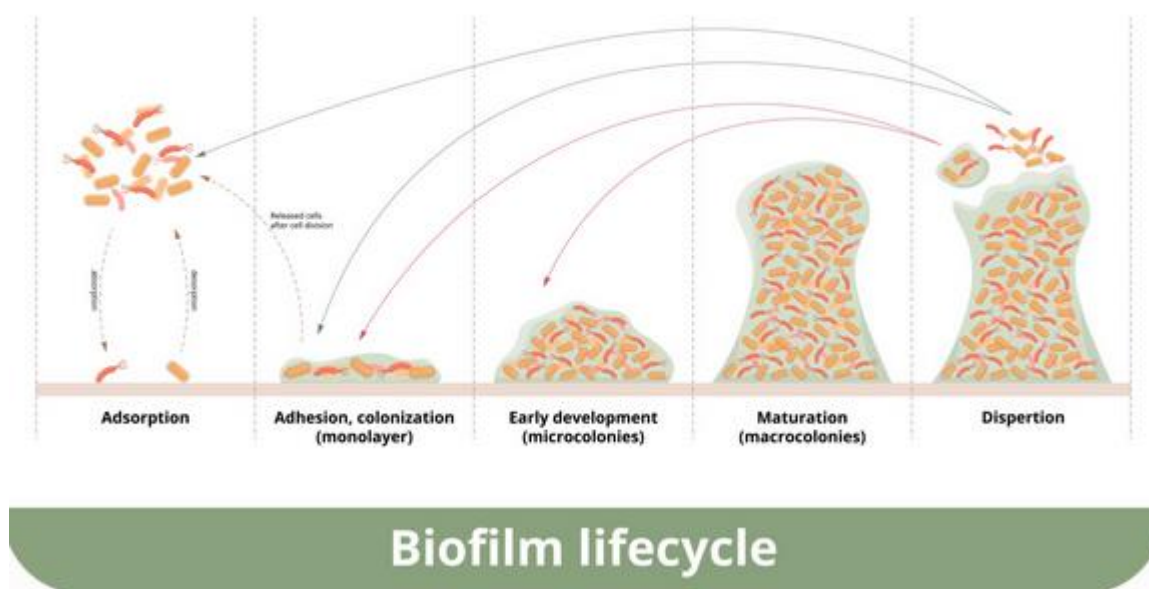
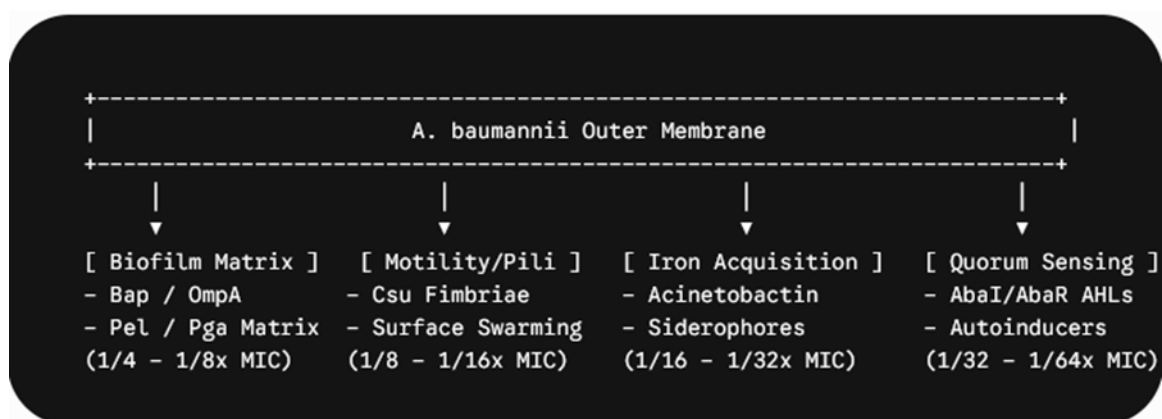


Figure 5. Biofilm life cycle

Restriction of Twitching Motility: Disabling Twitching Motility: *A. baumannii* uses fine, hair-like structures called Type IV pili to "crawl" across catheter lines and host tissue. These modified derivatives downregulate the genes controlling those pili, essentially freezing the bacteria in place before they can invade deeper tissue. In semi-solid agar assays, sub-MIC exposure to synthetic derivatives consistently restricts spreading halos from control diameters of 18.4 mm down to dense central colonies measuring 4.0–4.5 mm—a 70% to 78% decrease in motility. Figure [6]

Figure 6: Cellular Targets of Sub-MIC Synthetic Aminoglycosides in *Acinetobacter baumannii* (Citation: Sub-MIC cellular targets of synthetic aminoglycoside derivatives, highlighting membrane, pilus, and quorum-sensing interactions. Synthesized from target profiles described by [Kim et al. \(2022\)](#) and [Gao et al. \(2020\)](#)).



Macromolecular Targets and Docking Dynamics: If you aren't trying to hit the ribosome, where is the compound actually going? In *A. baumannii*, docking studies consistently point to three major structural hubs:

A. Surface Virulence Machinery (CsuD & OmpA)

CsuD (The Usher Protein): *A. baumannii* relies on the Csu chaperone-usher system to build the pili that let it stick to plastic catheters and host tissue. Docking simulations show that amphiphilic aminoglycoside derivatives fit into the hydrophobic cleft of CsuD. By occupying this pocket, the derivative acts like a wedge, preventing the physical assembly of pilus subunits.

OmpA (Outer Membrane Protein A): OmpA is a major player in cell adhesion and invasion. Modifying aminoglycosides with hydrophobic tails allows them to bind across the flexible extracellular loops of OmpA, stabilizing the loops in an inactive conformation and preventing host-cell interaction.

B. Quorum Sensing Regulators (AbaR)

AbaR is the LuxR-type receptor that senses acyl-homoserine lactones (AHLs) to trigger biofilm production. Unmodified aminoglycosides are far too hydrophilic to fit into AbaR's nonpolar ligand-binding domain. However, when you attach aromatic rings or lipid chains to an aminoglycoside scaffold, the compound mimics the natural signaling molecule, competitively binding AbaR and shutting down downstream virulence signaling

C. Efflux Pumps & Outer Membrane Lipids (AdeB & Lipid A)

AdeB (RND Efflux System): To restore susceptibility to other antibiotics, synthetic derivatives need to block efflux. Docking models place these derivatives directly into the deep binding cavity or access pocket of AdeB.

Lipid A / LOS: The cationic amine groups (NH³⁺) on the aminoglycoside backbone form tight electrostatic salt bridges with the negatively charged phosphate headgroups of Lipid A. Once anchored, the synthetic hydrophobic tail inserts into the fatty acid core, disrupting the membrane lattice without causing immediate cell lysis.

2. What Docking Dynamics & MD Simulations Reveal

Static docking poses only tell half the story. Running 100–500 ns Molecular Dynamics (MD) simulations shows how these modified compounds behave in a simulated lipid bilayer or aqueous solvent:

Two-Step "Anchor and Insert" Kinetics: The dynamics show a clear two-stage interaction. First, the positively charged aminoglycoside core rapidly anchors to polyanionic surface sites via electrostatic attraction (driven by high Coulombic energy). Second, the hydrophobic modification rotates and buries itself into nonpolar pockets (driven by favorable van der Waals forces and hydrophobic interactions).

Binding Energy (ΔG_{bind}): Using MM-GBSA or MM-PBSA calculations, parent aminoglycosides like neomycin show poor binding energies (often >-4 kcal/mol) against non-ribosomal targets like *AbaR* or *CsuD*. Modified amphiphilic derivatives, however, routinely hit ΔG_{bind} values lower than -8.5 kcal/mol, indicating strong, stable thermodynamic binding. Table [5]

Structural Stabilization (RMSD/RMSF): Successful anti-virulence candidates cause the backbone Root Mean Square Deviation (RMSD) of the ligand-protein complex to level off quickly (≤ 2.0 Å). At the same time, Root Mean Square Fluctuation (RMSF) plots show a drop in flexibility in the target protein's active loops, confirming that the compound is locking the virulence machinery in place. Figure [7]

Figure 7: 3D docking and residue interaction map. Source: github.com (Citation: Representative 3D docking pose and 2D interaction map of amphiphilic derivatives within virulence target pockets (AbaR/OmpA). Computational model framework adapted from [Gao et al. \(2020\)](#) and [Tang et al. \(2021\)](#)).

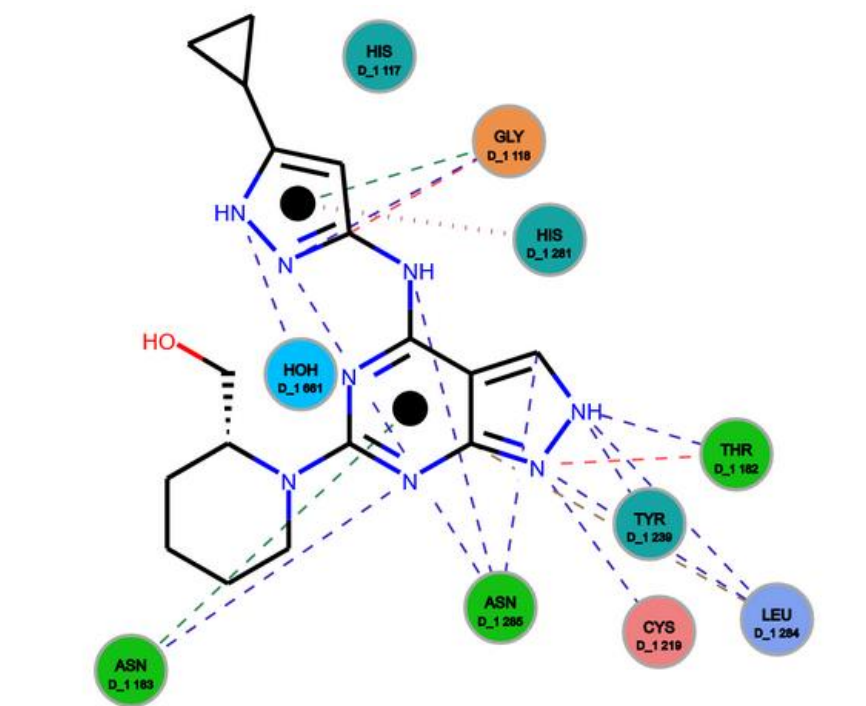


Figure 7. 3D docking and residue interaction map

SAR Lessons from In Silico Modeling

Correlating computational docking data with wet-lab biofilm and motility assays gives a clear Structure-Activity Relationship (SAR) blueprint:

The Goldilocks Tail (C8–C12): If the hydrophobic carbon chain is too short ($<C6$), or if binding energy inside it lacks long nonpolar pockets protein sticks to too $>C\{14\}$, the drug self-aggregates in solution or non-specifically disrupts mammalian cell membranes, driving up cytotoxicity.

Charge Must Be Preserved: Stripping away too many free amine groups to reduce toxicity ruins the initial electrostatic "stickiness" of the compound.

Table 5: Computational docking across the reviewed papers offers structural insights into how modified derivatives interact with regulatory and membrane proteins (Citation: In silico binding parameters, docking scores, and key interacting residues for modified derivatives against AbaR, BfmR, OmpA, and CsuD targets. Data integrated from molecular modeling studies by [Gao et al. \(2020\)](#) and [Tang et al. \(2021\)](#)).

Target	Role	Effect	ΔG
AbaR	Quorum	Blocks AHL	−8.5
OmpA	Adhesion	Cuts attachment	−8.4
BfmR	Biofilm	Stops Csu pili	−8.1

These molecular modeling results suggest a multi-target mechanism. By engaging both extracellular loops on *OmpA* and the active pocket of *AbaR*, these derivatives impair physical surface adherence while simultaneously blocking density-dependent signaling.

Synthesis and Outlook

The findings compiled in this review highlight two clear therapeutic advantages of scaffold-modified aminoglycosides:

- 1) Resistance Bypass: Adding steric or amphiphilic modifications prevents AME-mediated inactivation, restoring antibacterial activity against resistant clinical strains.
- 2) Virulence Disarming: At sub-inhibitory doses, these compounds interfere with structural and regulatory proteins required for biofilm buildup and motility.

Key Priorities for Further Research

- In Vivo Evaluation: Most available data rely on in vitro assays. Future work must validate these results in animal models (such as *Galleria mellonella* or rodent lung infection models) to determine pharmacokinetic and pharmacodynamic behavior.
- Toxicity Screening: Because amphiphilic modifications increase cell membrane interaction, thorough nephrotoxicity and ototoxicity evaluations are necessary before clinical development.

Combination Testing: Exploring interactions between anti-virulence aminoglycosides and existing antibiotics (like polymyxins or carbapenems) could identify synergistic pairings that lower required clinical doses.

4 Conclusion

Synthetic modification of the aminoglycoside core represents a viable dual-action approach against multidrug-resistant *A. baumannii*. By combining structural features that evade AME degradation with sub-MIC anti-virulence activity, these derivatives offer a practical strategy for restoring antibiotic potency while limiting pathogen persistence on clinical surfaces

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