Supplementary Table S1. Novel Antimicrobial Leads Against Multidrug-Resistant (MDR) Microorganism								
Author (Year), reference	**Compound**	**Chemical Class**	**Molecular Target**	**Mechanism of Action (MoA)**	**Target Organisms & Phenotypes**	**Activity Profile (MIC/IC50)**	**Design Strategy**	**Key Findings & Translational Status**
Mitcheltree et al. (2021) [1]	Iboxamycin (OPP-3)	Oxepanoprolinamide	23S rRNA (PTC / NPET)	(i) Binds PTC/NPET interface; (ii) Induces conformational shift of methylated nucleotide $m_2^6A2058$to restore binding; (iii) 7'-isobutyl group penetrates A-site cleft.	*S. aureus* (Clinical MDR $c-ermA$); *E. faecalis* (ATCC 29212); *E. coli* (Clinical $armA$); *A. baumannii* (ATCC 19606)	MIC: 1 µg/mL (*S. aureus* $c-ermA$); MIC: 0.06 µg/mL (*E. faecalis* $lsaA$); MIC: 8 µg/mL (*E. coli* $armA$); MIC: 4 µg/mL (*A. baumannii*)	SBDD	Synthetic scaffold overcomes *erm*, *cfr*, and *lsaA* resistance via steric displacement mechanism. Orally bioavailable (F=24%); 100% survival in systemic *S. pyogenes* model (3 mg/kg). Safe ($GI_{50} > 50\mu M$ in HepG2).
	Epi-Iboxamycin (epi-OPP-3)	Oxepanoprolinamide	23S rRNA (PTC)	(i) Binds PTC with 7'-β stereochemistry; (ii) Inefficient penetration of A-site cleft compared to 7'-α epimer.	*S. aureus* (ATCC 29213); *E. coli* (ATCC 25922); *H. influenzae* (ATCC 49247)	MIC: ≤0.06 µg/mL (*S. aureus*); MIC: 16 µg/mL (*E. coli*); MIC: 2 µg/mL (*H. influenzae*)	SBDD	Stereochemical control (7'-β epimer). Retains Gram-positive potency but shows reduced activity against Gram-negatives (2-fold increase in MIC vs IBX), confirming the necessity of 7'-α geometry for broad-spectrum coverage.
	OPP-1	Oxepanoprolinamide	23S rRNA (PTC)	Competitive inhibition of peptide bond formation (Lacks 7'-hydrophobic extension required for resistance breaking).	*S. aureus* (ATCC 29213); *S. pneumoniae* (Clinical $c-ermB$); *E. coli* (ATCC 25922)	MIC: 0.125 µg/mL (*S. aureus* WT); MIC: 64 µg/mL (*S. pneumoniae* $c-ermB$); MIC: >64 µg/mL (*E. coli*)	SBDD	First-generation bicyclic scaffold. Potent against wild-type strains but inactive against *erm*-methylated ribosomes (MIC 64 µg/mL), demonstrating that the bicyclic core alone is insufficient for resistance breaking

								without the C7'-isobutyl tail.
Bolatchiev et al. (2022) [2]	PEP-137	De Novo Cationic Peptide (32-mer)	Bacterial Membrane Surface	(i) Electrostatic accumulation on membrane surface (Charge +12.1); (ii) Lacks deep bilayer penetration (MD simulation).	*K. aerogenes*, *K. pneumoniae*, *P. aeruginosa* (Carbapenem-R CI)	MIC: 2 µg/mL (Median, all strains); Efficacy: 50% Survival (Murine Sepsis Model, p=0.027).	Generative LSTM RNN (De Novo Design)	High Potency/High Toxicity Risk: Most potent *in vitro* candidate but predicted to be hemolytic (HAPPENN PROB score: 0.962); demonstrates that high charge (+12.1) favors surface accumulation over penetration.
	PEP-36	De Novo Cationic Peptide (28-mer)	Host Immune System (Putative) / Bacterial Membrane	(i) Putative immunomodulation (in vivo); (ii) Unravelling to globular form, preventing membrane penetration (in vitro).	*K. pneumoniae* (Carbapenem-R CI)	MIC: >32 µg/mL (Inactive); Efficacy: 66.7% Survival (Murine Sepsis Model, p=0.0005).	Generative LSTM RNN (De Novo Design)	The "Paradox" Lead: Completely inactive in standard broth dilution assays yet achieved the highest survival rate in sepsis models; Low predicted toxicity (PROB: 0.236); highlights limitations of MIC as sole predictor of efficacy.
	PEP-38	De Novo Cationic Peptide (29-mer)	Bacterial Cytoplasmic Membrane (Lipid Bilayer)	(i) Direct deep bilayer penetration and Membrane permeabilization/lysis (Stable helix penetration	*K. aerogenes*, *K. pneumoniae* (Carbapenem-R CI)	MIC: 6–8 µg/mL; Efficacy: 0 % Survival (Ineffective in Murine Sepsis Model).	Generative LSTM RNN (De Novo Design)	In Vitro/In Vivo Disconnect: Demonstrated strong membrane penetration and *in vitro* potency but failed to reduce mortality in vivo; serves as a

								negative control for translation potential despite favorable MICs.
Domínguez-Méndez et al. (2025) [3]	Indolyl-acrylamide 12e	Indolyl-acrylamide derivative	FtsZ (GTP Binding Site)	(i) Inhibits FtsZ GTPase activity (51% inhibition at 32 µg/mL); (ii) Disrupts Z-ring formation; (iii) Increases membrane permeability.	*A. baumannii* (Clinical XDR A-564) / *S. aureus* (MRSA)	MIC: 4.3 µg/mL (*A.b.* XDR A-564); MIC: 1.2 µg/mL (*A.b.* BAA-747); MIC: 3.2 µg/mL (*S.a.* MRSA)	LBDD / SAR Optimization; Pharmacophore Hybridization / Conjugation.	Primary lead candidate with ethylenediamine tail. Demonstrates 13-fold higher potency than Cefepime against XDR strains. Low hemolytic toxicity (HC50 >40 µg/mL).
	Indolyl-acrylamide 12j	Indolyl-acrylamide derivative	FtsZ (GTP Binding Site)	(i) Inhibits FtsZ GTPase activity (30.5% inhibition); (ii) Membrane permeabilization.	*A. baumannii* (Clinical XDR A-564)	MIC: 1.2 µg/mL (*A.b.* XDR A-564); MIC: 4.4 µg/mL (*A.b.* BAA-747); MIC: 8.2 µg/mL (*S.a.* MRSA)	LBDD / SAR Optimization; Pharmacophore Hybridization / Conjugation.	The most potent analog against XDR *A. baumannii* (MIC 1.2 µg/mL), surpassing 12e. Features a longer aliphatic butyl chain (Homologation effect), which improves Gram-negative penetration
	Indolyl-acrylamide 12f	Indolyl-acrylamide derivative	FtsZ (Presumed)	Membrane permeabilization (Inferred from series).	*S. aureus* (MRSA) / *A. baumannii* (MDR)	MIC: 2.1 µg/mL (*S.a.* MRSA); MIC: 8.8 µg/mL (*A.b.* XDR A-564); HC50: >40 µg/mL	LBDD / SAR Optimization; Pharmacophore Hybridization / Conjugation.	Gram-positive selective lead. Most effective analog against MRSA (MIC 2.1 µg/mL). Structurally distinct from 12e via Chlorine substituent at C-5 (vs Bromine).
Lian et al. (2021) [4]	Compound 6c	2,3-diaminoquinoxaline	GyrB (ATPase Domain)	ATP hydrolysis competition; (i) Electrostatic interaction (Arg84); (ii) H-bonds (Lys118, Glu58).	*S. aureus* (ATCC 29213); MRSA CI (15-1, 15-2, 15-3)	MIC: 0.1 µg/mL (*S. aureus* ATCC), 0.5 µg/mL (MRSA 15-1), 0.5 µg/mL (MRSA 15-2), 0.5 µg/mL (MRSA 15-3); IC50: 5.2 µM (GyrB)	LBDD / SAR Optimization	High in vitro potency (equivalent to Vancomycin) compromised by narrow therapeutic window (SI ~4-9 vs Mammalian cells); serves as the pharmacophore template for virtual screening.

	AG-205/33156020	Arylaminotriazine	GyrB (ATPase Domain)	ATP hydrolysis competition; (i) H-bonds (Asp81, Gly85, His124); (ii) Hydrophobic interactions (Pro87, Ala98).	*S. aureus* (ATCC 29213); MRSA CI (15-1, 15-2, 15-3)	MIC: 6.25 μg/mL (*S. aureus* ATCC), 4 μg/mL (MRSA 15-1), 8 μg/mL (MRSA 15-2), 4 μg/mL (MRSA 15-3); IC50: 1.1 μM (GyrB)	LBDD / SAR Optimization	Identified via scaffold hopping (virtual screening); exhibits superior enzymatic affinity (IC50 1.1 μM) compared to 6c but lower whole-cell activity, suggesting permeation barriers; improved safety profile (CC_{50} 21 μM).
Bryan et al. (2023) [5]	TXH9179	Thiazolopyridine-benzamide (6-acetylene derivative)	SaFtsZ (Interdomain Cleft)	(i) GTP-dependent polymerization inhibition; (ii) Disruption of Z-ring assembly; (iii) Induces aberrant septal mislocalization (large foci).	*S. aureus* MRSA-USA100 (NRS705); *S. aureus* VISA (NRS27); *S. aureus* VRSA (VRS5); *S. aureus* LRSA (NRS127)	MIC: 0.25 μg/mL (MRSA NRS705); MIC: 0.25 μg/mL (VISA NRS27); MIC: 0.25 μg/mL (VRSA VRS5); MIC: 0.25 μg/mL (LRSA NRS127)	LBDD / SAR Optimization	Crystal structure (PDB: 8HTB) confirms that the 6-acetylene group enables a "straight" binding conformation, maximizing hydrophobic contacts; 4-fold potency increase vs comparator TXA707; Low resistance frequency (FOR ~10^{-8}); Bactericidal (6-log kill).
	TXH1033	Benzamide Carboxamide Prodrug	SaFtsZ (via active metabolite)	(i) Hydrolysis by serum acetylcholinesterases (t1/2 = 1.7 min); (ii) Release of active inhibitor TXH9179.	*S. aureus* MRSA-USA100 (NRS705)	Survival: 50% (30 mg/kg IV); Survival: 100% (45 mg/kg IV); MIC: 1.0 μg/mL (in 50% Mouse Serum)	LBDD / SAR Optimization	Overcomes solubility limits of parent TXH9179; Superior efficacy to comparator prodrug TXA709 (achieves efficacy (≥50% survival) at 33% lower dose); Validates oral bioavailability for systemic infection; Stable in acidic formulation.
Sciò P et al. (2025) [6]	C11	Benzothiophene-oxazole	FtsZ (Allosteric	(i) Inhibits FtsZ polymerization (non-competitive	*S. aureus* ATCC 25923; *S. aureus* TD276	MIC: 2 μg/mL (*S. aureus* ATCC 25923); 2–	SBDD	Identified via VS of 5M compounds; Synergistic with Meropenem

			Interdomain Cleft)	with GTP); (ii) Induces Z-ring delocalization; (iii) Disrupts biofilm architecture.	(FtsZ-mCherry); MRSA (CI BG9/BG10).	4 μg/mL (CF CI). IC50: 47.97 μM (Polymerization). Biofilm Inhibition: 4 μg/mL.		(restores susceptibility in MRSA); Non-cytotoxic to A549/CFBE41o- cells (>90% at 25 μM (A549); >90% at 12.5 μM (CFBE41o-)); Increased *G. mellonella* survival (77% vs 46%).
	C11.2	Benzothiophene-oxazole (Planar analogue)	FtsZ (Allosteric Interdomain Cleft)	Inhibits FtsZ polymerization via hydrophobic interaction with Val203/Leu200.	*S. aureus* ATCC 25923.	MIC: 8 μg/mL (*S. aureus*). IC50: 23.73 μM (Polymerization).	LBDD / SAR Optimization	SAR derivative lacking the methylene bridge; Demonstrates 2-fold superior enzyme inhibition compared to lead C11, but 4-fold lower antibacterial potency, indicating reduced membrane permeability.
Durcik et al. (2024) [8]	Conjugate 18b	Benzothiazole-Hydroxypyridinone Siderophore Conjugate	GyrB (ATPase Domain) / ParE (ATP-binding site)	(i) ATP-competitive inhibition (cation-π with Arg76); (ii) Iron(III) chelation (NMR confirmed); (iii) Siderophore-mediated "Trojan Horse" uptake.	*Escherichia coli* JW5503 (ΔtolC efflux-deficient)	MIC: 12.5 μM (Iron-depleted) / 25 μM (Iron-rich); IC50: 22 ± 6 nM (*E. coli* GyrB).	SBDD & Pharmacophore Hybridization	Paradox Lead: Nanomolar enzyme potency (IC50 22 nM) is masked by heavy efflux in wild-type strains (MIC >50 μM); activity is restored only in ΔtolC mutants. High TPSA (149.4 Å²) of the conjugate likely hinders passive diffusion, rendering siderophore uptake insufficient to overcome efflux.
	Conjugate 18a	Benzothiazole-Hydroxypy	GyrB (ATPase Domain)	(i) ATP-competitive inhibition; (ii)	*Escherichia coli* (Enzyme level)	IC50: 12 ± 5 nM (*E. coli* GyrB);	SBDD & Pharmacophor	SAR Insight: Pyranone moiety confers superior intrinsic enzyme affinity

		ranone Siderophore Conjugate		Siderophore mimicry.		MIC: >50 µM (*E. coli* ATCC 25922).	e Hybridization	compared to pyridinone (18b) but fails to translate to whole-cell activity. Demonstrates that position 4 modification is permissive for binding (unlike position 6), but permeability remains the bottleneck.
Reddyraj ula et al. (2024) [10]	PT6	*N*-acyl Phenothiazine-Benzimidazolone Hybrid	Mycobacterial F-ATP Synthase (Chain A/B Interface)	(i) Inhibits F-ATP synthase (Depletes intrabacterial ATP); (ii) Binds via H-bond (Glu65) and Pi-pi stacking (Phe69)	*M. tuberculosis* H37Rv (ATCC 27294); *M. tuberculosis* (Rifampicin-Resistant Mutant); *M. tuberculosis* (CI MDR)	MIC: 3.125 µM (M. tb H37Rv); MIC: 8.76 µM (RR-TB); MIC: 17.62 µM (MDR-TB); IC50: 0.788 µM (F-ATP Synthase); IC50: 30 µM (Whole Cell ATP Depletion)	Pharmacophore Hybridization	Lead Candidate: High (SI: 148.1 vs Vero cells); Excellent mitochondrial safety (SI: 253 vs mammalian ATPase); Minor synergy with Rifampicin (FICI: 0.56).
	PT1	*N*-acyl Phenothiazine-Benzimidazolone Hybrid	Mycobacterial F-ATP Synthase	(i) Inhibition of F-ATP synthase; (ii) Pi-pi stacking with Phe64 (Chain A) and Phe69 (Chain B).	*M. tuberculosis* H37Rv (ATCC 27294); *M. tuberculosis* (RR-TB); *M. tuberculosis* (MDR-TB)	MIC: 25 µM (*M. tb* H37Rv); MIC: 30.87 µM (RR-TB); MIC: 47.58 µM (MDR-TB)	Pharmacophore Hybridization	SAR Control: Unsubstituted phenothiazine core; Lower potency (8-fold higher MIC than PT6) confirms necessity of fluoro-benzyl tail for binding; High safety profile (CC_{50}: 386 µg/mL).
Jiang et al. (2025) [11]	H-10	AMP	Bacterial Cell Membrane (Anionic Lipids) / LPS	(i) Electrostatic sequestration of LPS; (ii) Rapid OM permeabilization; (iii) Inner membrane	*S. aureus* (MDR CI); *E. coli* (MDR CI); *A. baumannii* (MDR CI); *K.*	MIC: 1.56 μM (*S. aureus* MDR); 3.13 μM (*E. coli* MDR); 3.13 μM (*A. baumannii* MDR); 3.13 μM (*K.*	Peptidomimetics / Bio-inspired Design; LBDD / SAR Optimization	D-Ile substitution significantly enhanced proteolytic stability (t1/2 > 6h vs chymotrypsin) and (TI = 30.33); In vivo: 100% survival in toxicity

				depolarization via pore formation.	*pneumoniae* (MDR CI)	*pneumoniae* MDR).		model; significant load reduction in sepsis model. (10 mg/kg i.v.); Low resistance induction (15 passages); Additive with Imipenem/Levofloxacin (FICI ~0.56).
Zhang et al. (2025) [14]	Compound C9	1-Methylquinazoline derivative	FtsZ (PC Hydrophobic Pocket / T7-loop)	(i) Promotes/Stabilizes FtsZ polymerization (high-affinity conformation); (ii) Inhibits GTPase activity (IC50 ~90 µg/mL); (iii) Disrupts Z-ring assembly.	*S. aureus* ATCC 43300 (MRSA); *S. aureus* CI (Penicillin-R); *E. coli* BW25113 (ΔAcrB)	MIC: 0.125 µg/mL (*S. aureus* CI), 4.0 µg/mL (MRSA 43300), 0.0625 µg/mL (*B. subtilis*). MBC/MIC: 1–4 (Bactericidal).	LBDD / SAR Optimization	Lead Candidate. C-series scaffold confers bactericidal activity (unlike B-series); 4-fluorostyryl enhances potency. *In vivo* efficacy (mouse bacteremia) at 25 mg/kg comparable to Linezolid. Low hemolysis (<5% at 128× MIC). Identified as AcrB efflux substrate (MIC shifts from 256 to 16 µg/mL in *E. coli* ΔAcrB).
	Compound B3	1-Methylquinoxaline derivative	FtsZ (PC Hydrophobic Pocket)	(i) Promotes FtsZ polymerization; (ii) Induces filamentation (elongation) without cell lysis.	*B. subtilis* ATCC 9372; *S. aureus* ATCC 25923; *E. faecalis* ATCC 29212	MIC: 0.0625 µg/mL (*B. subtilis*), 0.25 µg/mL (*S. aureus*). MBC/MIC: >8 (Bacteriostatic).	LBDD / SAR Optimization	Pharmacological Contrast. Despite nanomolar potency (MIC), the quinoxaline core renders this compound purely bacteriostatic (unable to kill), contrasting with the bactericidal quinazoline C9. High lipophilicity (4-isopropylstyryl) correlates with potency but fails to trigger cell death.

Zheng et al. (2018) [15]	Compound 5	Benzofuroquinolinium derivative (N-isopropyl-N-propylpropan-1-amine substituted)	FtsZ (GTP-binding pocket)	(i) Competitive inhibition of GTP binding; (ii) Inhibition of GTPase activity; (iii) Suppression of FtsZ polymerization; (iv) Disruption of Z-ring formation.	*S. aureus* (MRSA BAA-41), *E. faecalis* (VRE 700221), *E. coli* (NDM-1 BAA-2469), *A. baumannii* (ATCC 19606), *P. aeruginosa* (BAA-2108).	MIC: 1 μg/mL (MRSA BAA-41), 1 μg/mL (VRE 700221), 1 μg/mL (NDM-1 *E. coli*), 4 μg/mL (*P. aeruginosa*). MBC: 1 μg/mL (*E. coli* 25922).	LBDD / SAR Optimization	Potency: Broad-spectrum bactericidal activity; superior to Vancomycin against VRE. Synergy: FICI 0.5 with Methicillin against MRSA (restores susceptibility). Resistance: No resistance observed after 25 passages. Safety: SI >32; HC50 >64 μg/mL (human erythrocytes).
Song et al. (2020) [18]	Compound A16 (Racemate)	4,5-dihydroisoxazole-benzamide	FtsZ (Interdomain Hydrophobic Pocket)	(i) Stimulates FtsZ polymerization (stabilizer); (ii) Induces filamentation; (iii) Bactericidal cell division inhibition.	*S. aureus* (MRSA, PRSA, MDR CI)	MIC: 0.25 μg/mL (MRSA ATCC 43300), 0.5 μg/mL (*S. aureus* PR), 0.5 μg/mL (*S. aureus* MDR-CI). MBC: 0.5–1.0 μg/mL (1-2x MIC).	LBDD / SAR Optimization	In vivo: Reduced bacterial load in blood infection model (10 mg/kg iv) comparable to Linezolid. Safety: Low cytotoxicity (HeLa IC50 >64 μg/mL); High metabolic stability in plasma.
	Compound A16-S (*S*-enantiomer)	4,5-dihydroisoxazole-benzamide	FtsZ (Interdomain Hydrophobic Pocket)	Stereospecific stabilization of FtsZ polymers; Inhibition of septum formation.	*S. aureus* (MRSA, PRSA, MDR CI)	MIC: ≤0.125 μg/mL (MRSA ATCC 43300), 0.25 μg/mL (*S. aureus* PR), ≤0.125 μg/mL (*S. aureus* MDR-CI).	LBDD / SAR Optimization	Potency: Eutomer (*S*-isomer) is 2-4x more potent than racemate and *R*-isomer; Demonstrates critical role of stereochemistry in fitting the FtsZ hydrophobic cleft.
Zhong et al. (2022) [21]	Compound A3	1-Methylquinolinium derivative	FtsZ (Interdomain Cleft)	(i) Promotes FtsZ polymerization (stabilizer); (ii) Induces bacterial filamentation; (iii) Disrupts Z-ring assembly.	*S. aureus* (MRSA); *S. epidermidis*; *E. faecium* (VRE)	MIC: 1 μg/mL (MRSA ATCC 43300); 0.25 μg/mL (*S. epidermidis*); 1 μg/mL (VRE ATCC 700221).	LBDD / SAR Optimization	Lead Candidate. 4-methylpiperidine substituted derivative. Exhibits bactericidal activity against *B. subtilis* but bacteriostatic against *S. aureus*. Low resistance

								potential (8-fold MIC increase after 35 passages) and low hemolytic toxicity (IC5 = 64 µg/mL). Synergistic with Methicillin against MRSA (FICI 0.31).
Ma et al. (2025) [22]	16e	1-methyl-2-phenylpyridin-1-ium / Indole hybrid (Series C)	FtsZ (Hydrophobic Slit) / Cell Membrane	(i) Allosteric stabilization of FtsZ T-state (promoting aberrant polymerization); (ii) Dissipation of proton motive force (ΔΨ) and membrane permeabilization.	*S. aureus* ATCC 43300 (MRSA); *E. faecium* ATCC 51559 (VRE); *A. baumannii* ATCC 19606	MIC: 0.0625 µg/mL (*S. aureus* ATCC 25923); MIC: 0.5 µg/mL (MRSA); MIC: 1.0 µg/mL (*A. baumannii*); MBC: 0.125 µg/mL (*S. aureus*); MIC: 1 µg/mL (VRE)	SBDD / Scaffold Hopping	Dual-targeting mechanism confers low resistance frequency (2-fold MIC increase vs 64-fold for Ciprofloxacin after 15 passages); Significant bacterial load reduction in murine bacteremia model; Low hemolytic toxicity (<10% at 32 µg/mL).
Krause et al. (2019) [24]	ACHN-975	Hydroxamate LpxC Inhibitor	LpxC (Zinc metalloenzyme)	(i) Competitive inhibition of UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase; (ii) Rapid bactericidal lysis.	*P. aeruginosa* (CI n=250; Phenotypes: MDR, CF-associated, Amikacin-R, Ceftazidime-R).	Enzyme IC50: 0.68 nM; MIC50: 0.06 µg/mL; MIC90: 0.25 µg/mL; MBC: 3-log10 reduction (≤4 h).	LBDD / SAR Optimization	First-in-class LpxC inhibitor to enter Phase 1 trials; demonstrated rapid bactericidal activity *in vitro* but failed in clinic due to dose-limiting transient hypotension (Cmax-driven) without tachycardia; insufficient therapeutic window.
	LPXC-516	Hydroxamate LpxC Inhibitor	LpxC (Zinc metalloenzyme)	(i) Inhibition of Lipid A biosynthesis; (ii) Membrane destabilization.	*P. aeruginosa* (MDR CI n=250).	Enzyme IC50: 0.71 nM; MIC50: 1 µg/mL; MIC90: 2 µg/mL; In Vivo: Stasis to 2-log kill	LBDD / SAR Optimization	Second-generation lead optimized for safety; showed wider therapeutic window than ACHN-975, but the program was terminated due to the reemergence

						(Neutropenic mouse lung model).		of cardiovascular toxicity in preclinical rat models; effective in the lung infection model where ACHN-975 failed.
	LPXC-313	Hydroxamate LpxC Inhibitor	LpxC (Zinc metalloenzyme)	Inhibition of Lipid A biosynthesis.	*P. aeruginosa* (MDR CI n=250).	Enzyme IC50: 4.8 nM; MIC50: 0.5 µg/mL; MIC90: 2 µg/mL; PK (Rat): Cl 1 .3 L/hr/kg.	LBDD / SAR Optimization	High enzymatic potency did not translate to superior MIC vs ACHN-975; demonstrated cross-resistance with other LpxC inhibitors via *nfxB* (efflux) and *fabG* mutations; halted due to class-wide cardiovascular toxicity.
	LPXC-289	Hydroxamate LpxC Inhibitor	LpxC (Zinc metalloenzyme)	Inhibition of Lipid A biosynthesis.	*P. aeruginosa* (MDR CI n=250).	Enzyme IC50: 13 nM; MIC50: 0.25 µg/mL; MIC90: 2 µg/mL; PK (Rat): Cl 1 .9 L/hr/kg.	LBDD / SAR Optimization	Lowest enzymatic affinity (13 nM) among leads but retained cellular potency (MIC 0.25 µg/mL), suggesting superior permeation; development halted due to safety signals consistent with the scaffold.
Fujita et al. (2022) [25]	TP0586532	2-hydroxymethyl imidazole derivative	LpxC (UDP-3-O-acyl-N-acetylglucosamine deacetylase)	(i) Competitive inhibition of Lipid A biosynthesis (LPS reduction); (ii) Chelation of catalytic Zinc ion via imidazole scaffold (avoiding hydroxamate-associated promiscuity).	*K. pneumoniae* ATCC BAA-1898 (KPC-2); *K. pneumoniae* ATCC BAA-2470 (NDM-1); *E. coli* NCTC 13846 (MCR-1/Colistin-R); *E. cloacae* ATCC	IC50: 0.101 µM (*E. coli* LpxC); MIC: 2 µg/mL (*K. pneumoniae* KPC-2), 4 µg/mL (*K. pneumoniae* NDM-1), 2 µg/mL (*E. coli* MCR-1), 8 µg/mL (*E. cloacae* KPC).	LBDD / SAR Optimization	Solves "Hydroxamate Toxicity" paradox (No hypotension/QT prolongation in guinea pigs); High selectivity vs human MMPs (>700-fold); Effective *in vivo* (Lung/Urinary models) against Colistin-resistant (*mcr-1*) strains; Low

					BAA-2341 (KPC).			resistance frequency (9.3×10^{-7}).
Piizzi et al. (2017) [27]	Compound 1 (-)	Hydroxamic Acid (L-Threonine scaffold)	LpxC (UDP Pocket / Hydrophobic Tunnel)	(i) Chelation of catalytic Zn^{2+}; (ii) Propargyl ether tail occupies hydrophobic tunnel; (iii) Inhibits Lipid A biosynthesis (deacetylation step).	*P. aeruginosa* (PAO1 strain K767; MDR CI)	MIC: 0.5 µg/mL (PAO1), 1.0 µg/mL (MIC_{50}, n=180), 2.0 µg/mL (MIC_{90}); IC_{50}: 0.001 µM (LpxC); Efficacy: 2-log reduction (Mouse Pneumonia (Lung), 20 mg/kg).	SBDD; LBDD / SAR Optimization	Lead Candidate. Achieved high selectivity over human metalloproteases (MMP/HDAC IC_{50} >30 µM) and low cytotoxicity (HepG2 IC_{50} >295 µM). Solved solubility issues of precursor (> 0.327 g/L). Narrow spectrum (inactive vs *E. coli*).
	Compound 15	Hydroxamic Acid	LpxC (Hydrophobic Tunnel)	(i) Competitive inhibition of LpxC; (ii) Propargyl tail fits hydrophobic tunnel geometry.	*P. aeruginosa* (PAO1 strain K767; ΔMexAB-oprM)	MIC: 2.0 µg/mL (WT), 0.25 µg/mL (ΔMexAB); IC_{50}: 0.006 µM (LpxC); Cytotoxicity: >419 µM (HepG2).	SBDD; LBDD / SAR Optimization	Safety Pivot. Identified via docking as the "best fit" geometry for the hydrophobic tunnel before gem-dimethyl optimization. Exhibits superior safety profile (higher CC_{50}) compared to the lead, though slightly less potent.
Gutierrez et al. (2024) [30]	Compound 3	Benzothiazole-pyrrole-2-carboxamide	DNA Gyrase B (GyrB) [ATP-binding pocket / Hydrophobic Floor]	ATP-competitive inhibition; Exploits "double rotor" conformational flexibility to maximize contacts within the hydrophobic floor subsite.	*Escherichia coli* (Recombinant GyrB Enzyme)	IC50: 19 ± 3 nM (Enzymatic	SBDD / SAR Optimization	Targeting the hydrophobic floor via N-benzyl substitution on the carboxamide nitrogen improved affinity ~3-fold over parent (Compound 1); QTAIM analysis confirms critical stabilization via Asp73 and Lys103 interactions.

Shi et al. (2019) [31]	Compound 33e	Spiropyrimidinetrione (Spirocyclopropane-oxazolidinone)	DNA Gyrase / Topoisomerase IV	Stabilizes bacterial DNA-cleavage complex (Interacts with Asp437)	MRSA, MRSE, PRSP, *N. gonorrhoeae*	MIC: <0.03–0.06 µg/mL (MRSA), ≤0.03 µg/mL (MRSE/PRSP); MIC90: 0.125 µg/mL (*N. gonorrhoeae*)	LBDD / SAR Optimization	Lead candidate with spirocyclopropane modification at oxazolidinone 5-position; Superior in vivo efficacy (ED50 3.87 mg/kg) vs ETX0914; Excellent oral bioavailability (F=96.6% in dogs).
	Compound 39e	Spiropyrimidinetrione (Thiazolidinone)	DNA Gyrase / Topoisomerase IV	Stabilizes bacterial DNA-cleavage complex	MRSA, MRSE, PRSP, *N. gonorrhoeae*	MIC: <0.03–0.25 µg/mL (MRSA), <0.03 µg/mL (PRSP); MIC90: 0.125 µg/mL (*N. gonorrhoeae*)	LBDD / SAR Optimization	(S)-5-methyl-2-thiazolidinone bioisostere of ETX0914; Demonstrated highest in vivo efficacy (ED50 2.54 mg/kg) in murine systemic infection; High metabolic stability (T1/2 = 7.68 h).
	Compound 39a [A]	Spiropyrimidinetrione (Thiazolidinone)	DNA Gyrase / Topoisomerase IV	Stabilizes bacterial DNA-cleavage complex	MRSA, *N. gonorrhoeae*	MIC: <0.03 µg/mL (MRSA); MIC90: 0.06 µg/mL (*N. gonorrhoeae*)	LBDD / SAR Optimization	Unsubstituted thiazolidinone analog; Exhibited superior potency against *N. gonorrhoeae* (2-fold more potent than 33e/39e); Validates thiazolidinone as a potent surrogate for the oxazolidinone ring.
Sidiq et al. (2026) [37]	Compound 7i	Coumarin-1,3,4-thiadiazole Schiff base	Putative: Enoyl-ACP Reductase (FabI) / DNA Gyrase B	(i) Competitive inhibition of NADH binding site (FabI); (ii) Blocking of ATPase domain (GyrB); (iii) Disruption of fatty acid biosynthesis.	*A. baumannii* (Carbapenemase-producing); *S. aureus* (β-lactamase-producing)	MIC: 16 µg/mL (*A. baumannii*); 32 µg/mL (*S. aureus*); 128 µg/mL (*P. aeruginosa*). ZOI: 19 ± 0.5 mm (*A. baumannii*).	Pharmacophore Hybridization / Conjugation	Lead Compound. Meta-nitro substitution confers highest potency, surpassing Ciprofloxacin (MIC >2 µg/mL) against MDR *A. baumannii*. High TPSA (176.94 Å²) suggests limited oral

								bioavailability; predicted low acute toxicity (Class IV).
	Compound 7c	Coumarin-1,3,4-thiadiazole Schiff base	Putative: Enoyl-ACP Reductase (FabI)	In silico prediction suggests preferential binding to FabI active site via hydrophobic stacking.	*P. aeruginosa*; *S. aureus* (β-lactamase-producing); *K. pneumoniae* (Carbapenemase-producing)	MIC: 32 µg/mL (*P. aeruginosa*); 64 µg/mL (*S. aureus*); 128 µg/mL (*K. pneumoniae*).	Pharmacophore Hybridization / Conjugation	Selectivity Lead. Meta-methoxy substitution shifts selectivity toward *P. aeruginosa* (4-fold more potent than 7i against this strain). Demonstrates SAR importance of electron-donating groups for *Pseudomonas* activity.
	Compound 7m	Coumarin-1,3,4-thiadiazole Schiff base	Putative: Enoyl-ACP Reductase (FabI)	Dual-target engagement via π-π stacking of heteroaryl moiety within enzyme hydrophobic pockets.	*S. aureus* (β-lactamase-producing); *A. baumannii* (Carbapenemase-producing)	MIC: 32 µg/mL (*S. aureus*); 128 µg/mL (*A. baumannii*); 256 µg/mL (*P. aeruginosa*).	Pharmacophore Hybridization / Conjugation	Bioisostere Lead. Replacement of phenyl ring with thiophene retains anti-staphylococcal activity (MIC 32 µg/mL) but loses Gram-negative potency. Validates heteroaryl scaffold viability with favorable predicted ADMET profile.
Wisal et al., (2024) [43]	ZINC85492658	Small Molecule (ZINC Library Hit)	Aspartate-semialdehyde dehydrogenase (Asd)	Competitive inhibition of the catalytic active site (Predicted via MD).	S. aureus (MDR)	ΔG (Binding): -57.72 kcal/mol (In Silico MM-GBSA)	SBDD	Identified as a novel inhibitor of Asd via subtractive genomics; top hit from TCM library. (Note: TrpG activity belongs to ZINC70455378).
Yarlagadda et al. (2014) [45]	Compound 4	Lipophilic Vancomycin Analogue (Octyl-QAC)	Cell Wall / Cell Membrane	Dual Mechanism: (i) Inhibition of cell wall biosynthesis (Lipid II binding); (ii) Membrane	*S. aureus* ATCC 33591 (MRSA); *S. aureus* (VISA); *E.*	MIC: 0.31 µM (MRSA), 0.4 µM (VISA), 12.5 µM (VRE). Hemolysis: Non-hemolytic	LBDD / SAR Optimization	Safety & In Vivo Lead. Selected for animal models due to superior safety profile (Non-hemolytic >1000

				depolarization and permeabilization.	*faecium* ATCC 51559 (VRE).	(HC50 >1000 µM).		µM (SI >3000)). *In vivo:* 12 mg/kg IV achieved >3-log reduction in bacterial load in neutropenic mouse thigh infection (MRSA), significantly outperforming Vancomycin (1-log reduction). No resistance observed after 52 passages.
	Compound 6	Lipophilic Vancomycin Analogue (Tetradecyl-QAC)	Cell Wall / Cell Membrane	Dual Mechanism: (i) Inhibition of cell wall biosynthesis; (ii) Rapid membrane disruption (Bactericidal).	*E. faecium* ATCC 51559 (VRE); *S. aureus* ATCC 33591 (MRSA); *S. aureus* (VISA).	MIC: 0.7 µM (VRE), 0.65 µM (MRSA), 0.36 µM (VISA). (Note: Vancomycin MIC for VRE is 750 µM).	LBDD / SAR Optimization	High-Potency Lead (VRE). The most potent analogue against Vancomycin-Resistant Enterococci (>1000-fold improvement over Vancomycin). Exhibits rapid bactericidal activity (>5 log10 reduction) via membrane depolarization, unlike the bacteriostatic action of Vancomycin.
Deslouches et al. (2013) [48]	WR12	Synthetic Amphipathic Peptide (Arg/Trp-rich eCAP)	Bacterial Cytoplasmic Membrane	(i) Electrostatic interaction with anionic lipids; (ii) Membrane permeabilization via amphipathic helical insertion; (iii) Rapid kinetic killing (>3-log reduction in <5 min).	*S. aureus* (MRSA USA300); *A. baumannii* (XDR Strain AB1); *P. aeruginosa* (MDR Strain TRPA108); *K. pneumoniae* (XDR Strain KP1).	MIC: 5 ± 3 µg/mL (MRSA USA300), 5 ± 3 µg/mL (*A. baumannii* AB1), 4 µg/mL (*P. aeruginosa* TRPA108), 27 ± 9 µg/mL (*K. pneumoniae* KP1).	LBDD / SAR Optimization	Optimized 12-residue sequence ("Goldilocks" length) retains potency in physiological saline (unlike WR10) and acidic pH (Cystic Fibrosis context). Displays superior SI (low hemolysis/PBMC toxicity) compared to longer variants (WR16).

Nagarajan et al. (2018) [49]	NN2_0018	Synthetic Cationic Peptide (LSTM-designed)	Cell Membrane (Anionic Lipids) / Respiratory Chain	(i) Electrostatic interaction and membrane rupture (pore formation); (ii) Functional inhibition of oxidative phosphorylation forcing Upregulation of anaerobic transport genes	*A. baumannii* (Carbapenem-R P1270); *E. coli* (Carbapenem-R P1645ec); *S. aureus* (MRSA).	MIC: 16 µg/mL (*A. baumannii* MTCC 9829), 16 µg/mL (*S. aureus* MTCC 3160), 32 µg/mL (*E. coli* K12). Efficacy: Significant reduction of peritoneal load (*A. baumannii* P1270) in mice (3.53×10^6 vs 1.98×10^8 CFU).	Machine Learning / De Novo Design (LSTM Language Model)	Sequence: YLARAIRR TLARLLL. The "Safe Lead": High SI with IC50 >128 µg/mL (HeLa/HaCaT) and no *in vivo* toxicity at 64 µg/g. Validates LSTM "grammar" approach for non-toxic AMP design.
	NN2_0050	Synthetic Cationic Peptide (LSTM-designed)	Cell Membrane	(i) Rapid membrane permeabilization; (ii) Induces massive cytoplasmic leakage and blebbing (SEM confirmed).	*E. coli* (K12 MG1655); *A. baumannii* (MTCC 9829); *K. pneumoniae* (MTCC 7407).	MIC: 4 µg/mL (*E. coli*), 4 µg/mL (*A. baumannii*), 32 µg/mL (*K. pneumoniae*), 128 µg/mL (*S. aureus*).	Machine Learning / De Novo Design (LSTM Language Model)	Sequence: SWKKFFKK ARSLPKLF. The "Toxic Lead": Superior potency against Gram-negatives compared to NN2_0018, but lacks specificity (IC50 <64 µg/mL against HeLa cells). Demonstrates critical trade-off between cationic charge density and mammalian toxicity.
Lohan et al. (2023) [50]	Peptide 8b	Amphipathic α-helical peptide (12-mer; Lys-rich)	Bacterial Cell Membrane (Anionic Phospholipid Bilayer)	(i) Electrostatic interaction with anionic headgroups; (ii) Helix formation and insertion into hydrophobic core; (iii) Membrane depolarization and pore formation (Calcein leakage).	*S. aureus* MRSA (ATCC BAA-1556); *E. coli* (ATCC 25922); *P. aeruginosa* (ATCC 27883); *K. pneumoniae* (Carbapenem-R; ATCC BAA-2470); *A.*	MIC: 3.1 µg/mL (MRSA); 6.2 µg/mL (*E. coli*); 6.2 µg/mL (*P. aeruginosa*); 12.5 µg/mL (*K. pneumoniae* NDM-1); 3.1 µg/mL (*A. baumannii*). HC50: 280 µg/mL (hRBCs).	SBDD	Lead candidate; Lys-substitution (vs Arg) reduced mammalian toxicity (HC50 280 vs 45 µg/mL) while maintaining potency; >75% viability in HEK-293 cells at 150 µg/mL; Rapid bactericidal kinetics (3h).

					baumannii (ATCC BAA-1605)			
	Peptide 8a	Amphipathic α-helical peptide (12-mer; Arg-rich)	Bacterial Membrane / Mammalian Membrane (Zwitterionic lipids)	(i) Non-selective membrane insertion; (ii) Strong hydrogen bonding with zwitterionic lipids (mammalian) via Arg residues; (iii) Loss of membrane integrity.	*S. aureus* MRSA (ATCC BAA-1556); *E. coli* (ATCC 25922); *P. aeruginosa* (ATCC 27883)	MIC: 6.2 µg/mL (MRSA); 12.5 µg/mL (*E. coli*); 12.5 µg/mL (*P. aeruginosa*). HC50: 45 µg/mL (hRBCs).	SBDD	Toxic comparator; Demonstrates "Arg-toxicity" principle; 6-fold higher hemolytic activity than 8b; High cytotoxicity against HEK-293 cells <30% viability at 250 µg/mL); Proves necessity of Lys for selectivity.
Xiang et al. (2022) [51]	PAX E35	*De novo* Amphipathic Peptide (16-residue; Trp/Arg-rich)	Bacterial Cell Membrane (Anionic Lipid Bilayer)	(i) Electrostatic attraction to surface; (ii) Hydrophobic insertion; (iii) Rapid, irreversible membrane permeabilization (<10 min).	*P. aeruginosa* PA239 (MDR/Colistin-R); *K. pneumoniae* KP125 (MDR); *K. pneumoniae* KP1041 (Colistin-R).	MBC/MIC: 2 µM (*P. aeruginosa* PA239), 2 µM (*K. pneumoniae* KP125), 2 µM (*K. pneumoniae* KP1041). MBC: 2 µM (*P. aeruginosa* PA239).	Peptidomimetics / Bio-inspired Design	Lead Candidate (Safety/Efficacy Balance). Shortest active sequence (16r) with optimized MOL. Negligible toxicity (RBC lysis <5% at 32 µM). *In vivo:* 5 mg/kg IV rescued 92% of mice from lethal sepsis; 4 mg/kg IV reduced lung burden by >3 log10.
	PAX E70	*De novo* Amphipathic Peptide (20-residue; Trp/Arg-rich)	Bacterial Cell Membrane	Membrane disruption (Overcoming Lipid A modifications).	*K. pneumoniae* KP1010 (Colistin-R); *K. pneumoniae* KP87 (Colistin-R); *K. pneumoniae* KP1045 (Colistin-R).	MIC: 1 µM (*K. pneumoniae* KP1010), 1 µM (*K. pneumoniae* KP87), 2 µM (*K. pneumoniae* KP1045). (Note: Colistin MICs for these strains are 16 to >16 µM).	Peptidomimetics / Bio-inspired Design	High-Potency Lead. 20-residue variant exhibiting superior potency against Colistin-resistant isolates compared to E35 (4-8x lower MIC). Maintains acceptable safety profile (<25% RBC lysis at 32 µM). Demonstrates ability to bypass resistance mechanisms involving

								lipid A charge modification.
Liao et al. (2024) [52]	Temporin-WY2	Cationic AMP (Natural)	Bacterial Membrane (Anionic Bilayer)	(i) Electrostatic attraction; (ii) Hydrophobic insertion; (iii) Membrane permeabilization.	*S. aureus* (MRSA BAA-1707); *E. faecalis* (NCTC 12697)	MIC: 2.89 µg/mL (MRSA); MBC: 11.56 µg/mL (*E. faecalis*); 2.89 µg/mL (ATCC 12493).	LBDD / SAR Optimization (for engineered analogs); Natural Product Discovery (The template was discovered, not designed)	Natural template isolated from *Amolops wuyiensis*. Displays narrow-spectrum activity (Gram-positive selective); ineffective against Gram-negatives (MIC >184.96 µg/mL vs *P. aeruginosa*) due to inability to penetrate LPS layer.
	QUB-1426	Cationic AMP (Engineered)	Bacterial Membrane Permeabilization	(i) Rapid random-coil to α-helix transition; (ii) Membrane rupture (SYTOX Green confirmed).	*S. aureus* (MRSA BAA-1707); *E. coli* (NCTC 8739); *K. pneumoniae* (ATCC 43816)	MIC: 2.85 µg/mL (MRSA); 5.7 µg/mL (*E. coli*); Kill Kinetics: 100% killing in 5 min (2×MIC).	LBDD / SAR Optimization (for engineered analogs); Bio-inspired Design (for the natural template).	Lead Compound. Rational design (Phe→Lys substitution; hydrophobic position swapping) achieved perfect amphipathicity. High (TI: 30.76); extremely safe against HaCaT cells (IC50: 162.8 µM). *In vivo:* 100% survival in *G. mellonella* model (12 mg/kg).
	6K-1426	Cationic AMP (Lysine-Cluster)	Bacterial Membrane / LPS	(i) "Anchor-and-Penetrate" via N-terminal cationic cluster; (ii) Instantaneous membrane permeabilization.	*E. coli* (NCTC 8739); *P. aeruginosa* (ATCC 9027); *K. pneumoniae* (ATCC 43816)	MIC: 4.39 µg/mL (*E. coli*); 17.56 µg/mL (*P. aeruginosa*); MBIC: 16-32 µM.	LBDD / SAR Optimization (for engineered analogs); Bio-inspired Design (for the natural template).	Toxicity Warning. Addition of N-terminal 6-lysine cluster significantly improved Gram-negative potency (via LPS charge exchange) but drastically increased mammalian cytotoxicity (HaCaT IC50: 1.178

								μM). Demonstrates that maximizing cationicity compromises safety (High Cytotoxicity (HaCaT IC50: 1.178 μM)).
Velkov et al. (2014) [58]	FADDI-002	Polymyxin Lipopeptide (Octanoyl/D-Phe/L-OctGly)	Lipid A (L-Ara4N modified)	(i) Hydrophobic insertion bypassing electrostatic repulsion; (ii) OM permeabilization.	*P. aeruginosa* (Colistin-resistant CI); *K. pneumoniae* (MDR); *A. baumannii* (MDR)	MIC: 2–8 mg/L (MDR CI); Efficacy: Burden: 4.75 ± 0.80 log CFU/lung reduction (Mouse model)	LBDD / SAR Optimization	Efficacy Lead: Demonstrated significant *in vivo* efficacy in neutropenic mouse lung model (Burden: 4.75 log CFU/lung vs 7.39 control). High plasma protein binding (>90%) and low clearance (0.66–1.30 mL/min/kg).
	FADDI-003	Polymyxin Lipopeptide (Biphenylacyl/D-Phe/L-OctGly)	Lipid A (L-Ara4N modified)	(i) Hydrophobic insertion bypassing electrostatic repulsion; (ii) OM permeabilization.	*P. aeruginosa* (Colistin-resistant CI); *K. pneumoniae* (MDR); *A. baumannii* (MDR)	MIC: 4 mg/L (Resistant *P. aeruginosa*); Time-Kill: ~6 log10 reduction at 4× MIC (2h).	LBDD / SAR Optimization	Safety Lead: Superior nephrotoxicity profile; mice treated with 105 mg/kg (accumulated) showed no significant histological lesions (Grade 0), whereas Polymyxin B caused mild tubular damage (Grade 1).
	FADDI-019	Polymyxin Lipopeptide (Octanoyl/D-OctGly/L-Leu)	Lipid A (L-Ara4N modified)	(i) Hydrophobic insertion bypassing electrostatic repulsion; (ii) OM permeabilization.	*P. aeruginosa* (Colistin-resistant CI); *K. pneumoniae* (MDR); *A. baumannii* (MDR)	MIC: 2–8 mg/L (MDR CI); MBC/MIC ratio: ≤4.	LBDD / SAR Optimization	Structural Variant: Demonstrates SAR flexibility at position R6 (D-OctGly). Exhibited mild tubular dilation (Grade < Polymyxin B) in histopathology, confirming reduced nephrotoxic potential compared to clinical standards.

Jahnsen et al. (2012) [59]	Compound 4	α-Peptide/ α-Peptoid Hybrid	Bacterial Cell Membrane (Anionic Lipid Bilayer)	Membrane permeabilization via induced amphiphilic conformation (non-receptor mediated).	*E. coli* NDM-1, *E. coli* CTX-M-15 (ESBL), *E. coli* CMY-2 (AmpC)	MIC: 2 μM (*E. coli* NDM-1), 4 μM (*E. coli* ATCC 25922), 8 μM (*E. coli* ESBL/AmpC)	Peptidomimetics / Bio-inspired Design	Lead candidate; alternating Lys/Phe-like hybrid backbone confers proteolytic stability and high selectivity (TI > 21) over HeLa cells (IC50: 100.9 μM) compared to pure peptoids.
	Compound 11	Homotypic β^3-Peptide Oligomer	Bacterial Cell Membrane	Membrane disruption facilitated by backbone flexibility	MRSA, *K. pneumoniae* KPC-2, *K. pneumoniae* NDM-1	MIC: 16 μM (MRSA), 32 μM (*K. pneumoniae* KPC-2/NDM-1), 32 μM (*E. coli* NDM-1)	Peptidomimetics / Bio-inspired Design	Demonstrates broad-spectrum activity including Gram-positives (MRSA) where hybrids failed; however, utility is limited by significant cytotoxicity (HeLa IC50: 31 μM) and hemolysis (HA10: 128 μM).
Song et al. (2025) [62]	5_Zn2	Zn(II)-Peptoid Conjugate (Mono-BPMP)	Anionic Phosphate Motifs (Lipid A/LPS, LTA)	(i) Zn-mediated phosphate recognition; (ii) Inner membrane permeabilization; (iii) LPS sequestration (Anti-inflammatory); (iv) NF-κB/MAPK pathway inhibition.	*E. coli* NMS 12 (Colistin-R/ESBL); *A. baumannii* NMS 1919 (Carbapenem-R); *S. aureus* (MRSA ATCC BAA-1556)	MIC: 6.3 µM (*E. coli* Col-R), 1.6 µM (*A. baumannii* Carb-R), 3.1 µM (MRSA). In Vivo: 50% survival at 48h (0.5 mg/kg, *E. coli* sepsis).	Peptidomimetics / Bio-inspired Design	Lead Candidate. Conjugation of Zn-dipicolylamine (BPMP) restores activity against Colistin-resistant strains. High (SI >15). Dual-action: kills bacteria and suppresses cytokine storm (TNF-α/IL-6) in sepsis model.
Wani et al. (2022) [63]	Amp1EP9	Isopeptide-modified AMP (Lysine-9 linkage)	Cytoplasmic Membrane	(i) Electrostatic surface accumulation; (ii) Rapid membrane permeabilization; (iii) Pore formation	*P. aeruginosa* (PAO1), *E. coli* (K12), *S. aureus* (ATCC 6538P), *B.*	MIC: 3.12 µM (*P. aeruginosa*), 3.12 µM (*E. coli*), 6.25 µM (*S. aureus*); Hemolysis: 0% at 80 µM (vs	Peptidomimetics / Bio-inspired Design	Lead Candidate. Site-specific isopeptide bond at Lys9 disrupts α-helicity, abolishing toxicity against hRBCs

				(confirmed by SYTOX-Green influx).	*subtilis* (ATCC 6051)	>90% for parent Amp1L).		and HEK293 cells while retaining bactericidal activity. Demonstrates high proteolytic stability in human plasma (>2h) where parent peptide degrades.
	Amp1EP2	Isopeptide-modified AMP (Lysine-2 linkage)	Cytoplasmic Membrane	Membrane disruption via helical insertion (Partial retention of α-helical structure compared to EP9).	*P. aeruginosa* (PAO1), *E. coli* (K12), *S. aureus* (ATCC 6538P), *B. subtilis* (ATCC 6051)	MIC: 1.56 µM (All tested strains); Toxicity: Reduced compared to parent, but higher than Amp1EP9.	Peptidomimetics / Bio-inspired Design	High Potency Analog. Modification at the N-terminus (Lys2) preserves more α-helical character than central modification, resulting in 2-4x higher potency than Amp1EP9 but lower selectivity (higher toxicity). Illustrates the structure-activity trade-off of helical content.
	Amp1EP10	Isopeptide-modified AMP (Lysine-10 linkage)	Cytoplasmic Membrane	Membrane permeabilization (Inferred from analog Amp1EP9)	*P. aeruginosa* (PAO1), *E. coli* (K12), *S. aureus* (ATCC 6538P), *B. subtilis* (ATCC 6051)	MIC: 3.12 µM (All tested strains); Cytotoxicity: Reduced RAW 264.7 viability by only 12% at 50 µM.	Peptidomimetics / Bio-inspired Design	Safety Profile Hit. Central placement of isopeptide bond (Lys10) mirrors the safety profile of Amp1EP9. Confirms that disrupting the continuous hydrophobic face of the helix via central isopeptide bonds is the key driver for reducing mammalian toxicity.
Magee et al. (2013) [66]	Compound 5x	Dap-3 Polymyxin Analogue	Lipid A (LPS) Phosphate Groups	(i) Electrostatic binding to Lipid A; (ii) Binding to Lipid A (General	*P. aeruginosa* PA-1646 (MDR, *pmrAB*	MIC: 4 µg/mL (PA-1646), 2 µg/mL (AB-1649); MBC: 8	LBDD / SAR Optimization	Replacement of Dab-3 with Dap-3 and a polar N-phenyl pyridone side chain eliminated *in*

		(Lipopeptide)		Class Mechanism); (iii) Membrane permeabilization.	mutant); *A. baumannii* AB-1649 (MDR)	µg/mL (PA-1646); Toxicity: h RPTEC TC50 >100 µM (vs 22 µM for PMB).		*vitro* renal cytotoxicity (TC50 >100 µM); however, the compound failed to demonstrate superior efficacy *in vivo* (murine thigh model) compared to Polymyxin B, highlighting a critical PK/PD disconnect.
	Compound 5m	Dap-3 Polymyxin Analogue (Lipopeptide)	Lipid A (LPS) Phosphate Groups	(i) Sequesters Lipid A; (ii) Competitively displaces; (iii) Membrane permeabilization.	*P. aeruginosa* PA-1646 (MDR, *pmrAB* mutant); *A. baumannii* AB-1649 (MDR)	MIC: 0.5 µg/mL (PA-1646), 1 µg/mL (AB-1649); Toxicity: h RPTEC TC50: 14 µM (High Cytotoxicity).	LBDD / SAR Optimization	Demonstrates the steep trade-off between potency and toxicity in the polymyxin class; this analogue was the most potent *in vitro* (MIC 0.5 µg/mL) but exhibited severe renal cytotoxicity (TC50 14 µM), confirming that high lipophilicity drives both bacterial killing and host nephrotoxicity.
	Compound 5u	Dap-3 Polymyxin Analogue (Lipopeptide)	Lipid A (LPS) Phosphate Groups	(i) Electrostatic binding to Lipid A; (ii) Displacement of divalent cations; (iii) Membrane permeabilization.	*A. baumannii* AB-1649 (MDR); *K. pneumoniae* KP-3700 (ESBL+); *P. aeruginosa* PA-1646	MIC: 1 µg/mL (AB-1649), 0.25 µg/mL (KP-3700), 4 µg/mL (PA-1646); Toxicity: h RPTEC TC50: 86 µM.	LBDD / SAR Optimization	Chloro-substitution on the distal ring resulted in a "Selective" profile; the compound retained high potency against MDR *A. baumannii* and *K. pneumoniae* with a favorable safety profile (TC50 86 µM), but lost significant potency against resistant *P. aeruginosa* (MIC 4 µg/mL).
	Compound 27	Ivacaftor-derived	Anionic Phosphol	(i) Membrane permeabilization	*S. aureus* ATCC 29213; *E.*	MIC: 0.78 µg/mL (*S. aureus*), 1.56	Peptidomimetics / Bio-	Lead candidate with optimal spacer length

		Peptidomimetic (Amphiphilic)	ipid Bilayer (Cytoplasmic) / LPS (OM)	(SYTOX Green/NPN uptake); (ii) Upregulation of cell envelope stress genes (*dltB, mprF, vraG*).	*coli* ATCC 25922; *P. aeruginosa* ATCC 9027; MRSA NCTC 10442	µg/mL (*E. coli*), 1.56 µg/mL (*P. aeruginosa*); Biofilm Inhibition: 99.61% (*S. aureus*).	inspired Design	($n = 4$); demonstrated rapid bactericidal kinetics (3.5-log reduction in 2h) and low resistance frequency. *In vivo*: Reduced bacterial load by 5.5 log in murine keratitis model with high safety index (CC_{50} ~62 µg/mL vs MIC 0.78).
Zhong et al. (2026) [68]	Compound 8	Ivacaftor-derived Peptidomimetic (Guanidine-modified)	Bacterial Lipid Bilayer (Non-selective)	Rapid electrostatic disruption of anionic lipid headgroups.	*S. aureus* ATCC 29213; *E. coli* ATCC 25922	MIC: 0.39 µg/mL (*S. aureus*), 0.78 µg/mL (*E. coli*); Toxicity: $CC_{50} < 10$ µg/mL (NCTC 929).	Peptidomimetics / Bio-inspired Design	Safety vs. Potency: This guanidine-substituted derivative was 2x more potent than the lead (Cpd 27) but exhibited high mammalian cytotoxicity ($CC_{50} < 10$ µg/mL), disqualifying it for systemic use despite superior antibacterial activity.
	Compound 29	Ivacaftor-derived Peptidomimetic (Long-spacer, $n = 8$)	Cytoplasmic Membrane (Gram-positive selective)	Selective disruption of cytoplasmic membrane; lacks OM translocation capability.	*S. aureus* ATCC 29213; *E. coli* ATCC 25922	MIC: 0.78 µg/mL (*S. aureus*), 25 µg/mL (*E. coli*).	Peptidomimetics / Bio-inspired Design	SAR Critical Finding: Extending the hydrophobic spacer to $n = 8$ maintained Gram-positive potency but caused a 32-fold loss of activity against Gram-negatives, confirming that shorter spacers ($n \leq 6$) are required for amphiphilic penetration of the OM.
Maset et al. (2022) [69]	g-D50	Peptidomimetic Guanidiniu	Bacterial Membran	(i) Electrostatic interaction with LPS causing	*S. aureus* (MRSA USA300,	MIC (Standard): 17.3 µM (*S. aureus*),	Peptidomimetics / Bio-	Safety Lead: Demonstrates "Paradox" activity

		m-Acrylamide Copolymer (Diblock)	es (Outer & Inner)	surface roughening/blebbing; (ii) Rapid dissipation of membrane potential (Depolarization); (iii) Lysis.	Newman); *P. aeruginosa* (LESB58)	8.7 µM (*P. aeruginosa* LESB58). MIC (Wound Fluid): 4.3 µM (*S. aureus* Newman), 8.7 µM (*S. aureus* USA300).	inspired Design	where potency against *S. aureus* increases 4-fold in SWF. Non-hemolytic and non-toxic to *G. mellonella* larvae (Survival >1024 µg/mL).
	a-T100-1	Peptidomimetic Ammonium-Acrylamide Copolymer (Triblock)	Bacterial Membranes (Outer & Inner)	(i) Hydrophobicity-driven membrane permeabilization; (ii) Aggressive depolarization; (iii) Induction of mass-fractal aggregation.	*P. aeruginosa* (PA14, LESB58); *S. aureus* (Newman)	MIC (Standard): 9.7 µM (*P. aeruginosa* PA14), 9.7 µM (*P. aeruginosa* LESB58). MIC (CF Sputum): 4.8 µM (PA14) and 9.7 µM (LESB58).	Peptidomimetics / Bio-inspired Design	High Compatibility: Maintains potent activity against *P. aeruginosa* even in host-mimicking sputum (SCFM). Unlike guanidinium analogs, the ammonium moiety is non-toxic to *G. mellonella* larvae and 3T3 cell lines at all tested concentrations.
Krucinska et al. (2022) [73]	UCP1228	Propargyl-Linked Antifolate (PLA)	DHFR [Isoforms: EcDHFR, DfrA1, DfrA5]	(i) Competitive inhibition at folate binding pocket; (ii) Stabilizes ternary complex (Enzyme:NADPH:Inhibitor); (iii) Overcomes D27E/L28Q resistance mutations via flexible linker.	*Escherichia coli* (MDR DfrA1/DfrA5 producers)	Ki: 2.73 nM (EcDHFR), 30.06 nM (DfrA1), 20.08 nM (DfrA5). MIC: 10 µg/mL (*E. coli* BW25113 WT), 0.625 µg/mL (*E. coli* JW0451 Δ acrB). Synergy: MIC 0.625 µg/mL (w/ Sulfamethoxazole).	SBDD; LBDD / SAR Optimization	Crystal structures (PDB 7MQP, 7REG, 7RGO) confirm binding mode mimics the 'occluded' conformation. High efflux liability observed (16-fold MIC improvement in Δ acrB mutant).
	UCP1223	Propargyl-Linked	DHFR [Isoforms:	(i) Competitive inhibition at folate binding pocket; (ii)	*Escherichia coli* (MDR	Ki: 1.58 nM (EcDHFR), 20.33 nM (DfrA1), 16.76	SBDD; LBDD / SAR Optimization	Slightly higher enzymatic potency against DfrA5 than

		Antifolate (PLA)	EcDHFR, DfrA1, DfrA5]	Restores NADPH-ligand cooperativity lost in TMP-resistant isoforms.	DfrA1/DfrA5 producers)	nM (DfrA5). MIC: 20 μg/mL (*E. coli* BW25113 WT), 1.25 μg/mL (*E. coli* JW0451 Δ acrB).		UCP1228, but lower cellular efficacy (MIC 20 μg/mL) due to poor membrane permeation/efflux.
Frey et al. (2012) [74]	Propargyl-linked antifolate 1	Pyridyl-linked Propargyl Antifolate	DHFR [Active site: Phe98/His30]	Competitive inhibition of NADPH-dependent reduction; Evasion of MDR efflux pumps	*S. aureus* ATCC 44300 (MRSA Progenitor); *S. aureus* (F98I mutant)	MIC: 0.078 μg/mL (Wild-type); MIC: 2.5 μg/mL (F98I mutant); MPC: 1.25 μg/mL; K_i: 0.0028 μM	SBDD	Unlike biphenyl analogs, the pyridyl ring prevents recognition by efflux pumps; Retains activity (MIC 2.5 μg/mL) against F98I (32-fold potency loss).
	Propargyl-linked antifolate 2	Meta-biphenyl Propargyl Antifolate	DHFR	Competitive inhibition of DHFR; Substrate for MDR efflux pumps	*S. aureus* ATCC 44300; *S. aureus* (H30N mutant); *S. aureus* (F98 strain)	MIC: 1.25 μg/mL (Wild-type); MIC: 20 μg/mL (H30N mutant); MIC (+Thioridazine): 2.5 μg/mL	SBDD	Demonstrates SAR liability: hydrophobic biphenyl moiety triggers efflux-mediated resistance (8-fold MIC reduction with EPIs)
Wang et al. (2020) [77]	Compound 3	Bis-cyclic Imidazolidine-4-one	Anionic Phospholipids (Negatively charged phospholipids)	(i) Recruits to anionic surface via electrostatic attraction; (ii) Depolarizes cytoplasmic membrane; (iii) Disintegrates lipid bilayer integrity.	MRSA (ATCC 33591); MRSE (RP62A); *E. coli* (ATCC 25922); *K. pneumoniae* (ATCC 13383)	MIC: 2 $\mu g/mL$ (MRSA), 5 $\mu g/mL$ (MRSE/*E. coli*/*K.pneumoniae*); MBC: 24 μg/mL (MRSA), 12 μg/mL (*E. coli*).	Peptidomimetics / Bio-inspired Design	Lead candidate with SI > 125 (MRSA) and HC50 > 250 $\mu g/mL$; demonstrates "Minimum Propensity" for resistance (MIC unchanged after 13 passages).
	Compound 4	Bis-cyclic Imidazolidine-4-one	Anionic Phospholipids (PG/CL)	(i) Inserts hydrophobic C12 tail into lipid bilayer; (ii) Disrupts membrane structural integrity.	*S. aureus* MRSA (ATCC 33591); *S. epidermidis* MRSE (RP62A); *E. coli* (ATCC 25922)	MIC: 1 μg/mL (MRSA), 2 μg/mL (MRSE), >25 μg/mL (*E. coli*).	Peptidomimetics / Bio-inspired Design	Gram-positive specialist; extending the alkyl tail to C12 increases potency against MRSA but abolishes Gram-negative activity due to OM permeability barriers.

	Compound 12	Bis-cyclic Imidazolidine-4-one	Anionic Phospholipids (Negatively charged phospholipids)	(i) Electrostatic attraction; (ii) Inferred from Lead Cmpd 3.	*S. aureus* MRSA (ATCC 33591); *K. pneumoniae* (ATCC 13383)	MIC: 1 µg/mL (MRSA), 5 µg/mL (*K. pneumoniae*), >25 µg/mL (*E. coli*).	Peptidomimetics / Bio-inspired Design	Toxicity trade-off; guanidine substitution maintains potency but increases hemolytic risk (HC50: 125 $\mu g/mL$), reducing the therapeutic window compared to amine 3.

Abbreviations:

Metrics & Pharmacokinetics: MIC: Minimum Inhibitory Concentration; **MBC**: Minimum Bactericidal Concentration; **MBIC**: Minimum Biofilm Inhibitory Concentration; **ATCC:** American Type Culture Collection; **IBX:** Iboxamycin; **GTP:** Guanosine triphosphate; **USA**: United States Agent**; PRSA:** Penicillin-Resistant *Staphylococcus aureus;* **NCTC:** National Collection of Type Cultures*;* **BAA:** Biological Agents and Allergens*;* **IC50**: Half-maximal Inhibitory Concentration; **CC_{50}/HC_{50}/TC_{50}**: Cytotoxic/Hemolytic/Toxic Concentration 50%; **GI_{50}**: Growth Inhibition 50%; **ED_{50}**: Effective Dose 50%; **Ki**: Inhibitory Constant; **FICI**: Fractional Inhibitory Concentration Index; **MPC**: Mutant Prevention Concentration; **ZOI**: Zone of Inhibition; **CFU**: Colony Forming Units; **TI/SI**: Therapeutic Index / Selectivity Index; **SAR**: Structure-Activity Relationship; **$T_{1/2}$**: Half-life; **Cl**: Clearance; **F**: Bioavailability; **TPSA**: Topological Polar Surface Area; **IV**: Intravenous; **ADMET**: Absorption, Distribution, Metabolism, Excretion, and Toxicity; **FOR**: Frequency of Resistance; **PK**: Pharmacokinetics; **HA10**: Hemolytic Activity at 10%; **MOL**: Minimum Optimal Length; **QT**: QT Interval; **SWF**: Synthetic Wound Fluid; **SCFM**: Synthetic Cystic Fibrosis Sputum Medium.

Methods & Computational: SBDD: Structure-Based Drug Design; **LBDD**: Ligand-Based Drug Design; **MD**: Molecular Dynamics; **LSTM**: Long Short-Term Memory; **RNN**: Recurrent Neural Network; **QTAIM**: Quantum Theory of Atoms in Molecules; **PDB**: Protein Data Bank; **SEM**: Scanning Electron Microscopy; **VS**: Virtual Screening; **MM-GBSA**: Molecular Mechanics-Generalized Born Surface Area; **NMR**: Nuclear Magnetic Resonance; **PROB**: Probability Score; **ZINC**: ZINC Database.

Targets & Mechanisms: FtsZ: Filamenting temperature-sensitive mutant Z; **GyrB**: DNA Gyrase subunit B; **ParE**: Topoisomerase IV subunit; **LpxC**: UDP-3-O-acyl-N-acetylglucosamine deacetylase; **DHFR**: Dihydrofolate Reductase; **FabI**: Enoyl-ACP reductase; **Asd**: Aspartate-semialdehyde dehydrogenase; **TrpG**: Anthranilate synthase component II; **LPS**: Lipopolysaccharide; **LTA**: Lipoteichoic Acid; **AcrB/TolC**: Efflux system components; **ATP**: Adenosine Triphosphate; **AMP**: Antimicrobial Peptide; **eCAP**: Engineered Cationic Antimicrobial Peptide; **PMB**: Polymyxin B; **PLA**: Propargyl-Linked Antifolate; **QAC**: Quaternary Ammonium Compound; **MMP**: Matrix Metalloproteinase; **HDAC**: Histone Deacetylase; **NPET**: Nascent Peptide Exit Tunnel; **PTC**: Peptidyl Transferase Center; **NADPH**: Nicotinamide Adenine Dinucleotide Phosphate; **PG**: Phosphatidylglycerol; **CL**: Cardiolipin; **DNA**: Deoxyribonucleic Acid; **RNA**: Ribonucleic Acid; **rRNA**: Ribosomal RNA; **BPMP**: Bis-picolylamine; **NF-κB**: Nuclear Factor kappa B; **MAPK**: Mitogen-Activated Protein Kinase; **TCM**: Traditional Chinese Medicine; **UDP**: Uridine Diphosphate; **NPN**: N-Phenyl-1-naphthylamine; **OM**: Outer Membrane.

Organisms, Cell Lines & Resistance Phenotypes: MDR: Multidrug-Resistant; **XDR**: Extensively Drug-Resistant; **WT**: Wild Type; **CI**: Clinical Isolate; **MRSA**: Methicillin-Resistant *Staphylococcus aureus*; **VRSA**: Vancomycin-Resistant *S. aureus*; **VISA**: Vancomycin-Intermediate *S. aureus*; **LRSA**: Linezolid-Resistant *S. aureus*; **MRSE**: Methicillin-Resistant *Staphylococcus epidermidis*; **VRE**: Vancomycin-Resistant *Enterococcus*; **PRSP**: Penicillin-Resistant *Streptococcus pneumoniae*; **RR-TB**: Rifampicin-Resistant Tuberculosis; **ESBL**: Extended-Spectrum β-Lactamase; **KPC**: *Klebsiella pneumoniae* Carbapenemase; **NDM**: New Delhi Metallo-β-lactamase; **MCR-1**: Plasmid-mediated Colistin Resistance; **CF**: Cystic Fibrosis; **PBMC**: Peripheral Blood

Mononuclear Cells; **hRBC**: Human Red Blood Cells; **hRPTEC**: Human Renal Proximal Tubule Epithelial Cells; **HeLa**: Henrietta Lacks (Cervical Cancer Cells); **HepG2**: Human Liver Cancer Cells; **HaCaT**: Human Keratinocytes; **HEK-293**: Human Embryonic Kidney Cells; **A549**: Adenocarcinomic Human Alveolar Basal Epithelial Cells; **RAW 264.7**: Murine Macrophage Cells; **G. mellonella**: *Galleria mellonella*.