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NOVLTEX: A New Class of Antibiotics with Potent Activity against Multidrug-Resistant Bacterial Pathogens

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1 THE PROBLEM

Antimicrobial resistance (AMR) **is one of the defining health threats of our time**. Resistance keeps rising while the discovery of **new classes of antibiotics has all but stopped,** and the burden falls hardest on low and middle income countries.





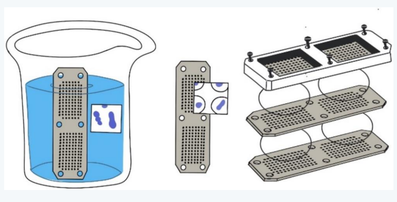
≈5 M
deaths associated with bacterial AMR worldwide (2019)

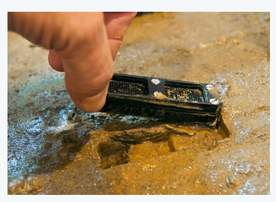
2
WHO-priority Gram-positive targets: MRSA and *E. faecium*

LMICs
carry a disproportionate share of the AMR burden

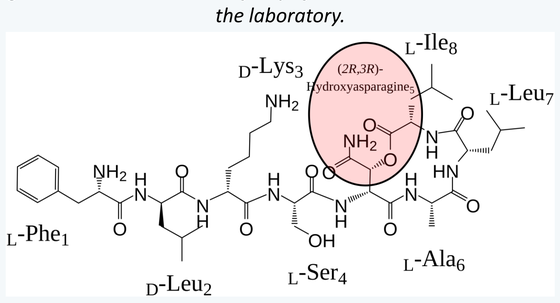
2 THE STARTING POINT: NOVO29

Clovibactin (Novo29):
A groundbreaking discovery of a highly effective Novel Antibiotic with lower risk of Bacterial Resistance





The iChip gives access to the vast majority of soil bacteria that cannot be grown in the laboratory.

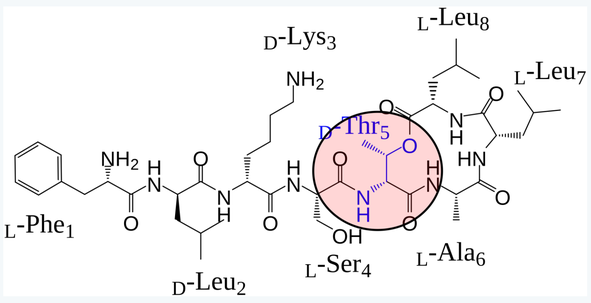


Novo29 / clovibactin: the unnatural D-hydroxy-asparagine$_5$ (D-Hyn$_5$, circled) links macrocycle and tail.

- ✕ Overall synthetic yield of only ≈1 %
- ✕ D-Hyn$_5$ is not commercially available
- ✕ Long, multistep and repetitive coupling route

3 THE DESIGN: NOVLTEX

Novltex fuses the **Leu^{10}-teixobactin macrocycle** to the **Novo29 N-terminal tail**, replacing the costly D-Hyn$_5$ with inexpensive, commercially available threonine.



Novltex analogue 4 — D-Hyn$_5$ replaced by D-Thr$_5$ (circled).

- ✓ D-Hyn$_5$ is not essential for antibacterial activity
- ✓ Rapid, simple and inexpensive synthesis
- ✓ High-yielding and ready for low-cost scale-up

4 SYNTHESIS

Fmoc-SPPS on 2-chlorotrityl resin: DIC/DMAP esterification, orthogonal Alloc/Trt protection, microwave DIC–Oxyma couplings and on-resin HATU cyclisation, **with a single purification after final cleavage.**

30 %
isolated yield, vs ≈1 % for Novo29

10 min
microwave coupling cycles

> 95 %
purity by HPLC

16
analogues in the library

5 STEREOCHEMISTRY DRIVES ACTIVITY

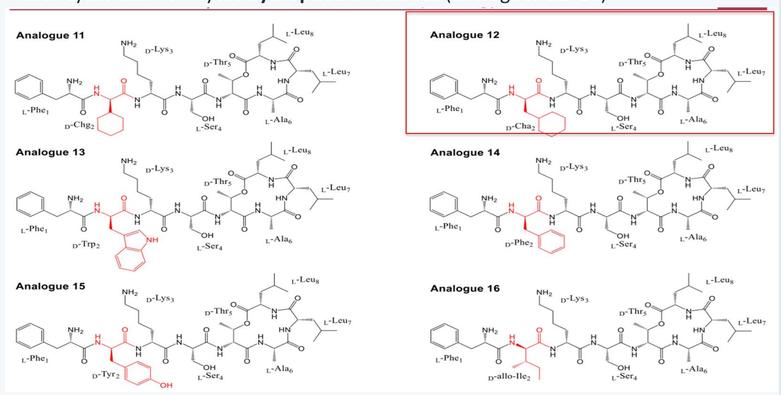
A systematic configuration scan of the tail and the macrocycle (analogues 1–10) against MRSA ATCC 33591:

#	Phe$_1$	Leu$_2$	Lys$_3$	Ser$_4$	Thr$_5$	Ala$_6$	Leu$_7$	Leu$_8$	MIC (µg/mL)
1	L	D	D	L	L	L	D	L	8
2	L	D	D	L	D	L	D	L	32
3	D	L	L	D	D	L	L	L	32
4	**L**	**D**	**D**	**L**	**D**	**L**	**L**	**L**	**2–4**
5	D	L	D	L	D	L	L	L	> 32
6	L	D	L	D	D	L	L	L	> 32
7	D	D	L	L	D	L	L	L	32
8	L	L	L	L	D	L	L	L	> 32
9	D	D	D	D	D	L	L	L	16
10	L	D	D	L	D	L	L	L[a]	8
Vancomycin	–	–	–	–	–	–	–	–	0.5–1

Analogue 4 (L$_1$DDL$_4$ tail + Leu^{10}-teixobactin macrocycle) is the initial lead — MIC 2–4 µg/mL, comparable to vancomycin. [a] Analogue 10 carries L-Ile$_8$.

6 POSITION-2 SCAN → THE HIT

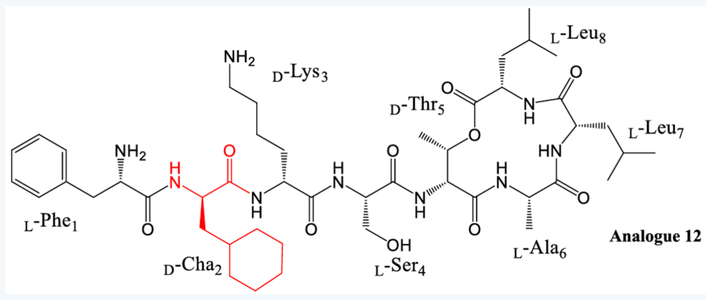
The Leu$_2$ side chain contacts the bacterial membrane, so position 2 was replaced with cyclic and non-cyclic **hydrophobic residues** (analogues 11–16).



Analogues 11–16 — built on the configuration of analogue 4; the residue replacing Leu$_2$ is red.

#	Residue at position 2	MIC vs MRSA (µg/mL)
11	D-Cyclohexylglycine (Chg)	8
12	**D-Cyclohexylalanine (Cha)**	**0.25**
13	D-Tryptophan (Trp)	> 32
14	D-Phenylalanine (Phe)	8
15	D-Tyrosine (Tyr)	> 32
16	D-allo-Isoleucine	16

Analogue 12 (D-Cha$_2$): MIC 0.25 µg/mL — 16× more potent than analogue 4 and 32× more potent than the one-carbon-shorter Chg analogue 11. Bulky, polar or aromatic side chains are not tolerated.



Novltex analogue 12 — the lead compound.

7 POTENT AGAINST MDR ISOLATES

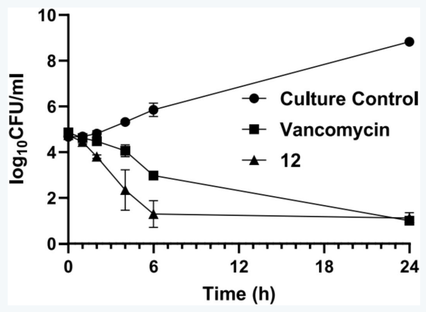
Analogue 12 was tested against MDR clinical isolates of *S. aureus* (NARSA) and *E. faecium* (IHMA), alongside licensed antibiotics and synthetic clovibactin.

MIC (µg/mL)	*Staphylococcus aureus*				*Enterococcus faecium*		
	NR 45914	NR 45926	NR 45930	NR 46062	1581582	1766686	1563254
Analogue 12	**0.125**	**0.125**	**0.125**	**0.063**	**0.5**	**0.125**	**0.25**
Clovibactin	0.063	0.063	0.25	0.063	0.25	0.25	0.063
Vancomycin	1	0.5	1	2	> 32	> 32	> 32
Linezolid	2	32	4	16	1	1	16
Cefotaxime	4	16	8	16	> 32	> 32	> 32
Levofloxacin	1	4	> 32	32	32	32	32
Ampicillin	2	32	8	8	> 32	> 32	> 32
Daptomycin	2	4	2	2	> 32	> 32	> 32

≤ 1 potent 2–4 moderate ≥ 8 poor

Analogue 12 matches clovibactin and outperforms vancomycin, linezolid, cefotaxime, levofloxacin, ampicillin and daptomycin across both WHO-priority species.

8 RAPID KILLING — NO RESISTANCE



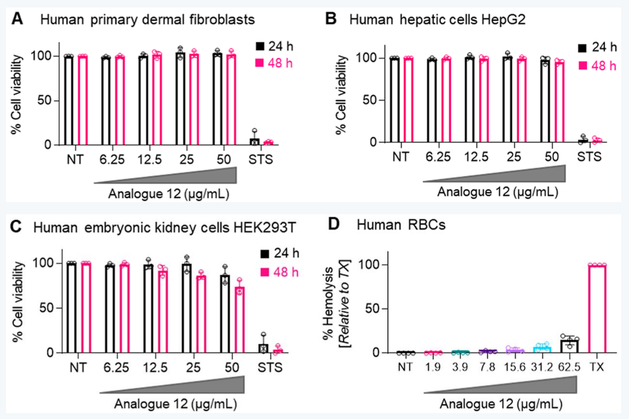
Time-kill kinetics of analogue 12 and vancomycin against MRSA ATCC 33591 (mean ± SD of two independent experiments in duplicate).

At 2.5 µg/mL (10× MIC), analogue 12 produced **significant killing of MRSA within 6 h**; vancomycin needed 24 h at twice that concentration.

- ✓ No resistant MRSA mutants after 24 h at 10× MIC

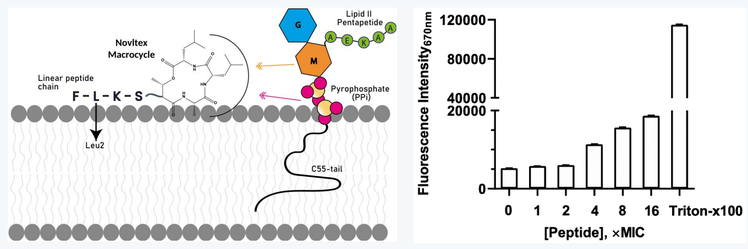
9 EXCELLENT SAFETY PROFILE

No major cytotoxicity up to 50 µg/mL at 24 and 48 h — **≈100× the average MIC** — in human primary dermal fibroblasts, HepG2 and HEK293T cells, and no detectable haemolysis up to 31.2 µg/mL (> 60× MIC).



Viability of human cells (MTS assay) and haemolysis of human red blood cells after exposure to analogue 12. NT = no treatment, STS = staurosporine, TX = Triton X-100.

10 MECHANISM RETAINED



Left: Novltex macrocycle binding the pyrophosphate of lipid II. Right: DiSC$_3$(5) fluorescence rises with analogue 12 — membrane depolarisation of intact MRSA.

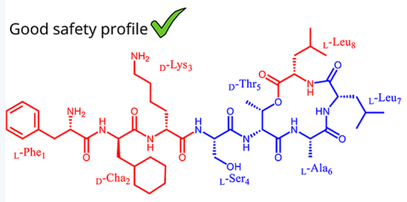
- ✓ Lipid II abolishes activity in spot-on-lawn assays
- ✓ Cytoplasmic membrane depolarisation, pronounced at 4× MIC

11 CONCLUSIONS • OUTLOOK • REFERENCES

- Novltex is a new hybrid antibiotic class, potent, inexpensive to make and scalable.
- Analogue 12 reaches MIC 0.063–0.5 µg/mL against MDR MRSA and *E. faecium*, surpassing several licensed antibiotics.
- It kills rapidly, selects no resistance *in vitro*, and spares human cells.
- The parent lipid II mechanism is fully preserved.

The lead at a glance

Potent activity: ✓
MRSA & *Enterococcus faecium* (MIC: 0.063 - 0.5 µg/mL)
Good safety profile ✓



High yielding novel synthesis 30% ✓

What's next — towards the clinic



References

1. Malkawi E, Parmar A, Das S, et al. J Med Chem 2025;68:19143–52.
2. IHME Pathogen Core Group. Lancet Infect Dis 2024;24(8):868–95.
3. Butler MS, et al. Antimicrob Agents Chemother 2022;66(3):e01991-21.
4. Iyer A, Madder A, Singh I. Future Microbiol 2019;14(6):457–60.
5. Shukla R, et al. Cell 2023;186(19):4059–73.
6. Parmar A, et al. Chem Sci 2017;8(12):8183–92.
7. Dallas H, et al. US Patent 11,203,616 B2, 2020.

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