

# Activity of NZ2114 against Staphylococcal and Streptococcal Isolates, Including Resistant Phenotypes

M.K. TORRES<sup>1</sup>, D.C. DRAGHI<sup>1</sup>, C.M. PILLAR<sup>1</sup>, N.P. BROWN<sup>1</sup>, V. ALLURU<sup>1</sup>, D.F. SAHM<sup>1</sup>, D. SANDVANG<sup>2</sup>, & H-H. KRISTENSEN<sup>2</sup>

<sup>1</sup>Eurofins Medinet, Chantilly, Virginia, USA, <sup>2</sup>Novozymes A/S, Bagsvaerd, Denmark

Contact information:  
HaHK@novozymes.com  
Phone: +45 44461823  
Mobile: +45 30771823

## Revised Abstract

**Background:** NZ2114 is a plectasin variant active against Gram-positive cocci currently being developed for the potential treatment of sepsis, upper respiratory infections, skin and soft tissue infections, pneumonia, and tonsillitis. Staphylococci and streptococci are major pathogens of these types of infections. The activity of NZ2114 was evaluated against these organisms, including isolates with clinically relevant resistance.

**Methods:** Clinical isolates including 134 *Staphylococcus aureus* (SA), 50 coagulase-negative staphylococci (CoNS), 50 *Streptococcus pneumoniae* (SP), 51 Group C and G streptococci (GCG), 45 *S. agalactiae* (SAG), and 47 *S. pyogenes* (SPY) were centrally tested by broth microdilution (CLSI M7-A7) against NZ2114 and comparators. Isolates resistant (R) or non-susceptible (NS) to oxacillin (OX), penicillin (PEN), or a macrolide (MAC) were included. Twenty-nine additional SA NS to vancomycin (VAN), linezolid (LZD), and/or daptomycin (DAP) from the NARSA (Network on Antimicrobial Resistance in *Staphylococcus aureus*) repository and isolates from the Eurofins repository were tested and analyzed.

Organism	Phenotype	Total n	MIC ( $\mu\text{g/mL}$ )			
			Range	Mode	MIC <sub>50</sub>	MIC <sub>90</sub>
SA	OX S	28	0.5-4	2	2	4
	OX R	106	0.12-32	2	2	4
	DAP NS	8	1-8	2	NA	NA
	LZD NS	13	1-8	2	2	4
	VISA	9	4-64	16	NA	NA
	VRSA	2	2-4	NA	NA	NA
CoNS	OX S	20	0.12-16	2	2	4
	OX R	30	0.06-16	2	2	4
SP	PEN S	25	$\leq 0.03$ -4	1	1	4
	PEN I	10	0.06-2	1	1	2
	PEN R	15	0.06-4	1	1	2
	MAC S	34	0.06-8	0.5	1	4
SAG	MAC NS	17	0.25-8	1	1	8
	MAC S	19	0.12-1	0.25	0.25	0.5
SPY	MAC NS	26	$\leq 0.03$ -1	0.25	0.25	0.5
	MAC S	19	$\leq 0.03$ -8	0.25	0.25	0.25
	MAC NS	28	$\leq 0.03$ -4	0.12	0.12	0.5

NA=not applicable

**Conclusions:** NZ2114 displayed potent *in vitro* activity against both staphylococci and streptococci. Based on MIC<sub>50</sub>/MIC<sub>90</sub>, NZ2114 had similar activity (within one doubling dilution) against OX-R staphylococci and PEN-R/MAC-NS streptococci populations relative to susceptible populations. Activity was also apparent against LZD/DAP/VAN-NS populations of SA, though NZ2114 MICs tended to be slightly higher against the evaluated VISA. This activity profile highlights the potential of NZ2114 for infections where STR and STA are commonly encountered.

## Introduction

NZ2114 is a derivative of plectasin, a novel class of antimicrobials, active against Gram-positive cocci. It has a novel mechanism of action making it active against isolates resistant to currently available therapeutics. NZ2114 is currently being developed for the potential treatment of sepsis, upper respiratory infections, skin and soft tissue infections, pneumonia, and tonsillitis. Staphylococci and streptococci are major pathogens of these types of infections. The activity of NZ2114 was evaluated against these organisms, including isolates with clinically relevant resistance.

## Methods

Clinical isolates including 134 *Staphylococcus aureus*, 50 coagulase-negative staphylococci (CoNS), 50 *Streptococcus pneumoniae*, 51 Group C and G streptococci, 45 *Streptococcus agalactiae*, and 47 *Streptococcus pyogenes* were obtained from Eurofins Medinet's repository and centrally tested by broth microdilution (CLSI M7-A7) against NZ2114 and comparators. Isolates resistant or non-susceptible to oxacillin (OX), penicillin (PEN), or a macrolide (MAC) were included. Twenty-nine additional *S. aureus* non-susceptible to vancomycin (VAN), linezolid (LZD), and/or daptomycin (DAP) contributed from the NARSA (Network on Antimicrobial Resistance in *Staphylococcus aureus*) repository and isolates from the Eurofins Medinet repository were tested and analyzed.

## Results

Table 1. Activity of NZ2114 against staphylococci

Organism	Phenotype <sup>a</sup>	Total n	MIC ( $\mu\text{g/mL}$ )			
			Range	Mode	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>S. aureus</i>	OX S	28	0.5-4	2	2	4
	OX R	106	0.12-32	2	2	4
	DAP NS <sup>c</sup>	8	1-8	NA <sup>b</sup>	NA	NA
	LZD NS	13	1-8	2	2	4
	VISA	9	4-64	NA	NA	NA
	VRSA	2	2-4	NA	NA	NA
Coagulase-negative staphylococci	OX S	20	0.12-16	2	2	4
	OX R	30	0.06-16	2	2	4

<sup>a</sup>OX=oxacillin; S=susceptible; R=resistant; DAP=daptomycin; LZD=linezolid; NS=non-susceptible; VISA=vancomycin intermediate *Staphylococcus aureus*; VRSA=vancomycin resistant *S. aureus*

<sup>b</sup>NA=not applicable for <10 isolates

<sup>c</sup>3 isolates that were DAP NS were concurrently LZD NS

Table 2. Activity of NZ2114 against streptococci

Organism	Phenotype <sup>a</sup>	Total n	MIC ( $\mu\text{g/mL}$ )			
			Range	Mode	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>S. pneumoniae</i>	PEN S	25	$\leq 0.03$ -4	1	1	4
	PEN I	10	0.06-2	1	1	2
	PEN R	15	0.06-4	1	1	2
Group C & G streptococci	MAC S	34	0.06-8	0.5	1	4
	MAC NS	17	0.25-8	1	1	8
<i>S. agalactiae</i>	MAC S	19	0.12-1	0.25	0.25	1
	MAC NS	26	$\leq 0.03$ -1	0.25	0.25	0.5
<i>S. pyogenes</i>	MAC S	19	$\leq 0.03$ -8	0.25	0.25	0.25
	MAC NS	28	$\leq 0.03$ -4	0.12	0.12	0.5

<sup>a</sup>PEN=penicillin; MAC=macrolide (erythromycin and/or azithromycin); S=susceptible; I=Intermediate; R=resistant; NS=non-susceptible

Figure 1. MIC distribution of NZ2114 against *S. aureus*

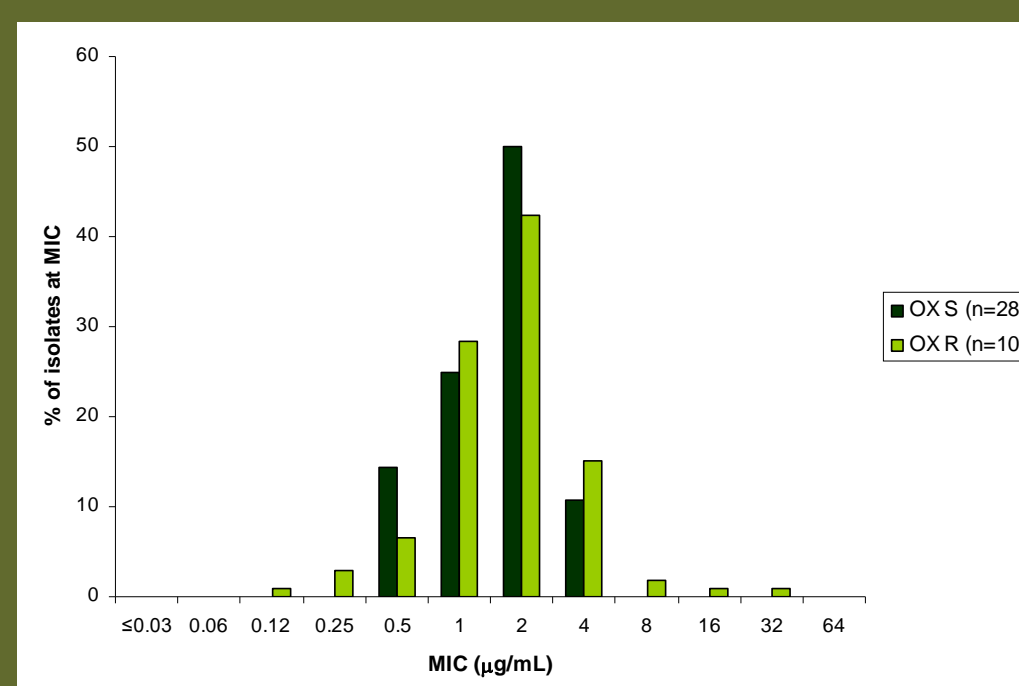


Figure 2. MIC distribution of NZ2114 against *S. aureus* of specific non-susceptible phenotypes

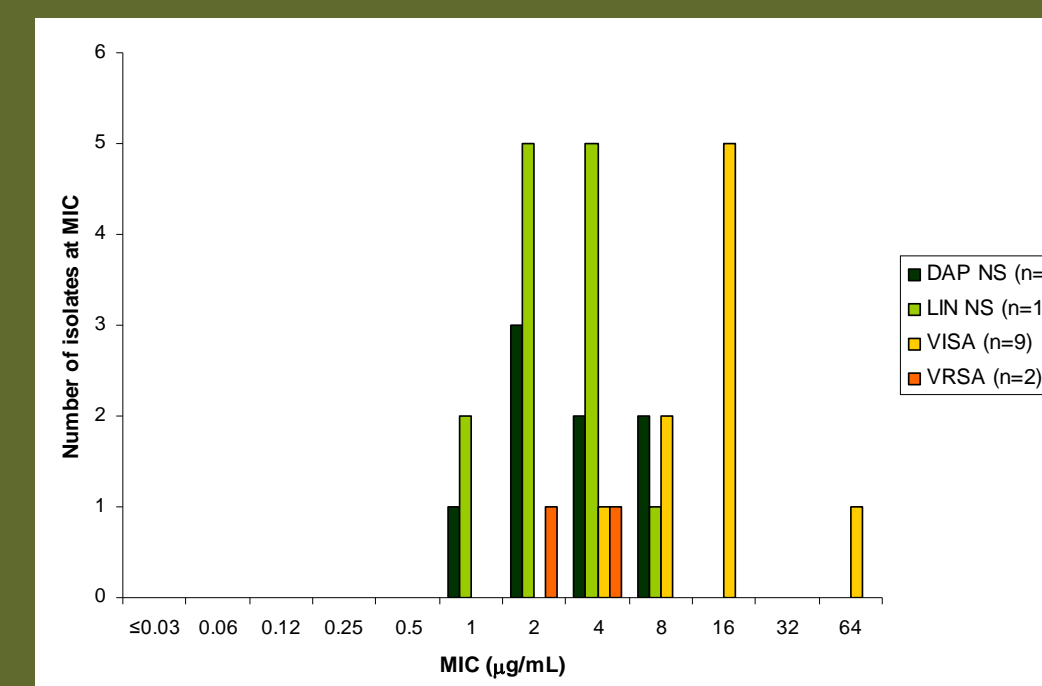


Figure 3. MIC distribution of NZ2114 against CoNS

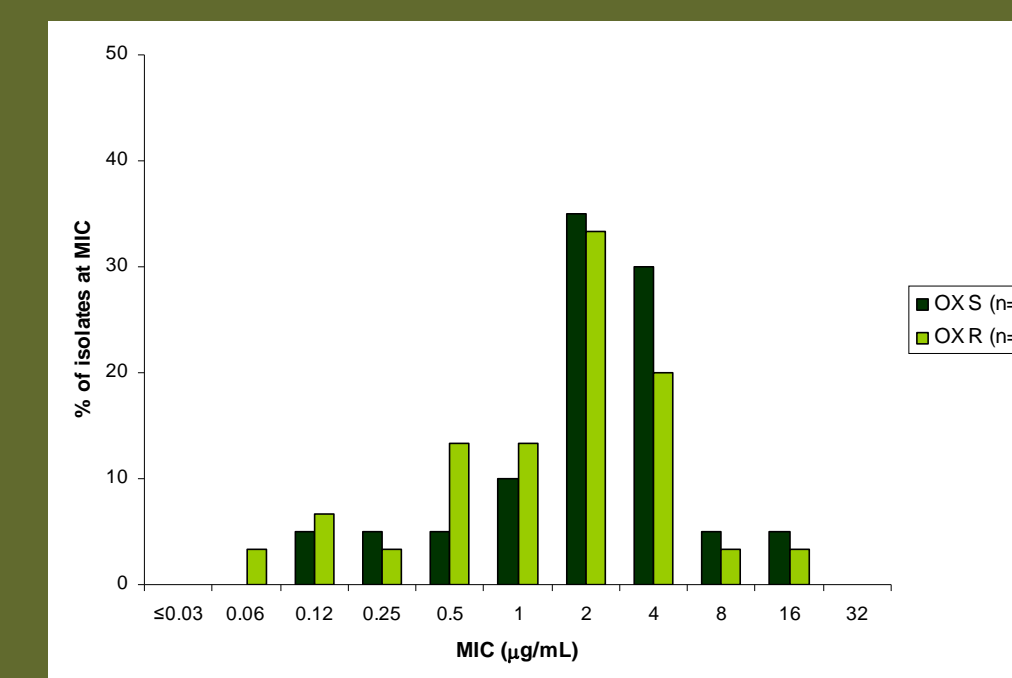


Figure 4. MIC distribution of NZ2114 against *S. pneumoniae*

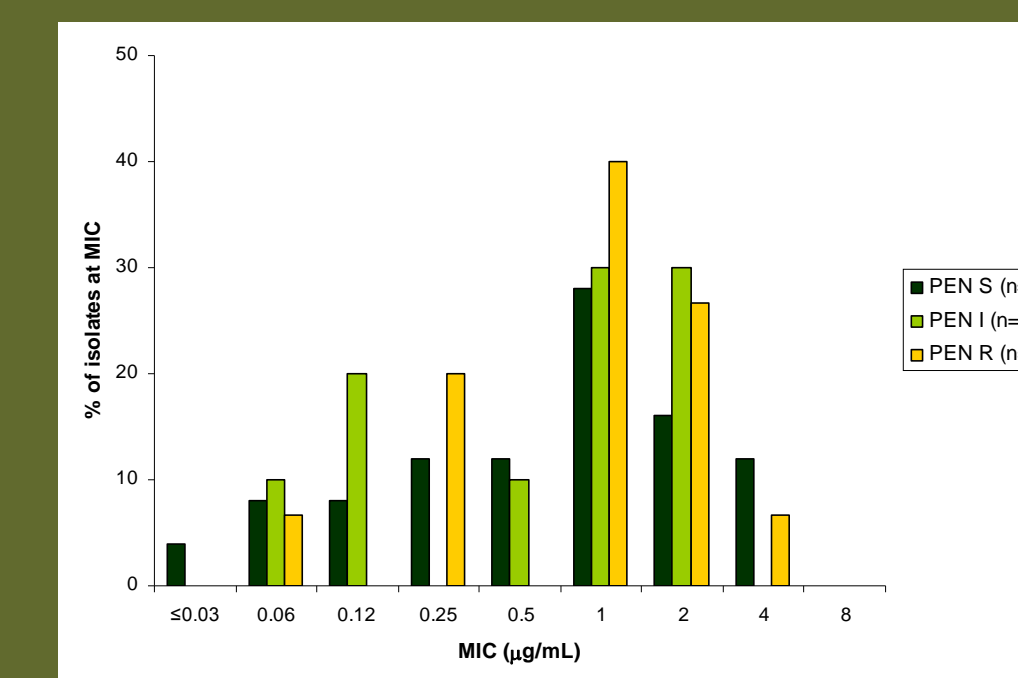


Figure 5. MIC distribution of NZ2114 against Group C & G streptococci

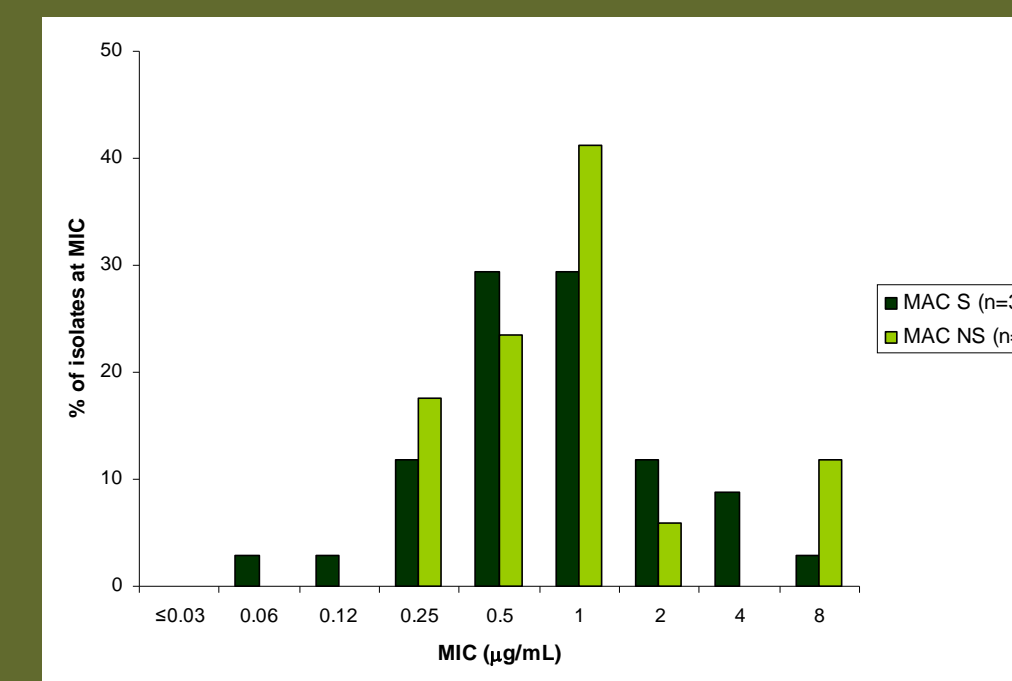


Figure 6. MIC distribution of NZ2114 against *S. agalactiae*

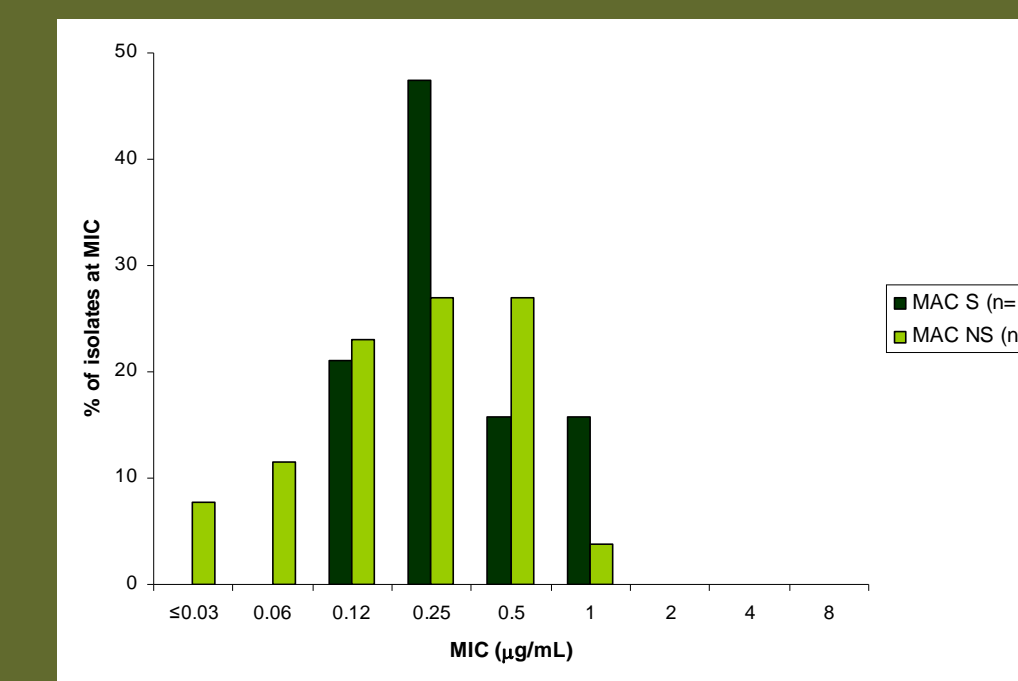


Figure 7. MIC distribution of NZ2114 against *S. pyogenes*

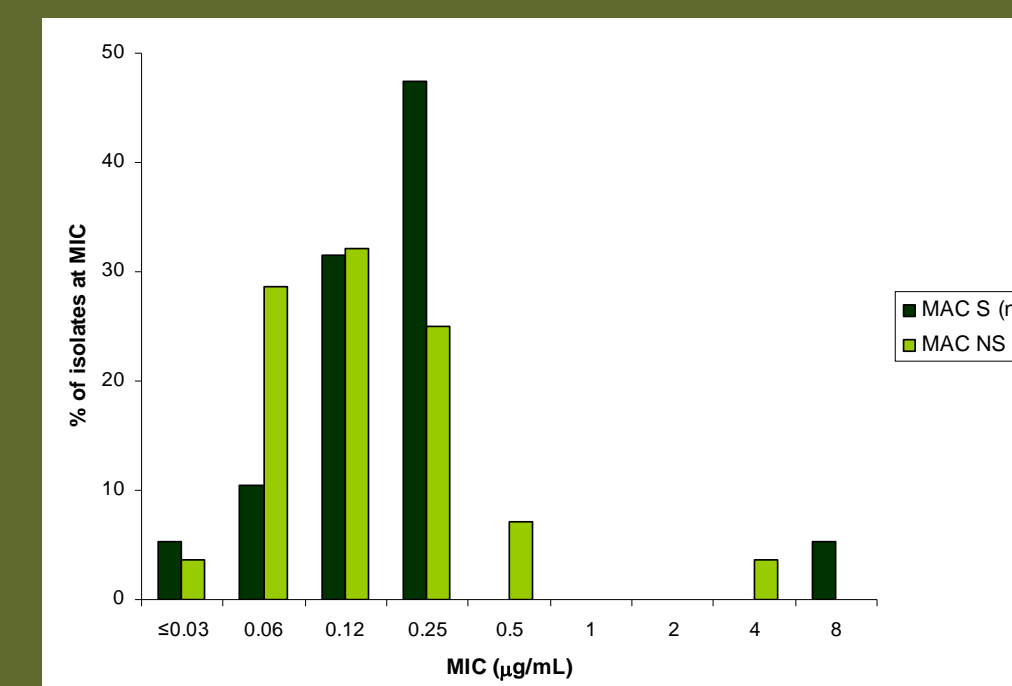
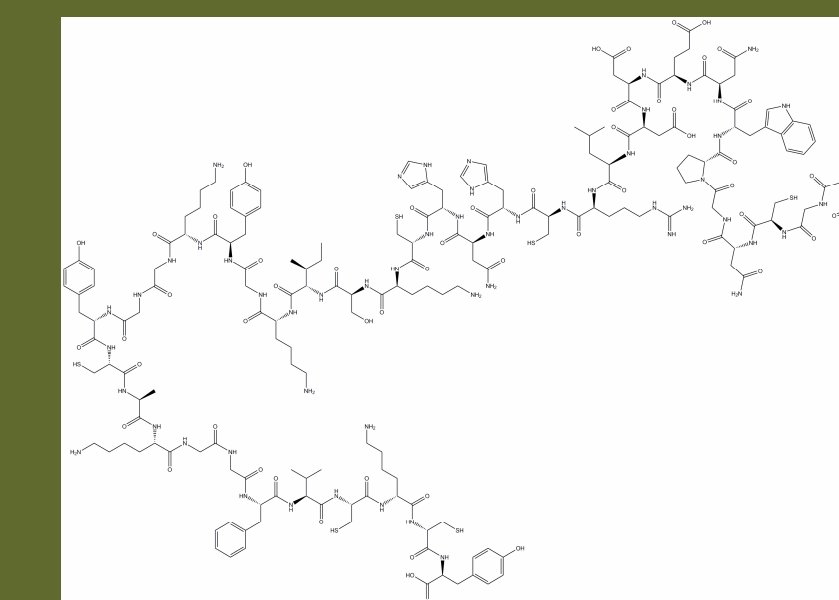


Figure 8. Compound structure of NZ2114



## Results

•Against *S. aureus* and CoNS isolates, NZ2114 had an MIC<sub>50</sub> of 2  $\mu\text{g/mL}$  and an MIC<sub>90</sub> of 4  $\mu\text{g/mL}$ , regardless of oxacillin phenotype (Table 1).

•Daptomycin and linezolid non-susceptible *S. aureus* isolates had an MIC range of 1 to 8  $\mu\text{g/mL}$ , VISAs had an MIC range of 8 to 64  $\mu\text{g/mL}$ , and VRSAs had MICs of 2 and 4  $\mu\text{g/mL}$  (Figure 2).

•Against *S. pneumoniae*, NZ2114 had an MIC<sub>50</sub> of 1  $\mu\text{g/mL}$ , regardless of penicillin phenotype, and an MIC<sub>90</sub> of 4  $\mu\text{g/mL}$  for penicillin susceptible isolates and 2  $\mu\text{g/mL}$  for penicillin intermediate and resistant isolates (Table 2).

•The MIC range of NZ2114 was  $\le 0.03$  to 4  $\mu\text{g/mL}$  against penicillin susceptible *S. pneumoniae*, 0.06 to 2  $\mu\text{g/mL}$  for penicillin intermediate isolates, and 0.06 to 4  $\mu\text{g/mL}$  for penicillin resistant isolates (Table 2 and Figure 4).

•Activity of NZ2114 was not notably impacted by macrolide resistance among the evaluated beta-hemolytic streptococci, either by MIC distribution, or MIC<sub>50</sub>/MIC<sub>90</sub> (Table 2, Figures 5-7).

•Against Group C and G streptococci, macrolide non-susceptible isolates had an MIC<sub>50</sub> of 1  $\mu\text{g/mL}$ , an MIC<sub>90</sub> of 8  $\mu\text{g/mL}$ , and an MIC range of 0.25 to 8  $\mu\text{g/mL}$  (Table 2 and Figure 5).

•Against *S. agalactiae*, macrolide non-susceptible isolates had an MIC<sub>50</sub> of 0.25  $\mu\text{g/mL}$ , an MIC<sub>90</sub> of 0.5  $\mu\text{g/mL}$ , and an MIC range of  $\le 0.03$  to 1  $\mu\text{g/mL}$  (Table 2 and Figure 6).

•Against *S. pyogenes*, macrolide non-susceptible isolates had an MIC<sub>50</sub> of 0.12  $\mu\text{g/mL}$ , an MIC<sub>90</sub> of 0.5  $\mu\text{g/mL}$ , and an MIC range of  $\le 0.03$  to 4  $\mu\text{g/mL}$  (Table 2 and Figure 7).

## Conclusions

•NZ2114 had potent *in vitro* activity against the staphylococcal and streptococcal isolates evaluated, including isolates with clinically relevant resistance.

•NZ2114 activity was not notably affected (MIC<sub>50</sub>/MIC<sub>90</sub> within one-doubling dilutions) by methicillin resistance among *S. aureus* and CoNS, penicillin resistance among *S. pneumoniae*, and macrolide non-susceptibility among beta hemolytic streptococci.

•NZ2114 maintained activity against daptomycin, linezolid, and vancomycin non-susceptible isolates of *S. aureus*, though the MICs of vancomycin intermediate isolates were slightly elevated.

•The activity profile of NZ2114 in this study highlights its potential for the treatment of infections caused by Gram-positive cocci, including those where resistant staphylococci and streptococci are frequently encountered.