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# *In Vitro* Activity And *In Vivo* Proof-of-efficacy of Epimutilin Derivatives AR-7732, AR-7731, AR-9842 And AR-10058 Against AMR Bacterial Pathogens

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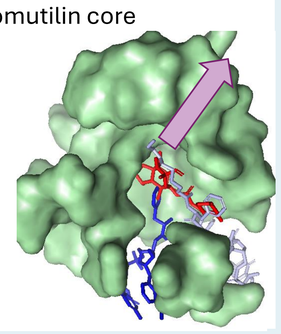
## BACKGROUND:

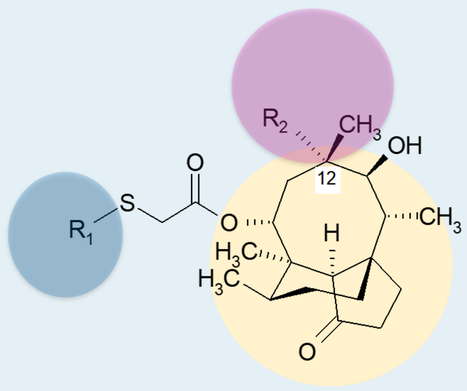
**Epimutilins**
Novel compounds for **oral and IV** administration addressing AMR

Epimutilins are a new class of antibacterials related to pleuromutilins

- Tricyclic core shared with pleuromutilins
- Unique 'epi'-$R_2$ extension into peptide exit tunnel of the ribosome = additional binding sites overcoming oxazolidinone and pleuromutilin resistance

Peptidyl transferase center with bound A- and P-site tRNAs and tricyclic-pleuromutilin core





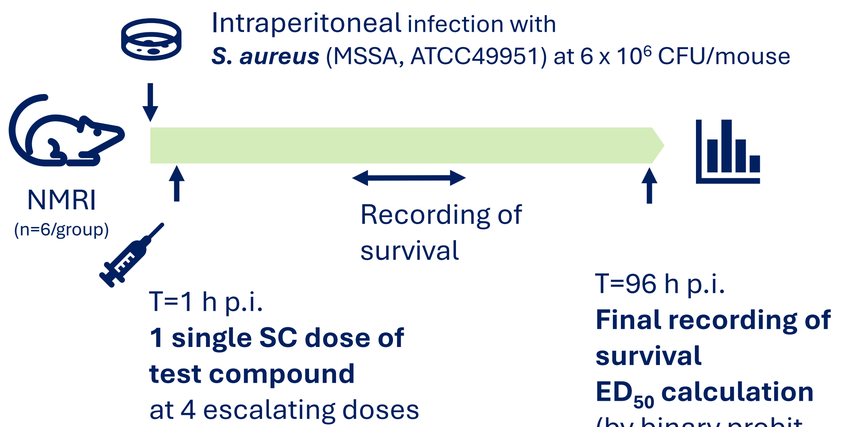

- Pleuromutilin
- A site tRNA
- P site tRNA
- Extension by epimutilins into peptide exit tunnel

### *In vitro* results

- ✓ **Potent antibacterial *in vitro* activity** demonstrated against the tested **Gram-positive** and **fastidious Gram-negative AMR pathogens** (Table 1)
- ✓ The epimutilins displayed lower MIC values than the comparators and were **unaffected by resistance to macrolides, fluoroquinolones, ß-lactams** or **tetracyclines**
- ✓ Epimutilins were **fully active against the linezolid-resistant** isolates due to the ribosomal mutation G2576T, and
- ✓ were significantly **less affected by** the methyltransferase **Cfr** or **ribosomal protection by *vga*(A)** or ***lsa*(E)** than lefamulin

## RESULTS:

### *PoE in the in vivo S. aureus* bacteremia screening model in mice




| Test compound | $ED_{50}$ (mg/kg) | $CI_{95}$ (UL-LL) |
|---|---|---|
| **Linezolid** | **10.3** | 7-4-15.1 |
| **Lefamulin** | **1.77** | 0.6-2.8 |
| **Vancomycin** | **0.77** | 0.5-1.07 |
| **AR-7731** | **3.71** | 2.1-5.3 |
| **AR-7732** | **2.99** | 0.06-5.6 |
| **AR-9842** | **1.80** | 0-3.7 |
| **AR-10058** | **16.1** | 8.7-146 |

- ✓ ***In vivo* proof of efficacy (PoE)** was demonstrated in a **lethal *S. aureus* bacteremia model** for all epimutilins in comparison to the tested standard antibiotics
  - ✓ 100% of untreated control died within 24 hours
  - ✓ A single SC dose of test compound at the highest dose cured the sepsis
  - ✓ $ED_{50}$ values of epimutilins were in a similar range as the comparators
    - Formulation and salt forms to be optimized

## CONCLUSIONS:

- ➲ The ***in vitro* and *in vivo* PoE data of this study** along with other **promising features** (as shown in other studies) support the further development of this novel antibiotic class and warrant further research. These include:
- ➲ **Potent antibacterial activity against top priority pathogens** and **AMR related health threats** as defined by the WHO and CDC
- ➲ **Lack of cross-resistance** with other major antibiotic classes
- ➲ **Oral** and **IV administration**
- ➲ **Good lung penetration**
- ➲ **Immunomodulatory activity**

**Table 1. *In vitro* activity of epimutilins and comparators**

| Species | Isolate number | Resistances | MIC (mg/L) Vanco-mycin | Linezolid | Azithro-mycin | Moxi-floxacin | Doxy-cycline | Lefamulin | Epimutilin AR-7731 | Epimutilin AR-7732 | Epimutilin AR-9842 | Epimutilin AR-10058 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gram-positives** | | | | | | | | | | | | |
| *Staphylococcus aureus* | B0009 | wildtype | 0.5 | 2 | 2 | 0.06 | 0.12 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Staphylococcus aureus* | B0029 | MRSA, MDR | 1 | 2 | **>32** | **1** | **8** | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Staphylococcus aureus* | B1145 | Linezolid (G2576T), Macrolides | 1 | **32** | **>32** | 0.03 | 0.12 | 0.25 | ≤0.03 | ≤0.03 | 0.12 | ≤0.03 |
| *Staphylococcus aureus* | B1232 | LEF (Vga(A)), MDR | 1 | 2 | **>32** | **4** | 0.12 | **8** | 0.5 | 1 | 4 | 1 |
| *Staphylococcus aureus* | B1152 | $PhLOPS_A$ (Cfr), MDR | 0.5 | **16** | **>32** | **16** | **8** | **16** | 0.5 | 1 | 1 | 1 |
| *Staphylococcus aureus* | B1296 | $PhLOPS_A$ (Cfr) | 1 | **16** | **>32** | **2** | 0.12 | **16** | 0.12 | 0.12 | 2 | 1 |
| *Staphylococcus epidermidis* | B0518 | MRSE, MDR | 2 | 1 | **>32** | **4** | 0.06 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Streptococcus pneumoniae* | B0011 | wildtype, ATCC 49619 | 0.12 | 1 | 0.06 | 0.12 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Streptococcus pneumoniae* | B0415 | wildtype | 0.25 | 2 | 0.06 | 0.25 | 0.12 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Streptococcus pneumoniae* | B0078 | PRSP, Macrolides | 0.5 | 1 | **>32** | 0.25 | **8** | 0.12 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Streptococcus pyogenes* | B0780 | FQ, Tetracyclines | 0.5 | 2 | 0.12 | **1** | **16** | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Streptococcus agalactiae* | B0790 | wildtype | 0.5 | 1 | 0.06 | 0.25 | 0.12 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Streptococcus agalactiae* | B1256 | LEF (lsa(E)) | 0.5 | 2 | 0.05 | 0.12 | **8** | **16** | 0.06 | ≤0.03 | 0.5 | 0.5 |
| *Streptococcus agalactiae* | B1258 | LEF (lsa(E)), MDR | 0.5 | 1 | **>32** | 0.12 | **8** | **16** | 0.12 | 0.06 | 1 | 1 |
| *Enterococcus faecium* | D0459 | MDR | 1 | 2 | **>32** | **4** | **32** | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Enterococcus faecium* | B1139 | Linezolid (G2576T), FQ | 1 | **32** | 0.5 | **>16** | 0.06 | 0.25 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| **Gram-negatives** | | | | | | | | | | | | |
| *Moraxella catarrhalis* | B0022 | BRO-1 ß-lactamase | **>32** | **8** | ≤0.03 | 0.06 | 0.12 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 | ≤0.03 |
| *Haemophilus influenzae* | B0035 | wildtype, ATCC 49247 | **>32** | **16** | 0.5 | ≤0.03 | 0.25 | 0.5 | 1 | 1 | 1 | 2 |
| *Haemophilus influenzae* | B0126 | wildtype | **>32** | **8** | 0.5 | ≤0.03 | 0.25 | 0.25 | 1 | 0.5 | 1 | 2 |
| *Bordetella pertussis* | B1505 | wildtype, DSM 4923 | ND | ND | 0.12 | ND | 0.12 | 0.03 | 0.06 | 0.06 | 0.06 | 0.06 |
| *Bordetella pertussis* | B1506 | wildtype, DSM 4924 | ND | ND | 0.06 | ND | 0.12 | 0.03 | 0.06 | 0.06 | 0.06 | 0.06 |