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Antibacterial *in vitro* activity of the novel epimutilins AR-7732, AR-7731, AR-10058, and AR-9842 against MDR and pre-XDR *Mycobacterium tuberculosis*

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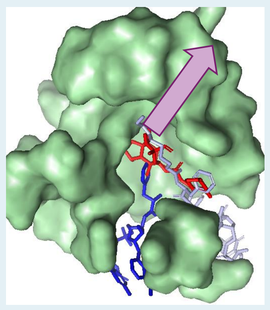
BACKGROUND:

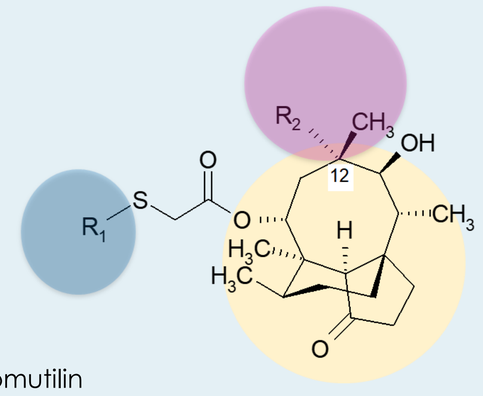
Epimutilins
A novel class for **oral and IV** administration addressing AMR

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





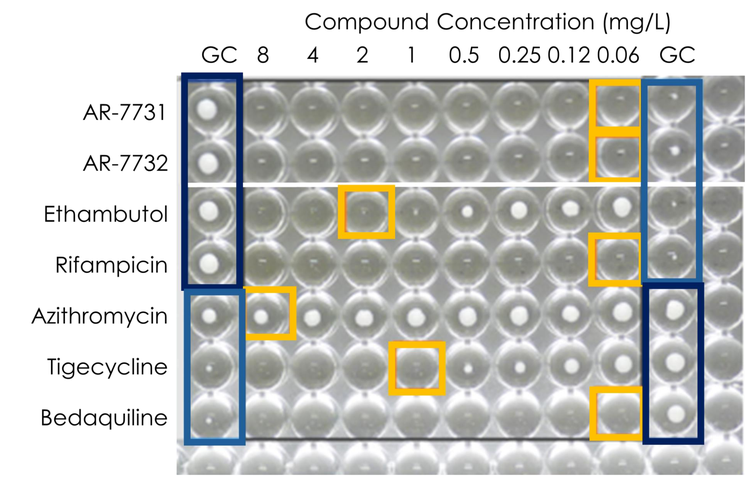
Pleuromutilin
A site tRNA
P site tRNA
Extension by epimutilins into peptide exit tunnel

RESULTS:

- ✓ The **epimutilin lead compound AR-7732 and its back-up lead candidates** displayed **potent antibacterial activity** against the attenuated ***M. tuberculosis* (*Mtb*) H37Ra**
- ✓ MICs ranged between 0.03 and 0.06 mg/L and were lower than other first and second line anti-TB drugs (Figure 1, Table 1)
- ✓ The potent **activity was confirmed** when evaluating **AR-7732** against a panel of **MDR and pre-XDR clinical isolates** using the more sensitive MGIT™ system (Table 2)
- ✓ The AR-7732 MICs ranged between 0.1 and 0.5 mg/L for all isolates including those that were **resistant to isoniazid, rifampicin, ethambutol, ethionamide, and/or moxifloxacin** (Table 2)

RESULTS:

Figure 1. MIC testing panel for *Mtb* H37Ra (EUCAST broth microdilution)



100% Growth Control (GC)
1% Growth Control (GC)
MIC

Table 1. *In vitro* activity of epimutilins and comparators against *Mtb* H37Ra

Antimicrobial Agent	MIC (mg/L) [1] *Mtb* H37Ra
Epimutilin AR-7732	**0.03 - 0.06**
Epimutilin AR-7731	**0.03 - 0.12**
Epimutilin AR-9842	**0.06 - 0.12**
Epimutilin AR-10058	**0.06 - 0.12**
Ethambutol	0.5 - 2
Isoniazid	0.5 - 0.8
Rifampicin	≤0.06
Bedaquiline	0.015 - 0.03
Amikacin	0.25
Levofloxacin	0.25
Tigecycline	1
Azithromycin	>8

1, MICs determined by EUCAST broth microdilution reference method in Middlebrook 7H9 after 2 and 3 weeks of incubation

CONCLUSIONS:

- ➲ The **potent *in vitro* activity of the epimutilin lead candidates against MDR and pre-XDR *Mtb* strains** are promising results and warrant further exploration of epimutilins for **tuberculosis treatment**
- ➲ The possibility of **oral and IV administration**, the **good penetration of the lung (ELF)** and **high intracellular concentrations of epimutilins** support these efforts

Table 2. Susceptibility of clinical MDR and pre-XDR *Mtb* isolates to AR-7732 and comparators determined using the MGIT™ System

Isolate	Resistance	Isoniazid (1 mg/L)	Rifampicin (1 mg/L)	Ethambutol (5 mg/L)	Ethionamide (5 mg/L)	Moxifloxacin (0.5 mg/L)	AR-7732 MIC (mg/L)
H37Ra (Control)	S	S	S	S	S	S	**0.1**
KV 46/23	MDR	**R**	**R**	**R**	**R**	S	**0.1**
KV 58/23	MDR	**R**	**R**	**R**	**R**	S	**0.1**
200896/23	MDR	**R**	**R**	S	**R**	S	**0.5**
220041/23	MDR	**R**	**R**	S	**R**	S	**0.5**
220026/23	MDR	**R**	**R**	S	S	S	**0.5**
220109/23	MDR	**R**	**R**	S	S	S	**0.5**
KV 55/23	pre-XDR	**R**	**R**	S	S	**R**	**0.5**
200528/23	pre-XDR	**R**	S	S	S	**R**	**0.1**

S, susceptible to the respective test compound at the indicated concentration
R, resistant to the respective test compound at the indicated concentration
MDR, multi-drug resistant according to definition by the World Health Organization (WHO; MDR = R to isoniazid and rifampicin)
pre-XDR, pre-extensively resistant defined as MDR plus R to a fluoroquinolone (e.g., moxifloxacin)
Susceptibility determined using the BACTEC460 TB System/BBL MGIT™ System (Becton Dickinson and Co, USA)

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