Auranofin derivatives as potent bactericidal antimicrobials against cystic fibrosis pathogen *Burkholderia cenocepacia*

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Introduction

Antimicrobial resistance is an ever-alarming issue affecting millions of people. We created chemical derivatives of the anti-arthritis drug auranofin, which has been shown to have antimicrobial activity, mostly in Gram-positive bacteria[1,2], in hopes to create novel antimicrobials against multi-drug resistant Gram-negative bacteria. In cystic fibrosis patients, a bacterium notoriously known for causing persistent lung infections is the multi-drug resistant bacterium *Burkholderia cenocepacia*[3]. *B. cenocepacia* is inherently resistant to many antibiotics currently available; thus, new antibiotics are urgently needed. Here, we show two derivatives of auranofin (AU118 and AU170) to have bactericidal activity to the genus *Burkholderia* and other CF pathogens.

Table 1. Minimum inhibitory concentrations (MICs) of AU118, AU170 and clinical antibiotics

Organism	MIC (μg/mL)				
	AU118	**AU170**	TOB	CAZ	CZA[a]
B. cenocepacia K56-2	4	8	512	32	4
B. lata BCC6	8	8	128	64	16
B. contaminans MF16	8	8	32	32	8
B. dolosa CEP021	16	32	128	16	8
B. multivorans ATCC17616	8	16	64	16	8
B. cenocepacia 140485	8	16	128	8	8

TOB, tobramycin; CAZ, ceftazidime; CZA, ceftazidime avibactam. [a]8 μg/mL avibactam.

Table 2. Percent survival shows AU118 and AU170 are non-toxic to *Caenorhabditis elegans* after 24 hours exposure

Antibiotic	Concentrations (μg/mL)						
	128	64	32	16	8	DMSO control	$Surv_{100}$/MIC ratio
AU118	81.8	94.7	92.9	100	100	100	4
AU170	97.6	100	100	100	**100**	100	8
Meropenem	97.4	100	100	**100**	100	100	4
AVI/CAZ[a]	100	100	100	100	100	100	32

[a]Ceftazidime + 8 μg/mL avibactam

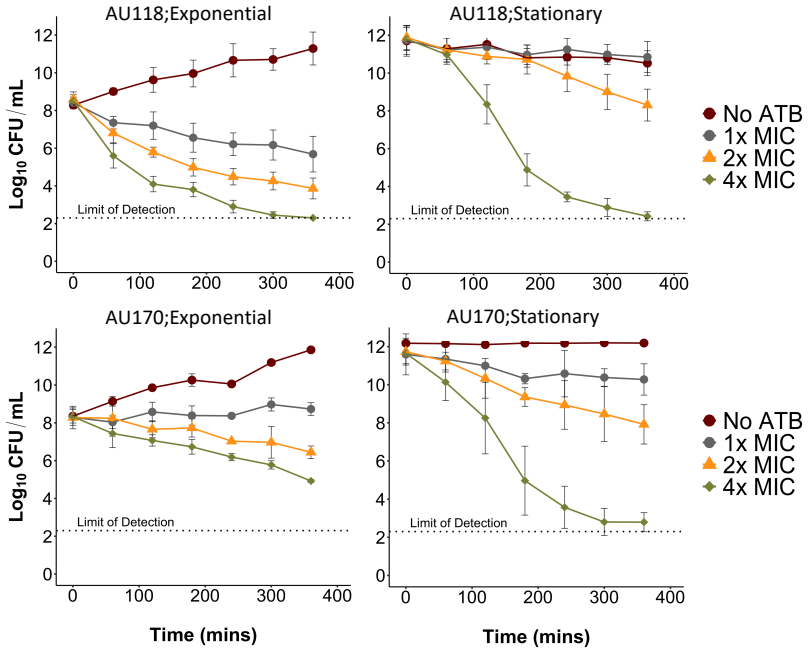

Figure 1. AU118/AU170 are bactericidal to both exponential (replicating) and stationary (non-replicating) cells

Table 3. AU118 and AU170 are bactericidal to other cystic fibrosis pathogens

Organism	MIC (μg/mL)		MBC (μg/mL)	
	AU118	AU170	AU118	AU170
Stenotrophomonas maltophilia DH57	1	2	4	8
Pseudomonas aeruginosa PA01	16	32	128	256
Klebsiella pneumoniae 120310	2	4	4	8
Acinetobacter baumannii ATCC 17978	2	2	4	8
Staphylococcus aureus 107094	0.25	0.25	1	1
Achromobacter xylosoxidans ACH03	8	16	8	32

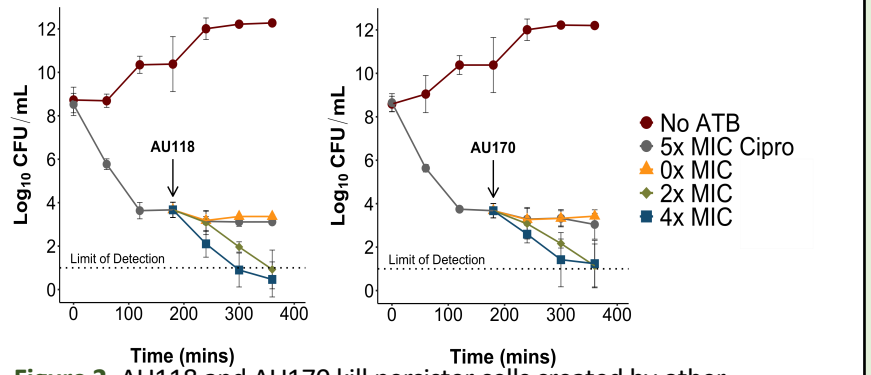

Figure 2. AU118 and AU170 kill persister cells created by other antibiotics. Exponentially growing cells were exposed to ciprofloxacin and once persisters were formed, exposed to AU118 and AU170.

Conclusion

Here, we have shown that AU118 and AU170 are bactericidal antimicrobials that are active against *Burkholderia* bacteria, including the multi-drug resistant pathogen *B. cenocepacia* and are non-toxic to *C. elegans*. These compounds are also bactericidal to other CF pathogens, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. AU118 and AU170 kill non-replicating cells including metabolically dormant persister cells. These compounds will be further explored to determine their mechanism of action and *in vivo* efficacy.

References

1. Epstein TD, Wu B, Moulton KD, Yan M, Dube DH. Sugar-Modified Analogs of Auranofin Are Potent Inhibitors of the Gastric Pathogen *Helicobacter pylori*. *ACS Infect Dis* 2019; **5**: 1682–7.

2. Harbut MB, Vilchèze C, Luo X, *et al.* Auranofin exerts broad-spectrum bactericidal activities by targeting thiol-redox homeostasis. *Proc Natl Acad Sci U S A* 2015; **112**: 4453–8.

3. Dupont L. Lung transplantation in cystic fibrosis patients with difficult to treat lung infections: *Curr Opin Pulm Med* 2017; **23**: 574–9.