Discovery of novel oxepanoprolinamide antibiotics effective against multidrug-resistant bacteria

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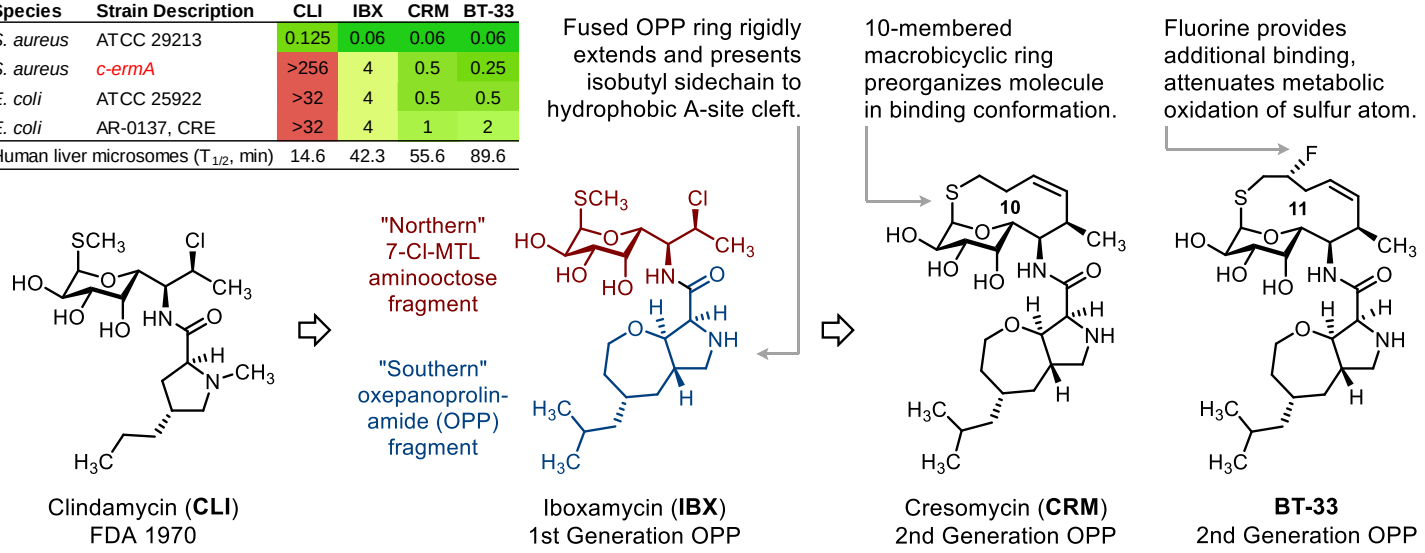
Species	Strain Description	CLI	IBX	CRM	BT-33
S. aureus	ATCC 29213	0.125	0.06	0.06	0.06
S. aureus	*c-ermA*	>256	4	0.5	0.25
E. coli	ATCC 25922	>32	4	0.5	0.5
E. coli	AR-0137, CRE	>32	4	1	2
Human liver microsomes ($T_{1/2}$, min)		14.6	42.3	55.6	89.6



The inhibition of bacterial protein biosynthesis (translation) is a key mechanism of action for clinically utilized antibiotics, as evidenced by the number and diversity of chemical classes which target the bacterial ribosome.[1] Within the large 50S ribosomal subunit, the peptidyl transferase center (PTC), broadly defined, is targeted by the broadest array of inhibitors.

In this poster, we present the design principles and potent antibacterial activities of a new class of synthetic PTC-targeting antibiotics, termed the oxepanoprolinamides (OPPs), against contemporary bacterial pathogens. The OPP antibiotics emerged from a decade of continuous research at the laboratory of Prof. Andrew G. Myers at Harvard University and were inspired by the lincosamide class of antibiotics, of which clindamycin (**CLI**) is the most recently approved (1970, FDA) and most widely known. For ease of description, the lincosamide and OPP classes of antibiotics can be conveniently separated by retrosynthetic hydrolysis of the central amide bond to yield a “northern” aminooctose fragment (red, see abstract figure) and a “southern” prolinamide fragment (blue). In 2021, we reported the discovery of the semisynthetic lincosamide antibiotic iboxamycin (**IBX**), which featured a synthetic OPP southern fragment connected to the 7-chloro-methylthiolincosamine (7-Cl-MTL) northern fragment of **CLI**.[2] More recently, we reported the discovery of cresomycin (**CRM**)[3] and **BT-33**[4], both of which are fully synthetic lincosamide antibiotics comprising distinct macrobicyclic northern thiolincosamine fragments coupled to the OPP southern fragment of **IBX**.

OPP antibiotics **IBX**, **CRM**, and **BT-33** are highly efficacious against a broad range of bacteria that are resistant to numerous diverse antibiotics in the modern pharmacopeia.[2–4] This includes strains encoding and expressing *erm*, *cfr*, or ATP-binding cassette F (ABC-F) genes that together confer resistance to all clinically relevant antibiotics targeting the large ribosomal subunit, namely macrolides, lincosamides, oxazolidinones, phenicols, pleuromutilins, and streptogramins. OPP antibiotics also exhibit demonstrable activity *in vitro* and *in vivo* against Gram-negative cUTI pathogens, including isolates of multidrug-resistant *E. coli* and *P. aeruginosa*[3]; heretofore neither **CLI** nor any other lincosamide antibiotic has shown measurable efficacy against such species.

References

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3. Wu, K. J. Y. *et al.* An antibiotic preorganized for ribosomal binding overcomes antimicrobial resistance. *Science (1979)* **383**, 721–726 (2024).
4. Tresco, B. I. C. *et al.* Discovery of a broad-spectrum, fluorinated macrobicyclic antibiotic through chemical synthesis. *ChemRxiv* (2024) doi:10.26434/chemrxiv-2024-llv6