TOTAL SYNTHESIS OF VANCOMYCIN ANALOGUES: OVERCOMING ANTIBIOTIC RESISTANCE

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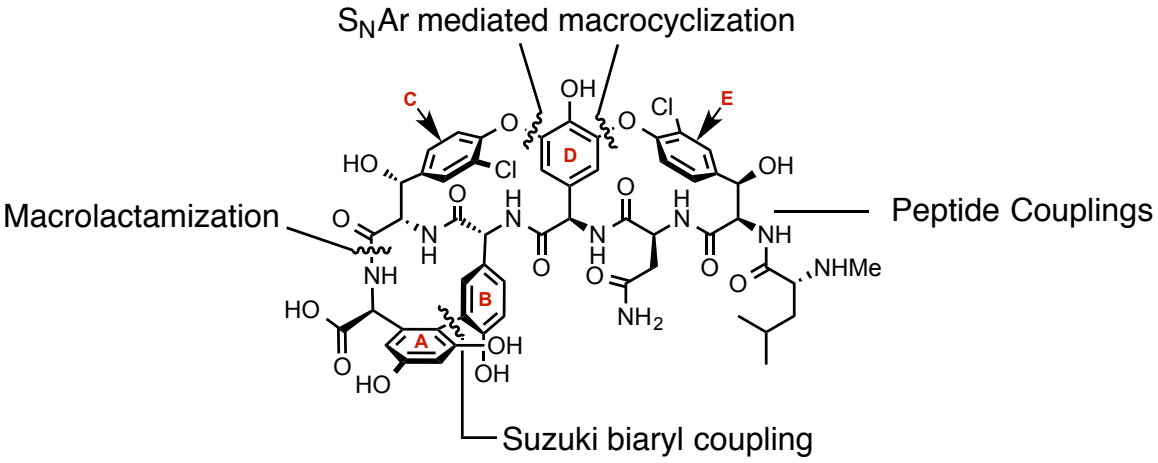
BACKGROUND:

Overcoming antibiotic resistance is one of the most important problems we face as scientists. The "age of antibiotics" began with the clinical use of penicillin in 1942; one year later, penicillin resistant bacteria were reported in the literature.[1] Methicillin was introduced to combat penicillin resistant strains, but methicillin resistant strains were reported only two years later.[2] In contrast, vancomycin resistance was not reported until nearly 30 years after vancomycin entered the clinic.[1] The complex structure, emergence of antibiotic resistance, and curious resilience against bacterial adaptation led many chemists to investigate the total synthesis of vancomycin, beginning in the late 1990s.[3,4]

SYNTHETIC STRATEGY AND CHALLENGES

Figure 1: Highlighted disconnections

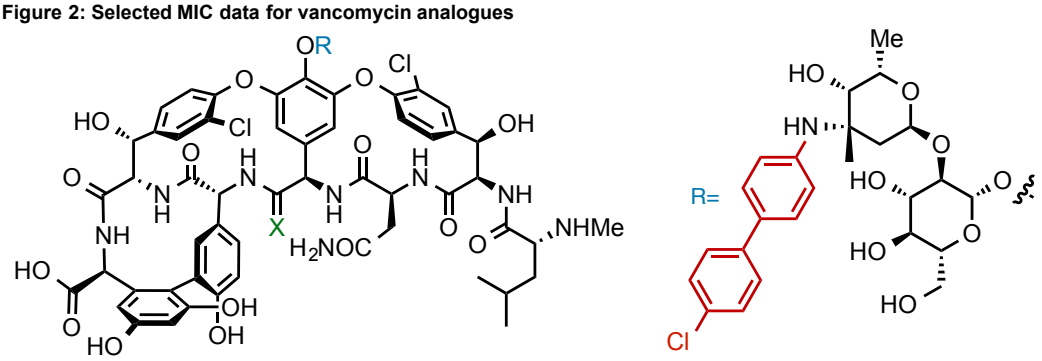


Boger's synthesis of the vancomycin aglycon utilized a S_NAr macrocyclization to construct the two challenging 16-membered biaryl ether ring systems. The C–C linkage between the sterically hindered A and B ring systems was made by a Suzuki coupling, followed by macrolactamization to complete the 12-membered A–B ring system. The C, A, and E rings each exist as a single atropisomer in naturally-derived vancomycin. In order to set these stereocenters, the Boger group relied on a series of ordered thermal atropisomer

equilibrations, with the undesired epimer being separated and recycled. The longest linear sequence gave the vancomycin aglycon in 24 steps and 1.0% yield (82.5% step average yield) from the constituent amino acids.[3]

BIOLOGICAL EVALUATION OF ANALOGUES:

Figure 2: Selected MIC data for vancomycin analogues



MIC Data for Vancomycin Analogues (μg/mL)	Sensitive	MRSA	VanA		*VanB*
	S. aureus	*S. aureus*	*E. faecium*	*E. faecalis*	*E. faecalis*
X = O (Eli Lilly, approved 2014)	0.03	0.03	**2.5**	**2.5**	0.03
X = NH (Boger, published 2015)	0.03	0.06	**0.005**	**0.005**	0.06

Once the total synthesis of the vancomycin aglycon was completed, the synthetic route was adapted to create a series of vancomycin analogues which bear core modifications.[5] These rationally-designed analogues show potent activity against vancomycin-resistant strains of bacteria. At this time, these core modifications can only be accessed by total synthesis. Inspired by semisynthetic vancomycin analogues recently developed to combat resistance, analogues bearing a 4,4'–chlorobiphenyl group as well as the Boger group's core modifications display low nanomolar potency against resistant bacteria.[4]

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