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C–H FUNCTIONALIZATION

Access to arylomycin antibiotics

> We hypothesized that the scaffolds of many narrow-spectrum antibiotics, like the arylomycins, have the potential to be much broader spectrum

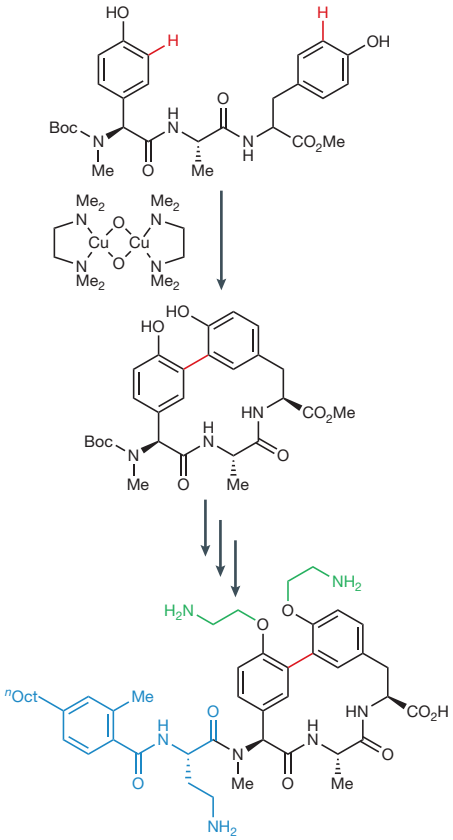
Antibiotic resistance is regarded by the World Health Organization as one of the biggest threats to global health, food security, and development today. There is, as a result, significant pressure to change the way that antibiotics are prescribed and used, but the problem also motivates the search for new broad-spectrum antibiotic compounds. Research described in the *Journal of the American Chemical Society* by David Peters, Floyd Romesberg and Phil Baran is aimed at facilitating access to new arylomycin antibiotics using C–H functionalization chemistry.

The arylomycins are regarded as a family of latent antibacterial natural products. "We hypothesized that the scaffolds of many narrow-spectrum antibiotics, like the arylomycins, have the potential to be much broader spectrum," explains Romesberg. "We speculate that they are narrow spectrum now because bacteria have evolved resistance as a response to high activity in the past. The β-lactams are the most versatile antibiotics known, and they had the most pre-existing resistance. We don't believe that is a coincidence." Thus, David Peters, a graduate student jointly supervised by Romesberg and Baran, set about finding a synthetic route that would provide access to a wide range of arylomycins.

The arylomycins consist of a biaryl-containing, 14-membered macrocyclic core with a lypophilic tail. The structures point to amino acids as precursors and formation of the macrocycle as the key step. The previous synthesis from the Romesberg lab used Suzuki–Miyaura-type cross-couplings to form the key biaryl bond in the macrocycle. This, however, requires prefunctionalization of the two aryl units with boronate and halogen functional groups as well as extensive manipulation of protecting groups.

To develop a next-generation synthesis, the team was attracted to the possibility of oxidatively coupling the phenolic side chains of two amino acids — a process which is believed to occur in the biosynthesis of the natural product. An extensive screen of common oxidants proved frustrating until the team tried copper(I) chloride which gave trace amounts of the macrocycle. Optimization of this finally led to the use of a preformed copper-oxo complex prepared by reaction of a copper source with oxygen and then reacted with the macrocycle precursor under inert atmosphere. The optimized procedure could be performed on a 5 g scale and provided the macrocycle in 60% isolated yield.

With a scalable macrocycle synthesis developed, the researchers are now collaborating with Genentech and were able to focus on a structure–activity relationship study and the search for derivatives with higher and broader spectrum antibacterial activity. The antibacterial activity of these derivatives was measured against a broad panel of bacteria and compared with a previously reported analogue called arylomycin A-C16. The results indicate that hydrogen bond acceptor functionality at the macrocycle C terminus is likely important — it is thought to interact with residues in the active site of the drug target bacterial type I signal peptidase — though a carboxylate is not essential. The most active derivative, originally described in a patent from Genentech, is additionally functionalized with alkylamine side chains appended to the biaryl unit in the macrocycle. The structure depicted here displayed better activity than arylomycin A-C_{16} for several Gram-positive bacteria and remarkably gains activity against Gram-negative human pathogens *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.



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It is anticipated that this new scalable synthesis will enable further explanation of this interesting activity as well as the development of further analogues for use as therapeutics.

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ORIGINAL ARTICLE Peters, D. S., Romesberg, F. E. & Baran, P. S. Scalable access to arylomycins via C–H functionalization logic. *J. Am. Chem. Soc.* **140**, 2072–2075 (2018)

FURTHER READING Smith, P. A., Roberts, T. C. & Romesberg, F. E. Broad-spectrum antibiotic activity of the arylomycin natural products is masked by natural target mutations. *Chem. Biol.* **17**, 1223–1231 (2010)