Unexpected bacterial origin of the antibiotic icosalide: Two-tailed depsipeptide assembly in multifarious *Burkholderia* symbionts.

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Abstract

Icosalide is an unusual two-tailed lipocyclopeptide antibiotic that was originally isolated from a fungal culture. Yet, its biosynthesis and ecological function have remained enigmatic. By genome mining and metabolic profiling of a bacterial endosymbiont (Burkholderia gladioli) of the pest beetle Lagria villosa, we unveiled a bacterial origin of icosalide. Functional analysis of the biosynthetic gene locus revealed an unprecedented nonribosomal peptide synthetase (NRPS) that incorporates two β-hydroxy acids by means of two starter condensation domains in different modules. This unusual assembly line, which may inspire new synthetic biology approaches, is widespread among many symbiotic Burkholderia species from diverse habitats. Biological assays showed that icosalide is active against entomopathogenic bacteria, thus adding to the chemical armory protecting beetle offspring. By creating a null mutant, we found that icosalide is a swarming inhibitor, which may play a role in symbiotic interactions and bears the potential for therapeutic applications.

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