

Cyclopropanol warhead in malleicyprol confers virulence of human- and animal-pathogenic *Burkholderia* species.

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Abstract

Burkholderia species such as *B. mallei* and *B. pseudomallei* are bacterial pathogens causing fatal infections in humans and animals (glanders and melioidosis), yet knowledge on their virulence factors is limited. While pathogenic effects have been linked to a highly conserved gene locus (*bur/mal*) in the *B. mallei* group, the metabolite associated to the encoded polyketide synthase, burkholderic acid (syn. malleilactone), could not explain the observed phenotypes. By metabolic profiling and molecular network analyses of the model organism *B. thailandensis* we found that the primary products of the cryptic pathway are unusual cyclopropanol-substituted polyketides. First, we identified sulfomalleicyprols as still inactive precursors of burkholderic acid. Furthermore, we discovered a highly reactive upstream metabolite, malleicyprol, and obtained it in two stabilised forms, chemically trapped as a sulfonate, and as an adduct. By means of cell-based assays and a

nematode infection model we show that the rare cyclopropanol-containing natural product confers cytotoxicity and virulence.

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