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### Abstract

The nematode *Caenorhabditis elegans* is a unique whole animal model system for identifying small molecules with in vivo anti-infective properties. *C. elegans* can be infected with a broad range of human pathogens, including *Enterococcus faecalis*, an important human nosocomial pathogen. Here, we describe an automated, high-throughput screen of 37,200 compounds and natural product extracts for those that enhance survival of *C. elegans* infected with *E. faecalis*. Using a robot to dispense live, infected animals into 384-well plates and automated microscopy and image analysis, we identified 28 compounds and extracts not previously reported to have antimicrobial properties, including six structural classes that cure infected *C. elegans* animals but do not affect the growth of the pathogen in vitro, thus acting by a mechanism of action distinct from antibiotics currently in clinical use.