Fighting the gram-negatives

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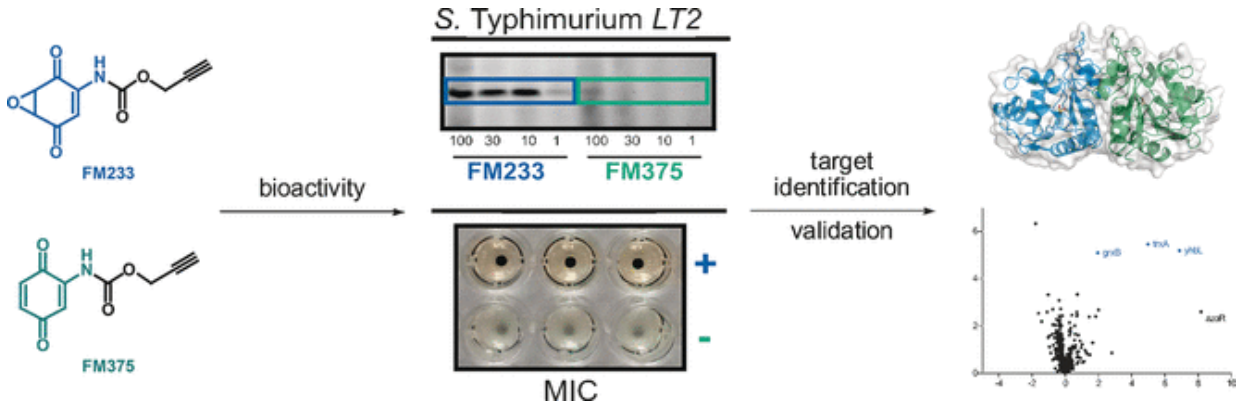

Credit: Wiley

Many microorganisms produce secondary natural products, the potential antibioticeffects of which are extensively investigated. German scientists have now examined a class of quinone-like substancescontaining an additional epoxide functional group for their antibiotic activities. As they report in the journal*Angewandte Chemie*, the compounds can kill problematic Salmonella pathogens, probably by interfering with theirbacterial stress response system.

Multidrug resistance is one of the most urgent problems in clinical research. It particularly concerns the gram-negativebacteria strains, which possess an outer membrane largely impermeable for small molecules. Scientists are continuallyscreening natural secondary products of various structural motifs to investigate their effects as possible

antibiotics, whichcould enter in the microorganism and possibly inhibit essential enzymes. Stephan Sieber, Iris Antes and their colleagues atTechnical University of Munich were particularly interested in a class of molecules with a structural scaffold present invarious natural products. Its quinone-epoxide motif could be crucial for antibacterial bioactivity, they assumed.

The scientists used click chemistry to label the molecular candidates with fluorescent dyes. Thus, in a proteomicapproach, their—at this point unknown—protein targets within the microorganisms could be identified, once they interactedwith the candidates. One of the candidates called FM233 was not only found to kill Salmonella, which is one of themost problematic pathogens, but its target proteins were identified as well. The scientists reported that two of the three proteins belonged to thecellular stress response machinery. "FM233 antibiotic activity stemmed to a large extend fromdownregulation of enzymatic stress response, and corresponding sensitization of cells to stress," they wrote. Thefunction of the third of the three targeted proteins had been unknown before. However, after employing test systems on various possibleactivities, the scientists concluded "that this protein is not involved in the antibacterial mechanism ofaction."

The notion that FM233 can intervene in the bacterial stress response system could be a good starting point for furtherresearch on the antibacterial activities of that particular molecular scaffold. As only small chemical changes can causestrong responses, the battle against resistance is ongoing.

More information: Franziska A. Mandl et al, Natural-Product-Inspired Aminoepoxybenzoquinones Kill Members of the Gram-Negative Pathogenby Attenuating Cellular Stress Response, *Angewandte Chemie International Edition* (2016). DOI: 10.1002/anie.201607338

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