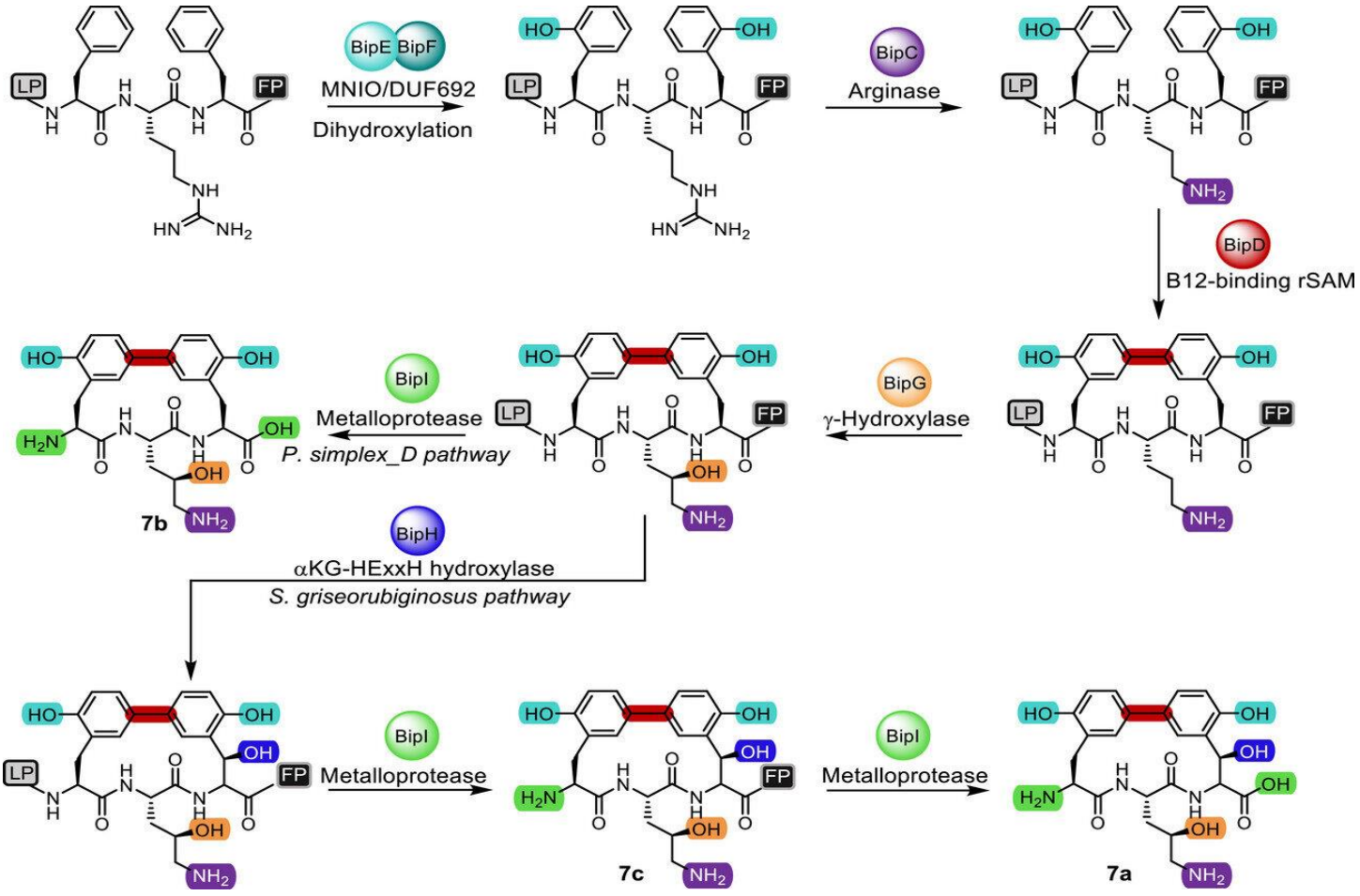
Biphenomycin biosynthetic pathway decoded, opening door to new antibiotic development



Biphenomycins, natural products derived from bacteria, show excellent antimicrobial activity, but have long remained out of reach for drug development. The main obstacle was the limited understanding of how these compounds are produced by their microbial hosts.

A research team led by Tobias Gulder, department head at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), has now deciphered the biosynthetic pathway of the biphenomycins, establishing the foundation for their pharmaceutical advancement. The team published its findings in the journal *Angewandte Chemie International Edition*.

Antibiotic resistance and biphenomycin potential

Staphylococcus aureus can trigger a wide range of infections—from skin and postoperative wound infections to pneumonia and life-threatening sepsis—making it one of the most problematic pathogens in clinical settings. Because this bacterium frequently develops resistance to commonly used antibiotics, treatment is increasingly difficult.

In Germany alone, roughly 132,000 cases of methicillin-resistant Staphylococcus aureus (MRSA) are reported each year. With drug-resistant S. aureus infections continuing to rise worldwide, new antibiotics capable of overcoming resistance are urgently needed. Biphenomycins, natural products discovered in the 1960s, show strong activity against S. aureus and other Gram-positive pathogens.

Despite their potency and good tolerability in animal models, they were never developed into therapeutics—primarily because their natural producer, a Streptomyces strain, only produces them in small amounts that are insufficient for drug development. In addition, the genes responsible for their biosynthesis remained unknown, preventing production in a more suitable host organism.

Together with colleagues at TU Dresden, HIPS researchers have now fully elucidated the biosynthetic pathway of the biphenomycins. HIPS is a site of the Helmholtz Center for Infection Research (HZI) in collaboration with Saarland University.

Elisabeth Strunk, first author of the study and doctoral researcher in the Gulder group, highlights the significance of this achievement: "For the first time, we were able to unravel all enzymatic steps that convert a simple peptide into the biologically active biphenomycin molecule. This understanding of the biosynthetic pathway now provides a basis for targeted improvement of this natural product family."

Enzyme discoveries and future applications

The study shows that the bacterial producer first synthesizes a simple peptide that contains regions guiding subsequent modifications. Several specialized enzymes then process the peptide in a defined order. Particularly remarkable is the enzyme pair BipEF, which combines two functions in one: it introduces specific chemical groups into the peptide and simultaneously cleaves it at a defined position. Such a dual function has not previously been observed within this enzyme family.

With the biosynthetic pathway now elucidated, the researchers can begin to systematically modify the involved genes and transfer them into more suitable production strains. This paves the way to produce sufficient quantities of biphenomycins for further studies and to generate new variants with improved pharmaceutical properties.

"For decades, biphenomycins were scientifically intriguing but practically inaccessible. Now that we understand how they are assembled, we can start to actively engineer them and create entirely new derivatives. This is a crucial step that enables us to develop innovative drug candidates for infections that no longer respond to standard therapies," says Gulder, head of the department Natural Product Biotechnology at HIPS and professor at Saarland University.

These findings lay the foundation for future efforts to turn biphenomycins into viable therapeutic options and represent an important contribution to the global search for new solutions to antibiotic resistance.

More information: Elisabeth Strunk et al, Biosynthesis of the Biphenomycin Family of Potent Antibiotics, *Angewandte Chemie International Edition* (2025). DOI: 10.1002/anie.202516156
Journal information: Angewandte Chemie International Edition

News Source:

https://phys.org/news/2025-12-biphenomycin-biosynthetic-pathway-decoded-door.html