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Selective antibiotics following nature's example

Chemists from Konstanz develop selective agents to combat infectious diseases – based on the structures of natural products

With multi-resistant germs becoming more and more of a threat, we are in need of new antibiotics now more than ever. Unfortunately, antibiotics cannot distinguish between pathogens and beneficial microbes. They can destroy the delicate balance of the microbiome – resulting in permanent damages. The research team around chemist Dr Thomas Böttcher has now made a significant step towards solving these problems. In collaboration with the team around biologist Professor Christof Hauck, also from Konstanz, the researchers discovered antibiotic properties of a natural product that so far had been considered merely a bacterial signal molecule. The team, including the doctoral researchers Dávid Szamosvári and Tamara Schuhmacher, developed and investigated synthetic derivatives of the natural substance that proved surprisingly efficient against the pathogen *Moraxella catarrhalis*. In the process only the growth of these pathogens was inhibited, not the growth of other bacteria. In a further project, the researchers succeed in developing another selective agent to combat the malaria parasite. These results might lead to a new basis for novel precision antibiotics. The research results are published in the current editions of the journals Chemical Science and Chemical Communications.

As important as antibiotics are to treat infectious diseases, they leave a trail of destruction in the human microbiome. Gastrointestinal disorders following antibiotic treatments are one of the slightest problems in this context. Quite often, resistant pathogens replace beneficial microbes. Later on, these can cause severe infectious diseases or chronic illnesses. However, not all microbes are dangerous. On the contrary, many microorganisms live in peaceful coexistence with us, and are even vital for human health. We humans are true microcosms and host more microbes than human cells. Yet this ecosystem, the human microbiome, is fragile. Allergies, overweight, chronic inflammatory bowel diseases and even psychiatric disorders may be the result of a damaged microbiome. The question is how can we maintain this ecological diversity in case of a microbial infection?

The research team originally studied the signals of the bacterium *Pseudomonas aeruginosa*. A compound aroused their interest as it was highly selectively inhibiting the growth of the pathogen *Moraxella catarrhalis.* This pathogen causes, for example, otitis media in children as well as infections in patients with chronically obstructive pulmonary diseases. The synthetic scaffold engineering of this natural product resulted in a new compound class with enormous antibiotic efficiency. What was really surprising was the substance's selectivity: Only the growth of *Moraxella catarrhalis* was inhibited, not that of other bacteria. Even closely related bacteria from the same species remained completely unaffected.

Currently, Thomas Böttcher and Christof Hauck are investigating the mechanism of action of this highly selective antibiotic against the pathogen *Moraxella catarrhalis.* Antibiotics with such selectivity would make precision treatment possible and specifically eliminate pathogens while preserving the diversity of beneficial microbes.

In another current project, described in the journal Chemical Communications, the research team around Thomas Böttcher and doctoral researcher Dávid Szamosvári, in collaboration with researchers from Duke University (USA), succeeded in developing highly selective agents against the malaria parasite. These also were inspired by Nature's example and the team created novel, previously undescribed quinolone ring systems. One compound proved to be extremely specific to a critical stadium in the life cycle of the malaria parasite. At first, this parasite settles in the liver before invading blood cells. The researchers were able to target and eliminate the parasite at this stage of malaria. The new findings can now be used for targeted research and the development of selective therapies to combat malaria based on new chemical compound classes.

Facts:

- Relevant original publications:
  - D. Szamosvári, T. Schuhmacher, C. Hauck, T. Böttcher (2019) A thiochromenone antibiotic derived from Pseudomonas quinolone signal selectively targets the Gram-negative pathogen Moraxella catarrhalis. Chem. Sci. 10: 6624-6628 https://pubs.rsc.org/en/content/articlepdf/2019/SC/C9SC01090D
  - D. Szamosvári, K. Sylvester, P. Schmid, K.-Y. Lu, E. R. Derbyshire*, T. Böttcher* (2019) Close the ring to break the cycle: Tandem quinolone-alkyne-cyclisation gives access to tricyclic pyrrolo[1,2-*a*]quinolin-5-ones with potent anti-protozoal activity. Chem. Commun. 55: 7009-7012. https://pubs.rsc.org/en/content/articlelanding/2019/cc/c9cc01689a
- Chemists from Konstanz develop selective agents to combat infectious diseases – based on natural products
- Agents to combat pathogens causing otitis media in children, infections in patients with chronically obstructive lung diseases, as well as malaria
- Selective antibiotics can make precision treatment possible
- Funding provided by the Emmy Noether Programme (Emmy Noether research group of Dr Thomas Böttcher), CRC 969 and the Konstanz Research School Chemical Biology (KoRS-CB)

Note to editors:
You can download pictures here:
https://cms.uni-konstanz.de/fileadmin/pi/fileserver/2019/Bilder/selektive_antibiotika.jpg
Caption: Selective antibiotics enable precision interventions in the microbiome (computer graphic)

https://cms.uni-konstanz.de/fileadmin/pi/fileserver/2019/Bilder/selektive_antibiotika_boettcher.jpg
Caption: Dr Thomas Böttcher, Department of Chemistry, University of Konstanz

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