Scientists turn toxic pesticide into treatment against antibiotic-resistant bacteria

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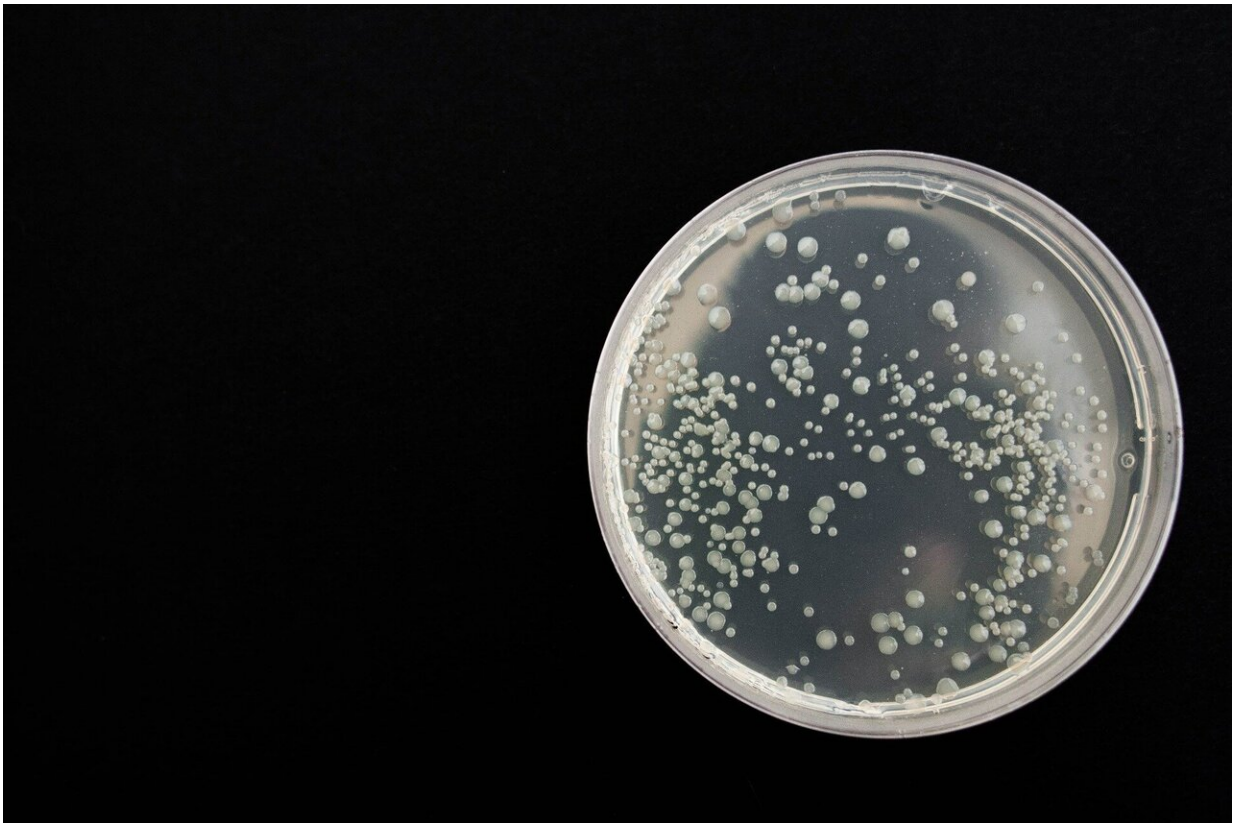

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N-Aryl-C-nitroazoles are an important class of heterocyclic compounds. They are used as pesticides and fungicides. However, these substances could be toxic to humans and cause mutations. As they are not

frequently used, there is little data about them in the medicinal chemistry literature. However, it has been suggested recently that the groups of compounds that are traditionally avoided can help to fight pathogenic bacteria.

Yet, to reduce toxic effects, a great amount of work must be carried out at the molecular level, including accurate optimization of the molecular environment of the nitro-heteroaromatic 'warhead.' The validity of this approach was demonstrated in the early 2000s through the development of anti-tuberculosis drugs delamanid and pretomanid, currently approved for medical use. They act like prodrugs, that is, the substance itself is inactive, but acquires new properties when it enters the human body.

In terms of this work, scientists from the Baltic Federal University together with colleagues from St. Petersburg State University, the L. Pasteur Research Institute of Epidemiology and Microbiology, and the Research Institute of Phthisiopulmonology in St. Petersburg, are looking for new, effective antibacterial drugs, studying various nitrogen heteroaromatic compounds with a nitro group which might be used in medicine further.

The compound OTB-021 was found to work well against drug-sensitive strains of tuberculosis pathogens, but was powerless against strains of pathogens that belong to the so-called ESKAPE panel. ESKAPE is an abbreviation for the names of bacterial species most often developing resistance to antibiotics: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter aerogenes. It is a kind of a pun: 'eskape' sounds like 'escape,' and the bacteria of this panel are known to be resistant to most of the known antibiotics—that is, they seem to 'escape' from drugs.

To understand how to modify the compound so that it could act on these

pathogenic bacteria the scientists constructed two isomeric (identical in atomic arrangement) series based on OTB-021. Side amino groups changed their position to make the aromatic nitrogen-rich core of the substance more compact, which should reduce the toxicity of the substance. The sensitivity of microorganisms to a new compound was tested via disk diffusion method. Zones of the inhibition of bacterial growth by antibiotic disks and dried solution of the compound in Petri dishes were measured.

It turned out that the ESKAPE bacteria were easily suppressed by the new substances. The minimal concentration of the chemical that prevents the growth of bacteria (μg/ml) for the tested substance shows a result comparable to the use of a ml of the antibiotic ciprofloxacin: for example, 0.3 μg/ml of an antibiotic for Enterococcus acts the same as 2 μg/ml of one of the new substances.

"Starting from the structure of the antimycobacterial OTB-021 which has no activity against ESKAPE pathogens, we developed, synthesized, and tested two isomeric series of novel analogs with an amino group that changes its position in the structure." These compounds can inhibit the growth of all ESKAPE pathogens.

"Probably, they will help to develop new effective drugs against bacterial diseases which are sometimes very difficult to treat," says Mikhail Krasavin, Doctor of Chemical Science, Professor of the Russian Academy of Sciences, professor and researcher at the Immanuel Kant Baltic Federal University.

More information: Sergey Chuprun et al, Mutually Isomeric 2- and 4-(3-Nitro-1,2,4-triazol-1-yl)pyrimidines Inspired by an Antimycobacterial Screening Hit: Synthesis and Biological Activity against the ESKAPE Panel of Pathogens, *Antibiotics* (2020). DOI: 10.3390/antibiotics9100666