

Inhibitors of the non-mevalonate isoprenoid biosynthesis pathway - a new class of antibiotics against tuberculosis and malaria.

Malaria and tuberculosis are two of the most dangerous infectious diseases known. According to WHO, estimated number of malaria cases in 2022 was approximately 249 million, including 608 000 deaths, among which 76% were children aged under 5 years. In parallel, the estimated number of new tuberculosis infections worldwide in 2023 was 10.8 million, while the number of people who died of tuberculosis is estimated to be 1.25 million. Noteworthy, during the COVID-19 pandemic, both the number of malaria and tuberculosis cases alarmingly increased, reversing the declining trend of new infections. Moreover, due to the progressing climate changes and global warming, the risk of reintroducing malaria to Europe is projected to increase in the following years with a high level of confidence.

Effective antimicrobial drugs are essential for the curation and prevention of infectious diseases. The rapidly progressing development of antimicrobial resistance, caused mainly by misuse and overuse of antibiotics in medicine and food production, is a serious threat for the effective application of the existing antibiotics. Emergence of pathogens such as multidrug-resistant *Mycobacterium tuberculosis* or recently observed artemisinin-resistant *Plasmodium falciparum* highlights the importance of the antimicrobial resistance problem. One of the key elements of WHO's Global Action Plan on Antimicrobial Resistance is the development of new, effective medicines. Nevertheless, it is important not only to develop medicines similar to those that are already in use, but to develop new classes of antibiotics with different mechanisms of action. This approach will significantly help in the fight against multidrug-resistant pathogens.

In this context, non-mevalonate pathway inhibitors represent a new class of antibiotics which are likely to be very safe, effective medicines. It is because the non-mevalonate pathway exists only in the targeted pathogens, such as *M. tuberculosis* or *P. falciparum*, but not in humans, which makes this pathway an attractive therapeutic target. Noteworthy, so far this class of drug candidates consist of rather simple structures which do not require elaborate, time consuming and, most of all, expensive synthetic routes to obtain them. This fact is a clear advantage for further development and potential market introduction of the non-mevalonate pathway inhibitors, especially considering that the main recipients of antitubercular or antimalarial drugs are low income countries.

Initial clinical tests of the most studied non-mevalonate pathway inhibitor – fosmidomycin – as an antimalarial drug, are very promising, however its low bioavailability and short pharmacological half-life hampers its implementation. Furthermore, despite the successful *in vitro* inhibition of a key step of the non-mevalonate pathway, the drug has no effect on the growth of living *M. tuberculosis* because of the lack of its uptake into the bacterial cell, caused by its chemical structure, thus making it ineffective as antitubercular agent. Our research project is aimed to overcome these problems, by the development of new non-mevalonate pathway inhibitors with improved activity and pharmacological properties as a new class of antibiotics.