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https://www.gesundheitsindustrie-bw.de/en/article/press-release/novel-compounds-for-fighting-against-parasitic-diseases

Novel compounds for fighting against parasitic diseases

Parasites of the Trypanosomatidae family cause a number of serious human diseases. Researchers from Italy, Belgium, and Germany have published the identification of novel anti-parasitic compounds targeting an enzyme unique to the parasites. These compounds are promising for the development of drugs with fewer side-effects than current medical treatments.

Dr. Rebecca Wade

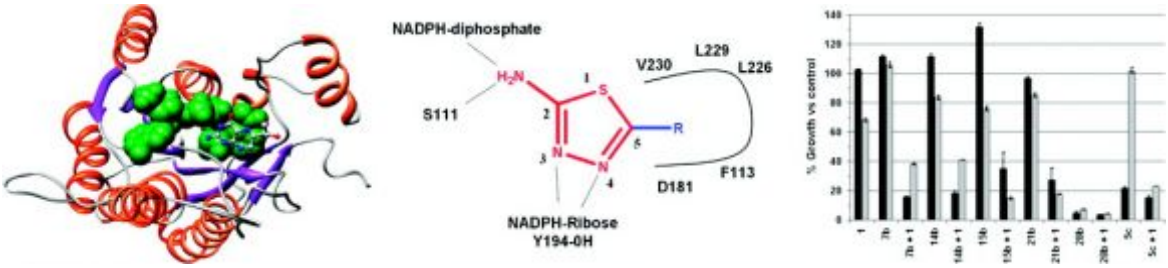
Trypanosomatid parasites cause diseases like African sleeping sickness, Chagas' disease and leishmaniasis. Leishmaniasis affects about 12 million people worldwide, mostly in developing countries. Current drug treatments are inadequate due to drug toxicity and resistance.

Now, a group of European scientists has discovered new compounds that may help to fight these diseases more effectively. The project was carried out by research groups headed by Maria Paola Costi (University of Modena and Reggio Emilia, Italy), Rebecca Wade (HITS, Heidelberg Institute for Theoretical Studies, Germany) and Paul Michels (De Duve Institute , Belgium). It was supported by the Cassa di Risparmio di Modena Foundation. The research results have been published in the Journal of Medicinal Chemistry.

Trypanosomatids require folates and biopterins. These are reduced by the enzymes dihydrofolate reductase (DHFR) and pteridine reductase (PTR1). When DHFR is inhibited, DNA replication is impaired, resulting in cell death. However in trypanosomatids, PTR1 is overexpressed when DHFR is

inhibited, and PTR1 can take on the role of DHFR by reducing folates, ensuring parasite survival. For the treatment of anti-parasitic diseases, it is thus necessary to block two metabolic pathways by simultaneously inhibiting DHFR and PTR1 by a single drug or a combination of two specific inhibitors. PTR1 is not present in humans and is thus an excellent target for the design of specific compounds that target the parasite.

In this project, the scientists used a virtual screening approach combined with experimental screening methodologies, to identify non-folate-like inhibitors of Leishmania PTR1. Optimization was performed in two rounds of structure-based drug design cycles to improve specificity for PTR1 and selectivity against human DHFR, resulting in 18 drug-like molecules with low micromolar affinities and high in-vitro specificity profiles. Assays of efficacy in cultured Leishmania cells showed six compounds that were active in combination with a DHFR inhibitor. One of these was also effective alone. Several of these compounds showed low toxicity profiles, and one of them is a known drug approved for treatment of diseases of the central nervous system, suggesting potential for label extension of this compound as an anti-parasitic drug candidate.



Virtual screening identifies non-folate compounds, including a CNS drug, as antiparasitic agents inhibiting pteridine reductase.
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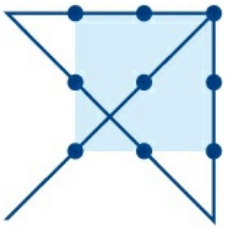

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