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KERATINOPHILE PHOTOSENSITIZERS FOR SAFE AND RAPID TREATMENT OF ONYCHOMYCOSIS

Keywords: onychomycosis, nail fungus, photodynamic therapy (PDT), photosensitizer, reactive oxygen species (ROS), nail penetration, keratinophile

INVENTION NOVELTY

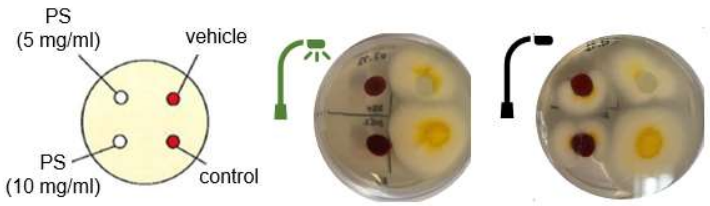
Onychomycosis, commonly known as nail fungus, is a prevalent health problem affecting millions of people worldwide. It is caused by fungal infection of the nail bed and plate, leading to thickened, discolored, and brittle nails. The condition is not a cosmetic problem but mandatory for therapeutic treatment. It can also cause pain and, in severe cases, lead to systemic mycosis. Currently available treatment options include topical and oral antifungal medications, laser therapy, and surgical removal of the affected nail. However, all these options are associated with numerous shortcomings, including low efficacy, very long treatment duration, high cost, and potential side effects. Photodynamic therapy (PDT) is a promising alternative for the focused treatment of onychomycosis, which involves the use of a photosensitizer and light to generate reactive oxygen species (ROS) that effectively kill both vegetative fungus cells and spores. However, known photosensitizers for PDT suffer from low penetration into the nail and diffusion into the neighboring soft tissues, posing the risk of negatively affecting these adjacent areas during PDT. The present invention discloses innovative photosensitizers that overcome these problems and provide effective, safe, and rapid treatment of onychomycosis.

VALUE PROPOSITION

The present technology features novel photosensitizers for PDT-based treatment of onychomycosis that are characterized by high nail-penetration (→ keratinophilicity) without diffusion into the surrounding soft-tissue, this way ensuring both optimal efficacy in the infected nail and minimal side effects in the surrounding tissues. Accordingly, these photosensitizers are a game changer in field of onychomycosis, facilitating safe, efficacious, and rapid treatment, and a significant improvement over conventional treatment options for fungal nail infections.

TECHNOLOGY DESCRIPTION

The innovation concerns novel naphthazarin derivatives with optimized properties for the PDT-based treatment of onychomycosis. Chemical modifications at the naphthazarin scaffold yielded compounds with enhanced antifungal activity and retained keratinophilicity. Antifungal activity was determined against the two most important pathogens of onychomycosis, *Trichophyton rubrum* and *Candida albicans*, revealing PDT activities in the low nM range, respectively, only after photoactivation. This photodynamic activity was verified in a nail fungus model on keratin membranes infected with *T. rubrum* (see Figure). To investigate nail penetration, diffusion tests were performed in a bovine *in vitro* nail model, using the commercially available topical antifungal agents Loceryl® and Ciclopoli® as reference. Under the test conditions, no penetration into the keratin membrane was detectable for Loceryl®, while the penetration depth of Ciclopoli® was about 40 µm. In comparison, the naphthazarin derivatives of the invention showed penetration depths of >60 µm. Further tests are ongoing, or in preparation.



***in vitro* nail infection model.** Bovine keratin membranes were incubated with *T. rubrum* for 1 d at 29°C. After application of 15 µl H_2O (control), liquor (vehicle) or test substance (5 or 10 mg/ml PS in liquor) membranes were incubated for another day and then transferred to fresh agar plates. Some of the plates were exposed to light (middle; 2x 5 min @ 519 nm), while others were kept in the dark (right). After incubation for 7 d in the dark, fungal growth was checked *(Jansen, Baier, Peifer et al., unpublished)*.

DEVELOPMENT STATUS

The innovative naphthazarin derivatives have been extensively studied *in vitro* on keratin membranes. Further tests to determine their safety and efficacy e. g. in human nails are in preparation. The same is due for the optimization of the drug formulation and pre-treatment measures.

COMMERCIAL OPPORTUNITY

The invention is available for co-development and in-licensing.

PATENT SITUATION

International application PCT/EP2023/068695 has been filed in July 2023.

FURTHER READING

Jansen, Baier, Peifer *et al.*, 2023, manuscript submitted to ACS Pharmacology & Translational Sciences.

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