UNIVERSITY OF MINNESOTA
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High-Affinity Farnesyltransferase Inhibitors for Treating Cryptococcal Infections

A novel class of antifungal compounds that inhibit Ras protein farnesylation in Cryptococcus neoformans, offering superior efficacy over current clinical treatments.

IP Status: US Patent Pending; Application No. 18/907,040

Applications

- Treatment of Cryptococcus neoformans infections
- Antifungal drug development
- Combating antifungal resistance

Key Benefits & Differentiators

- **High global impact:** Targets cryptococcosis, responsible for 181,000 deaths annually and 100% fatal if untreated.
- **Superior potency:** Inhibits fungal growth with 3–6 μM MICs—4–8× more effective than Fluconazole.
- **Novel mechanism of action:** Targets Ras farnesylation, a critical step in fungal infectivity.
- **Dual-site inhibition:** Compounds bind to two overlapping FTase sites via distinct conformations, enhancing efficacy.
- **Mechanism-driven design:** Chemical modifications control inhibitor conformation and mechanism, optimizing in vivo performance.

Technology Overview

Invasive fungal infections affect over a billion people globally, causing more than 1.6 million deaths each year. Among these, cryptococcosis—caused by Cryptococcus neoformans—is a leading killer, particularly in immunocompromised individuals such as those with HIV/AIDS, organ transplants, or cancer. Current antifungal treatments are limited and increasingly ineffective due to drug resistance.

Researchers at the University of Minnesota have developed a new class of antifungal agents that inhibit protein farnesyltransferase (FTase), a critical enzyme responsible for the farnesylation of Ras proteins. Farnesylation is essential for Ras membrane localization and function, which in turn is vital for fungal infectivity. By blocking this process, the compounds effectively halt fungal growth. These inhibitors demonstrate nanomolar binding affinities and outperform existing antifungals in vitro. Structural studies reveal a dual-site binding mechanism, where distinct inhibitor conformations engage overlapping FTase sites. This unique feature ensures robust inhibition even at low enzyme and substrate levels, a common challenge in vivo. The platform also enables rational drug design by linking chemical structure to inhibitory mechanism.

Phase of Development

TRL: 3-4

Technology ID

2021-099

Category

All Technologies
Life Sciences/Biochemicals & Small Molecules
Life Sciences/Human Health
Life Sciences/Pharmaceuticals
Life Sciences/Therapeutics
Agriculture & Veterinary/Veterinary Medicine

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Validated in vitro and in fungal growth inhibition assays.

Desired Partnerships

This technology is now available for:

- License
- Sponsored research
- Co-development

Please contact our office to share your business' needs and learn more.

Researchers

- **Mark Distefano, PhD** Professor, Department of Chemistry

References

1. You Wang, Feng Xu, Connie B. Nichols, Yuqian Shi, Homme W. Hellinga, J. Andrew Alspaugh, Mark D. Distefano, Lorena S. Beese(2022) , https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c00902, Journal of Medicinal Chemistry, 65, 13753–13770