Efficient synthesis route toward lipopeptides with application to fluorescent antifungal echinocandins

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Résumé

Invasive fungal infections (IFIs) are increasing significantly in nosocomial settings and are responsible for 2.5 to 3.8 million deaths per year worldwide. Only four families of antifungal drugs are currently used to fight against IFIs and rising resistances are alarming. The present work belongs to a global project conducted at the Laboratoire d'Innovation Therapeutique in Illkirch, France, whose goal is to identify new antifungal candidates and understand their mode of action following a chemical biology approach.
Among the antifungal agents currently used, one family stands out. First proposed in the 2000s, Echinocandins (EC) are cyclic lipopeptides of natural origin that non-competitively inhibit ß-(1-3)-D-glucan synthase, an enzyme essential for the integrity of the fungal cell wall. Despite their great interest, their exact mechanism of action remains unclear. In addition, their intensive use has led to the emergence of resistances. All this results in a loss of sensitivity found in many fearsome fungi, especially those isolated from hospitalized and immune-compromised patients.

There is therefore a need for molecular probes to explore ECs' mechanism of action and resistance modalities. Due to their structural complexity, only few total syntheses and very limited fluorescent analogues have been reported yet.

Here, we present a versatile solid-phase strategy to readily access to cyclic lipopeptides derived from ECs. Using a safety-catch linker resin, a cyclization-release approach affords high-purity ECs azido-analogues that retain activity against *Candida albicans* following the EUCAST reference method. A subsequent click ligation with several alkyne-fluorophores, permitted to analyse the influence of diverse fluorophores and their linker on the antifungal

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activity. Thus this strategy was successfully applied to the synthesis of unprecedented fluorescent ECs to visualize their interaction with fungal cells by confocal microscopy.

This versatile methodology delivers the first fully synthetic fluorescent echinocandins, providing powerful tools to explore EC action and fungal resistance mechanisms.

Mots-Clés: echinocandins, lipopeptides, invasive fungal infections