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Targeting pathogenic fungi, bacteria and fungal-bacterial biofilms by newly synthesized quaternary ammonium derivative of pyridoxine and terbinafine with dual action profile

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ABSTRACT

Many pathogenic bacteria and microscopic fungi form rigid polymicrobial biofilms this way enhancing their resistant to treatment. A series of novel pyridoxine-based quaternary ammonium derivatives of terbinafine characterized by both antifungal and antibacterial activities was designed. The leading compound named **KFU-127** exhibits promising antifungal and antibacterial activities against various bacteria and micromycetes in both planktonic and biofilm-embedded forms demonstrating MIC values comparable with those of conventional antifungals and antimicrobials. Similar to other antiseptics like benzalkonium chloride and miramistin, **KFU-127** is considerably toxic for eukaryotic cells that limits is application to topical treatment options. On the other hand, **KFU-127** reduces the number of viable biofilm-embedded bacteria and *C. albicans* by 3 orders of magnitude at concentrations 2–4 times lower than those of reference drugs and successfully eradicates *S. aureus-C. albicans* mixed biofilms. The mechanism of antimicrobial action of **KFU-127** is bimodal including both membrane integrity damage and pyridoxal-dependent enzymes targeting. We expect that this bilateral mechanism would result in lower rates of resistance development in both fungal and bacterial pathogens. Taken together, our data suggest **KFU-127** as a new promising broad spectrum topical antimicrobial capable of one-shot targeting of bacterial and fungal-bacterial biofilms.

1. Introduction

Rapid development of the multi-drug resistant fungal pathogens in the last decades appears a great challenge for the public health due to increasing number of immunocompromised patients [1]. Although *Candida albicans* is one of the commensal fungi commonly colonizing various mucous membranes in humans, it is also one of the most widespread dimorphic micromycetes responsible for up to 90% of deep and cutaneous forms of candidiasis characterized by high morbidity and mortality in immunocompromised patients [2,3]. Besides *C. albicans*, various other pathogenic fungi like *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Fusarium, Paecilomyces, Rhizopus, Rhodotorula* often lead to both primary and secondary mycoses [4,5].

To date, the treatment options of fungal diseases are limited to only several classes of available antifungal drugs, including polyenes (amphotericin B, nystatin), azole antifungals (fluconazole, etc), allylamines (terbinafine), pyrimidine analogues (5-flucytosine) and novel echinocandins (caspofungin) [6–8]. However, rapid development of fungal pathogens resistant to antifungals requires the development of new drugs [9,10].

C. albicans possesses a number of mechanisms to avoid both antimycotics and the immune system of the host. Besides many other

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