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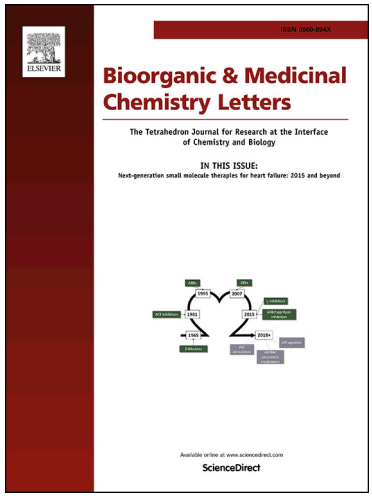

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Biofilm inhibition and anti-*Candida* activity of a cationic lipo-benzamide molecule with twin-nonyl chain

Tushar Jain [a,b] Prathap Reddy Muktapuram[c], Komal Sharma[c] , Owk Ravi[b,c] Garima Pant,[d] Kalyan Mitra,[d] Surendar Reddy Bathula,*[b,c] Dibyendu Banerjee*[a,b]

[a]*Molecular and Structural Biology Division, CSIR-Central Drug Research Institute, Lucknow-226 031, U.P., India.*

[b]*Academy of Scientific and Innovative Research (AcSIR), Chennai, India,*

[c]*Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad -500007, India.*

[d]*Electron Microscopy Unit, Sophisticated and Analytical Instruments Facility, CSIR-Central Drug Research Institute, Lucknow-226 031, U.P, India.*

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ABSTRACT

A series of cationic lipo-benzamide compounds with varying lengths of hydrocarbon chains (C2M-C18M) were evaluated for anti-Candida activity. Four compounds harbouring 8-11 hydrocarbon chains demonstrated concentration-dependent inhibition of fungal cell growth with Minimum Inhibitory Concentration (MIC) of ≤ 6.2 µg ml^{-1}. The most active compound (C9M) inhibited growth of both Candida albicans and non-albicans strains and is equally active against pairs of azole sensitive and resistant clinical isolates of C. albicans. Compound C9M also inhibited different stages of Candida biofilms. Scanning Electron Microscopy (SEM) of Candida cells after C9M treatment was also done and no significant cell lysis was observed. Hemolysis assay was performed and only 2.5% haemolysis was observed at MIC concentration.

Introduction

Fungal infections are one of the most pressing public health care concerns worldwide [1]. The human microbiota also consists of fungi that render several beneficial functions. In spite of tremendous health benefits, some microbiota can cause mild to severe infections, especially in conditions of immune-suppression [2]. *Candida albicans* is one such fungus which is a part of commensal microflora in humans but becomes invasive and lethal when the immune system of an individual is compromised [3]. *Candida* causes cutaneous, subcutaneous, mucosal (localized-*candidiasis*), as well as systemic infections (*Candidemia*) [4]. Candidemia or *Candidiasis* has been a leading type of nosocomial infection with high morbidity and mortality rates (20–40%) [5]. Conventional antifungal treatment for *Candidiasis* includes polyenes, azoles and recently launched echinocandins [6]. However, conventional treatment options have a narrow therapeutic index, poor bio-availability, severe side effects and the chance of emergence of resistant strains [7]. Therefore, the limitations associated with conventional treatment necessitate the exploration of new drug candidates that can get rid of drug-resistant and lethal systemic mycoses.

Quaternary ammonium compounds (QACs) have been known to be the most useful antiseptics and disinfectants [8]. The cationic agents supposedly react with the phospholipid components of the cytoplasmic membrane, thereby producing membrane distortion and a net positive charge on microbial cells [9]. The positive charge on microbial cells has often been correlated to their biocidal action. Some polymeric QACs have been shown to induce lysis of spheroplasts of *Serratia marcescens*, but not those of *C. albicans* [10]. The critical phenomenon determining the antifungal effect of cationic surfactants and lipids is not cell lysis but rather the reversal of cell surface charge from negative to positive that leads to membrane distortion [9]. QAC's fused to varying length of carbon chains are reported to have antimicrobial activities. It was reported that QAC's fused to 10-12 methylene linkers showed growth inhibitory effect against drug-resistant bacterial strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) [11]. Moreover, molecules with a net positive charge were not only able to kill microorganisms in solution but also upon attachment or adsorption onto solid surfaces [12]. The organic monolayers containing quaternary ammonium groups have been shown to prevent deposition and growth of bacterial biofilm [13]. However,