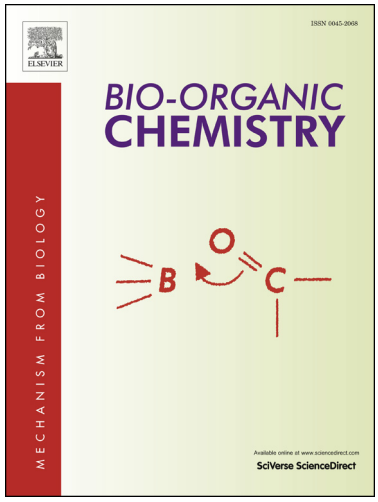

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PII: S0045-2068(15)00045-0
DOI: http://dx.doi.org/10.1016/j.bioorg.2015.05.007
Reference: YBIOO 1817

To appear in: *Bioorganic Chemistry*

Received Date: 20 April 2015

Please cite this article as: K. Kral, T. Bieg, U. Nawrot, K. Włodarczyk, A. Lalik, P. Hahn, I. Wandzik, New monomeric and dimeric uridinyl derivatives as inhibitors of chitin synthase, *Bioorganic Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bioorg.2015.05.007

New monomeric and dimeric uridinyl derivatives as inhibitors of chitin synthase

Katarzyna Kral[1], Tadeusz Bieg[1], Urszula Nawrot[2], Katarzyna Włodarczyk[2], Anna Lalik[3], Przemysław Hahn[1], Ilona Wandzik[1*]

[1]Department of Organic Chemistry, Bioorganic Chemistry and Biotechnology, Silesian University of Technology, B. Krzywoustego 4, 44-100 Gliwice, Poland
[2]Department of Pharmaceutical Microbiology and Parasitology, Wroclaw Medical University, Borowska 211A, 50-368 Wrocław, Poland
[3]Systems Engineering Group, Institute of Automatic Control, Silesian University of Technology, B. Krzywoustego 8, 44-100 Gliwice, Poland

Abstract: This study described the synthesis and *in vitro* evaluation of eight new derivatives of uridine as antifungal agents and inhibitors of chitin synthase. Dimeric uridinyl derivatives synthesized by us did not exhibit significant activity. One of the studied monomeric derivative, 5'-(N-succinyl)-5'-amino-5'-deoxyuridine methyl ester (compound **7**) showed activities against several fungal strains (MIC range 0.06-1.00 mg/mL) and inhibited chitin synthase from *Saccharomyces cerevisiae* (IC_{50} = 0.8 mM). Moreover compound **7** exhibited synergistic interaction with caspofungin against *Candida albicans* (FIC index = 0.28)

Keywords: Uridine, chitin synthase inhibitors, antifungal agents, synergism

1. Introduction

Fungal cells are protected by the cell wall, comprised mostly of two polysaccharides, β-1,3-glucan and chitin. Biosynthesis of these polysaccharides is accomplished by two glycosyltransferases, 1,3-β-glucan synthase and chitin synthase respectively [1]. The newest class of antifungal drugs that affect synthesis of the cell wall 1,3-β-glucans are echinocandins (e.g., caspofungin, micafungin, and anidulafungin) [2, 3]. Echinocandins are characterized as very effective and relatively safe therapies. However, there is some concern regarding resistance, because a number of cases of breakthrough infections have been reported. One reason is attenuation of activity at higher concentrations of echinocandins, called the paradoxical effect, which has been reported *in vitro* in several fungi, such as *Candida albicans* and *Aspergillus fumigatus* [4-6]. In addition, upon treatment with echinocandin drugs, the chitin biosynthesis pathway responded to reinforce the fungal cell wall with extra chitin [6-8]. This is known as compensation or the salvage mechanism. Therefore chitin synthase inhibitors do have potential for development as antifungal agents when used in combination with echinocandins. Both glycosyltransferases, chitin and glucan synthases are absent in mammalian cells, making them ideal targets for drug development [9-11].

Numerous types of nucleoside antibiotics found in nature have been shown to exhibit activity against a broad variety of microbes. Among them, polyoxins and nikkomycins, the first reported competitive inhibitors of chitin synthase, showed antifungal, insecticidal and acaricidal activities [12]. Despite favorable activities *in vitro*, these inhibitors were not acceptable drug candidates, because they were charged, and did not readily transport across the cell membrane. Structural analogues of these antibiotics were more often utilized to design and discover more powerful chitin synthase inhibitors [12-14]. To improve the pharmacokinetic properties of polyoxins and nikkomycins, many analogues contain

*Corresponding author: tel.: +48 32 2372028; fax: +48 32 2372094; e-mail address: ilona.wandzik@polsl.pl