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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of piplartine analogs and preliminary findings on structure–antimicrobial activity relationship

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Abstract In this work it is described the synthesis, characterization and antimicrobial and toxicity evaluation of a series of analogs of piplartine, a piperamide found in *Piper* sp. The compounds structures were confirmed by infrared spectroscopy, ^{1}H, ^{13}C nuclear magnetic resonance, high resolution mass spectroscopy and were evaluated against strains of *Candida* spp., *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Derivative **24** was almost four-fold more potent (IC_{50}: 48.83 µM) and five-fold less toxic (SI > 3) than piplartine (IC_{50}: 189.2 µM; SI: 0.21) against *Candida krusei*, as well as two-fold more potent than fluconazole (IC_{50}: 104.48 µM). This compound was also active against *Candida tropicalis* at 97.67 µM. Benzoyl derivative **17** was three-fold more potent (IC_{50}: 85.2 µM) and more than five-fold less toxic (CC_{50}: 231.71 µM) than piplartine (IC_{50}: 315.33 µM and CC_{50}: 41.14 µM) against *Staphylococcus aureus*. Given these findings, we have found analogs of piplartine which can be assumed as prototypes for the optimization and the development of new antimicrobial (compounds **24** and **17**) agents.

Keywords Piplartine · Analogs · Antifungal activity · Antibacterial activity

Introduction

Fungal and bacterial infections represent a serious problem of public health and, especially among immunocompromised patients related to AIDS, cancer, organ transplants, old age, and others factors. The increase in the cases of microbial resistance to available drugs has contributed to the rise in mortality rates associated with those infections. Thus, these factors justify the need for research and development of new antibacterial and antifungal agents as an alternative to improve the therapeutic arsenal. (Ling et al. 2015; Low and Rotstein 2011).

Natural products are one of the most rational sources of new drugs. They evolved naturally to perform specialized functions in plants and other organisms, so their refined structural backbones often allow the possibility for biological activity or structural modification to improve potency and pharmacokinetics (Chen et al. 2015). Many plant species produce secondary metabolites that are naturally toxic to bacteria, fungi and other parasitic organisms, as a defense response and fight for survival in competitive environments (Chin et al. 2006; Balunas and Kinglorn 2005; Paterson and Anderson 2005). Moreover, edible plant species often contain bioactive compounds, which justify the medicinal effects resulting from observations of their intake (Lampe 2003; Cragg and Newman 2005).

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