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RESEARCH ARTICLE

Chemical reactivity and antimicrobial activity of *N*-substituted maleimides

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Abstract
Several *N*-substituted maleimides containing substituents of varying bulkiness and polarity were synthesised and tested for antimicrobial and cytostatic activity. Neutral maleimides displayed relatively strong antifungal effect minimum inhibitory concentrations (MICs in the 0.5–4 μg ml^{-1} range); their antibacterial activity was structure dependent and all were highly cytostatic, with IC_{50} values below 0.1 μg ml^{-1}. Low antimicrobial but high cytostatic activity was noted for basic maleimides containing tertiary aminoalkyl substituents. Chemical reactivity and lipophilicity influenced antibacterial activity of neutral maleimides but had little if any effect on their antifungal and cytostatic action. *N*-substituted maleimides affected biosynthesis of chitin and β(1,3)glucan, components of the fungal cell wall. The membrane enzyme, β(1,3)glucan synthase has been proposed as a putative primary target of *N*-ethylmaleimide and some of its analogues in *Candida albicans* cells.

Keywords: Antimicrobial action, fungicidal activity, inhibitors, glucan synthase

Introduction

Microbial resistance to antimicrobials is an emerging challenge for clinicians and pharmaceutical industry. The multi-drug-resistant bacteria and fungi are the major cause of failure in chemotherapy of infectious diseases. Thus, the need for novel antimicrobial agents is especially urgent. Among different strategies of searching for new potential drugs, identification of novel, unexploited molecular targets and their inhibitors seems one of the most promising. These days many researchers concentrate on bacterial and fungal enzymes that catalyse important biochemical reaction in microbial cells. Bioactive compounds that selectively inactivate such proteins and block metabolic pathways in human pathogenic bacteria and fungi could be potential antimicrobial drugs.

Although *N*-ethyl maleimide (NEM) may react with amines and imidazole derivatives to form *N*-acylation products, it is widely known as a thiol-reacting compound[1] and as such is an effective inhibitor of several enzymes containing reactive cysteinyl residues, essential for their catalytic activity[2–4]. Because many of these enzymes are important for growth and survival of micro-organisms, antimicrobial activity of NEM is not surprising. Antimicrobial properties of NEM and other *N*-substituted maleimides have been already reported[5–9]; however, none of those studies related antimicrobial activity of substituted maleimides to their physicochemical properties, including chemical reactivity and lipophilicity. In the present work, such correlation has been attempted for 12 various *N*-substituted maleimides. Moreover, novel information on molecular mechanism of antifungal action of compounds studied has been provided.

Materials and methods

Chemistry

Solvents and reagents were purchased from Sigma-Aldrich. Melting points are uncorrected. ^{1}H NMR

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