Bis-guanylhydrazones as efficient anti-*Candida* compounds through DNA interaction.

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Abstract

Candida spp. are leading causes of opportunistic mycoses, including life-threatening hospital-borne infections, and novel antifungals, preferably aiming targets that have not been used before, are constantly needed. Hydrazone- and guanidine-containing molecules have shown a wide range of biological activities, including recently described excellent antifungal properties. In this study, four bis-guanylhydrazone derivatives (BG1-4) were generated following a previously developed synthetic route. Anti-Candida (two C. albicans, C. glabrata, and C. parapsilosis) minimal inhibitory concentrations (MICs) of bis-guanylhydrazones were between 2 and 15.6 μg/mL. They were also effective against preformed 48-h-old C. albicans biofilms. In vitro DNA interaction, circular dichroism, and molecular docking analysis showed the great ability of these compounds to bind fungal DNA. Competition with DNA-binding stain, exposure of phosphatidylserine at the outer layer of the cytoplasmic membrane, and activation of metacaspases were shown for BG3. This pro-apoptotic effect of BG3 was only partially due to the accumulation of reactive oxygen species in C.

albicans, as only twofold MIC and higher concentrations of BG3 caused depolarization of mitochondrial membrane which was accompanied by the decrease of the activity of fungal mitochondrial dehydrogenases, while the activity of oxidative stress response enzymes glutathione reductase and catalase was not significantly affected. BG3 showed synergistic activity with amphotericin B with a fractional inhibitory concentration index of 0.5. It also exerted low cytotoxicity and the ability to inhibit epithelial cell (TR146) invasion and damage by virulent C. albicans SC5314. With further developments, BG3 may further progress in the antifungal pipeline as a DNA-targeting agent.

Involved units

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Topics

Damage to the host

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