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Mechanism and structure-activity relationship of the antimicrobial imidazole-based carboxamidrazones

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The emergence of infectious diseases caused by new pathogens or multidrug-resistant microorganisms has been a global health threat over the last decades.[1] These infections are among the most severe healthcare problems and have been associated with several deaths and heavy economic burdens per year.[2] The interest in the search for new antifungal agents is also increasing in the scientific community due to the appearance of new pathogenic organisms multi-resistant to the available drugs and therapy. Thus, novel antifungal agents with new mechanisms of action and fewer side effects are increasingly needed.

The imidazole ring is present in several natural and synthetic molecules with biological activity, namely on effective antimicrobial agents, making it a vital anchor for developing new therapeutic molecules in this field.[3]

Furthermore, amidrazones are known for their high reactivity thus being useful intermediates for the synthesis of compounds with a wide range of biological activities, including antimicrobial. The amidrazone derivatives have been applied in different areas of chemistry, specifically in the synthesis of azo molecules.[4]

In previous work, novel imidazole-based 5-aminoimidazole-4-carboxamidrazones were prepared and exhibited antimicrobial activity against *C. krusei* and *C. albicans*.[5] Further biological studies to elucidate the action mechanism revealed interference with intracellular ROS production.[6]

As these carboxamidrazones had previously evidenced a particular susceptibility to the presence of oxygen, herein we report the studies conducted to find a correlation between the oxidation-reduction reactivity of these compounds and their antimicrobial activity, to elucidate the underlying mechanism of action.

The electrochemical characterization of some of these carboxamidrazones by cyclic voltammetry to determine the oxidation potentials of these compounds was performed. The effect of the substituents on their oxidation potential was analysed to obtain a correlation between chemical structure and antimicrobial activity. Kinetic studies were also carried out in the presence and absence of oxidants and the resulting products and intermediates were identified by NMR spectroscopy. These oxidation reactions were then scaled up and the products were isolated and fully characterized by UV, IR and NMR spectroscopy (including ^{1}H RMN, D_2O shake, ^{13}C RMN, HMQC and HMBC techniques). The antifungal activity of these new products has also been evaluated and highly promising results were obtained.

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