Nitrofuran drugs beyond redox cycling: Evidence of Nitroreduction-independent cytotoxicity mechanism

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Abstract

Nitrofurans (5-nitro-2-hydrazonylfuran as pharmacophore) are a group of widely used antimicrobial drugs but also associated to a variety of side effects. The molecular mechanisms that underlie the cytotoxic effects of nitrofuran drugs are not yet clearly understood. One-electron reduction of 5-nitro group by host enzymes and ROS production via redox cycling have been attributed as mechanisms of cell toxicity. However, the current evidence suggests that nitrofuran ROS generation by itself is uncapable to explain the whole toxic effects associated to nitrofuran consumption, proposing a nitro-reduction independent mechanism of toxicity.

In the present work, a series of nitrated and non-nitrated derivatives of nitrofuran drugs were synthesized and evaluated in vitro for their cytotoxicity, ROS-producing capacity, effect on GSH-S-transferase and antibacterial activity.

Our studies showed that in human cells non-nitrated derivatives were less toxic than parental drugs but, unexpectedly preserved the ability to generate intracellular ROS in similar amounts to nitrofurans despite not entering into a redox cycle mechanism. In addition, some non-nitrated derivatives although being uncapable to generate ROS exhibited the highest cell toxicity among all derivatives. Inhibition of cytosolic glutathione-S-transferase activity by some derivatives was also observed. Finally, only nitrofuran derivatives displayed antibacterial effect.

Results suggest that the combined 2-hydrazonylfuran moiety, redox cycling of 5-nitrofuran, and inhibitory effects on antioxidant enzymes, would be finally responsible for the toxic effects of the studied nitrofurans on mammalian cells.

Palabras clave

Palabras clave de autor: Nitrofurans; Cytotoxicity; Reactive Oxygen Species; Nitroreduction; Hydrazone

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