ABSTRACT

Iron is an essential micronutrient for life, but can be toxic in uncontrolled excess. Iron chelators have therefore become established therapeutics for the treatment of iron-overload disease, but they also show promise as anti-cancer drugs because of the additional role of iron in cell proliferation. Iron chelators have also been shown to protect skin cells from the effects of exposure to harmful levels of Ultraviolet A radiation (UVA). In fact, the harmful effects of UVA are now understood to be related to an increase in potentially harmful 'labile' intracellular iron, which results in the formation of cytotoxic reactive oxygen species (ROS) which subsequently promote necrotic cell death. However the long-term administration of powerful iron chelators for therapeutic purposes is associated with severe iron depletion from healthy tissue, culminating in unacceptable side-effects.

The concept of ‘caged’ iron chelators (CICs) which are selectively activated in situ by light of an appropriate wavelength is highly attractive, as iron chelation may then be delivered in a context-specific fashion, when it is required and appropriate to the level of UV light exposure. Such photoactivatable agents could have numerous applications: firstly as therapeutic agents for the targeted treatment of dermatological pathologies, including cancer, and secondly as photoprotectants in sunscreen formulations.

The work herein describes the preparation of a series of CICs based on aroylhydrazone and thiosemicarbazone compounds, which have already been studied for their iron chelating and anti-proliferative activity. We have shown that caging may be achieved by chemical blockade of a key iron-chelating function with various photoremovable protecting groups (PRPGs). These include well-established PRPGs belonging to the nitrobenzyl and coumarin-4-yl family of compounds, as well as the more recently elucidated aminocinnamoyl and hydroxycinnamoyl moieties. This latter class is of particular interest as a caging group, owing to the phototransformation of cinnamates into cyclic coumarin derivatives, some of which have been reported to possess potent antioxidant activity. Such CICs may therefore have potential applications in sunscreen formulations as “multifunctional” photoprotectants that provide synergistic protection against UVA damage.

The uncaging of novel CICs with varying doses of UVA has been studied, along with their cytotoxic and photoprotective effects in human FEK4 fibroblasts and HaCAT keratinocyte cell lines, in the presence and absence of applied radiation.
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