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Synthesis and antimelanogenic activity of *N3*-aryliden-2-thiohydantoin derivatives

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The main goal of this study was to synthesize novel potent and safe inhibitors of melanogenesis based on the 2-thiohydantoin moiety for therapeutic application in the treatment of skin hyperpigmentation disorders in humans (freckles, chloasma, melasma, solar lentigo, senile lentigines, ephelides and melanoderma). A series of 15 *N3*-aryliden-2-thiohydantoin derivatives was synthesized, fully characterized, and subjected to extensive in vitro and in vivo biological evaluation. All compounds have been tested on the zebrafish model, a powerful and highly predictive animal platform used for toxicity assessment and biological activity evaluation of novel bioactive molecules, thus simplifying the path to clinical trials and reducing the failure at later stages of testing. Their antimelanogenic activity and toxicity were compared to those of kojic acid and hydroquinone, well-known depigmenting agents used for the treatment of skin hyperpigmentation disorders. Most of the compounds reduced body pigmentation of the treated zebrafish embryos with different efficacy. Derivatives which exhibited the best melanogenesis inhibitory activity exerted much better therapeutic profile than kojic acid and hydroquinone, the former of which was non-toxic and poorly effective and the latter highly effective but extremely toxic. The presented results of biological activity evaluation *in vivo* clearly demonstrate that compounds with 2-thiohydantoin moiety could present a novel effective and safe antimelanogenic compounds with a large potential for further clinical evaluation and therapeutic application in humans.

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