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Synthesis and evaluation of phenyl hydrazone derivatives as tyrosinase inhibitors

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Melanogenesis which refers to the process of melanin formation and distribution is controlled by epidermal units in the skin. The activation of tyrosinase, a key enzyme that plays a major role in propagation of melenogenesis, is boosted when the skin is exposed to UV radiation. Abnormal melanin production in the skin resulting in highly pigmented patches could cause an esthetic concern. Therefore, inhibitors of tyrosinase could be an attractive treatment option for hyperpigmentation. Although several natural, semisynthetic, and synthetic down-regulators of tyrosinase have been discovered to date, the development of novel selective and effective classes of tyrosinase inhibitors that are less toxic to human health are still under development stage. In this study, four Schiff bases, 4-[(*E*)-(phenylhydrazono)methyl]phenol (K-1), 2-[(*E*)-(phenylhydrazono)methyl]phenol (K-2), *N*-benzylidene-*N*'-phenyl-hydrazine (K-3) and *N*-(4-methoxy-benzylidene)-*N*'-phenyl-hydrazine (K-4) were synthesized by refluxing phenyl hydrazine in 95% ethanol with 4-hydroxy benzaldehyde, 2-hydroxy benzaldehyde, benzaldehyde and 4-methoxybenzaldehyde respectively. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H-NMR, and ^{13}C-NMR experiments. Inhibitory potentials of the synthesized derivatives were examined against *Agaricus bisporus* mushroom tyrosinase. L-DOPA was used as the substrate in the enzyme assay. The inhibition of tyrosinase activity by kojic acid (the standard tyrosinase inhibitor), K-1, K-2, K-3 and K-4 at 1 mg mL^{-1} were measured and were 62.89%, 63.55%, 56.45%, 39.95% and 37.03%, respectively. These results demonstrate that all synthesized compounds possessed tyrosinase inhibitory activity *in-vitro* at the measured inhibitor concentration. It's evident that K-1 and K-2 which have hydroxyl groups attached to the para and ortho positions of the aryl aldehyde, respectively play a vital role in the potency of the compounds. Moreover, the hydroxy group in the para position showed a more pronounced inhibitory activity than in the ortho position.

Keywords: Human skin, Tyrosinase inhibition, Phenyl hydrazones.