Inhibitory Effect of Hydroxyindoles and their Analogues on Human Melanoma Tyrosinase

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A recent study showed that *N*-acylserotonin derivatives have strong inhibitory activity against tyrosinase. To clarify the role of the 5-hydroxy group in the indole ring, 2-, 4-, 5-, 6-, and 7-hydroxyindole and 11 related compounds such as 5-hydroxyindan and 6-hydroxyquinoline were tested for their inhibition of catecholase activity of tyrosinase from human HMV-II melanoma cells. 6-Hydroxyindole (**5**) and 7-hydroxyindole (**6**) were potent inhibitors, while 5-hydroxyindole (**4**) was a weaker inhibitor than the above-mentioned compounds (IC_{50} = 20, 79, 366, and 342 εM for **5**, **6**, **4**, and kojic acid, respectively). 2-Hydroxycarbazole was also active (IC_{50} = 190 εM), 5-hydroxyindan, 4-aminophenol, and harmalol were slightly active, and other compounds were inactive as an inhibitor. A similar pattern of inhibition was found with these compounds against mouse B16 melanoma tyrosinase, but with some differences from that for HMV-II tyrosinase. Kinetic analysis with HMV-II tyrosinase showed that the inhibition by hydroxyindoles **4**, **5**, and **6** was competitive with respect to the substrate L-DOPA. Melanin formation in HMV-II cells was suppressed by 14% with 10 εM **5** without cytotoxicity, but 30 or 100 εM **5** decreased the cell viability. The present results suggest that 6-hydroxyindole is a potential and useful pharmacophore of antimelanogenic agents and that the position of a phenolic hydroxy group in a specific heterocyclic ring such as in indole is possibly optimized to yield more active inhibitors for tyrosinase.

Key words: Tyrosinase, Inhibitor, Hydroxyindole