

Tyrosinase Inhibitor Activity of a New Series of Bis-salicylaldehydes

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Tyrosinase (EC 1.14.18.1, syn. polyphenol oxidase) is involved in the biosynthesis of dark macromolecular pigments, i.e., melanin [1], food browning, moulting process of insects [2] and adhesion of marine organisms [3]. Tyrosinase inhibitors are useful as skin-whitening agents used in cosmetics [4] and in treatment of hyperpigmentation.

Several benzaldehydes from natural and synthetic sources have been tested as tyrosinase inhibitors. In the past decade, a large number of benzaldehydes and other derivatives have been also isolated and characterized as mushroom tyrosinase inhibitors [5].

The interest on benzaldehydes is arise afterwards the literature data analysis. The aldehyde reacts with biologically important nucleophilic groups such as sulfhydryl, amino, and hydroxyl so it has been proposed that its inhibitory effect is due to the formation of a Schiff base with the primary amino group of the enzyme [6]. The effect of the inhibitory activity of different chemical groups substitution in benzaldehydes ring of bis-salicylaldehydes has been investigated, also in relation on their relative position.

We report the synthesis and evaluation of five 5,5'-methylene-bis-salicylaldehyde compounds to establish a structure and activity relationship for these type of compounds. In the literature, the IC_{50} value for the tyrosinase inhibitors, are incomparable due to different assay conditions, including substrate concentrations, incubation time, and batches of commercial tyrosinase. Fortunately, in most studies conducted to discover new tyrosinase inhibitors, a well-known tyrosinase inhibitor such as kojic acid is often used as a positive standard at the same time. All compounds investigated displayed more potent tyrosinase inhibitory activities than the reference inhibitor, salicylaldehyde. The inhibitory mechanism of these compounds on mushroom tyrosinase for the oxidation of L-DOPA was determined from Lineweaver-Burk double reciprocal plots. Among the compounds tested, two of these, have showed the best value of IC_{50} . The results showed that in one case, the plot of $1/V$ versus $1/[S]$ gave

three straight lines with different slopes, but intersected horizontal axis on the same point. Accompanying the increase of the concentration of compound, the value of V_{max} descend but the value of K_m remained the same, which suggest that this compound was a non-competitive inhibitor of the tyrosinase. The inhibition constant (K_i) of this compound (K_i of 0.048 mM) was determined by the plot of the values of intercept versus the concentration of the corresponding compound.

The experimental results reported show for the first time that, bis-salicylaldehyde compounds had better inhibitory effects on the diphenolase activity of mushroom tyrosinase than the reference salicylaldehyde compound.

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