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Aryl-Thiosemicarbazones Derivatives as a New Class Compounds Exhibit and Potent Inhibitory Effect on the Diphenolase Activity of Mushroom Tyrosinase

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Extended Abstract

The widely distributed in the environment enzyme tyrosinase (EC 1.14.18.1) belongs to the class of enzymes oxidoreductases and is characterized as a catalytic metalloprotein which possess Type III dicopper active site. The copper ions are linked with the six conservative histidine residues inside catalytic site (Thian-Hua et al., 2013).

Depending on the valence of these ions in the active site, the enzyme exists in the free primary forms: *oxy*, *deoxy* and *meta*, which are involved in the formation of the melanin pigments (Xiao-Xin et al., 2013). Tyrosinase possess two different activities: monophenolase which is connected with hydroxylation of monophenols to *o*-diphenols and diphenolase activity related to oxidation of *o*-diphenols to corresponding *o*-quinones (Thian-Hua et al., 2013).

The activity of the enzyme is crucial in the pathway of melanin biosynthesis in mammals. The products of this process are melanin pigments which prevent UV-induced skin damage. Although, abnormal activity of tyrosinase can be the cause of excessive accumulations of pigments in tissues resulting in occurrence of skin disorders such as melasma, age spots and hyperpigmentation (Zhi-Cong et al., 2010).

Over the years of intensive research the numerous inhibitors of tyrosinase, such as hydroquinone, ascorbic acid, arbutin, kojic acid, aromatic aldehydes, aromatic acids, aromatic alcohol, tropolone, and polyphenols has been discovered and found application in various fields, including cosmetic, medicinal and food industries (Ubeid et al., 2012). They originate from the both synthetic and natural sources. Most of these compounds such as hydroquinone, ascorbic acid derivatives and kojic acid are commonly used in cosmetic preparations as skin whitening agents. However, their clinical potential have been questioned because of a numerous side effects during its application such as contact dermatitis, skin cancer and neurodegenerative diseases. Furthemore, most of them are not powerful enough to find a practical application (Thian-Hua et al., 2013).

Because of the role, which abnormal activity of tyrosinase plays in numerous pathological states, it seems reasonable to search new and effective inhibitors of this enzyme, which do not cause any cytotoxic side effects.

The recent research revealed that some thiourea derivatives demonstrate moderate antityrosinase activity and the benzaldehyde thiosemicarbazone derivatives are characterized by potent tyrosinase inhibitory effect (Zhi-Cong et al., 2010). These observations can be caused that the sulfur atom of the

thiosemicarbazide moiety is able to chelate the two copper ions in the active site of the enzyme (Liang-Hua et al., 2012).

In the reference to these literature data, we decided to synthesize the class of compounds being aryl thiosemicarbazones derivatives and investigate their inhibitory potency toward the diphenolase activity of mushroom tyrosinase. Here, we present the results of the preliminary studies of the biological research of presented compounds as a novel potent inhibitors of mushroom tyrosinase. The tested compounds showed different types of the reversible inhibitory activities on diphenolase activity of the enzyme, with the micromolar inhibition constants. These research could be base to further studies on new and effective inhibitors of tyrosinase.

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