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Research paper

Study on the design, synthesis and structure-activity relationships of new thiosemicarbazone compounds as tyrosinase inhibitors

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ABSTRACT

52 Structure-based thiosemicarbazone compounds bearing various substituted-lipophilic part, including substituted-benzaldehyde, substituted-phenylalkan-1-one and their biphenyl-type thiosemicarbazone analogs, were designed, synthesized and evaluated as new tyrosinase inhibitors. The results demonstrated that 22 compounds have potent inhibitory activities against tyrosinase with the IC_{50} value of lower than 1.0 μM. On the basis of the obtained experimental data, the structure-activity relationships (SARs) were rationally derived. Besides, the inhibition mechanism and the inhibitory kinetics of selected compounds **3d** and **6e** were investigated, revealing that such type of compounds were belonged to the reversible and competitive tyrosinase inhibitors. To verify the safety of these developed thiosemicarbazone compounds, four randomly selected compounds **3d**, **4e**, **6a** and **9a** were also tested in 293T cell line for the evaluation of the cytotoxicity. Interestingly, all these compounds almost did not perform any toxicity to 293T cells even at a high concentration of 1000 μmol/L. Taken together, these results suggested that such compounds could serve as the highly efficient and more safe candidates for the treatment of tyrosinase-related disorders.

1. Introduction

Tyrosinase is the key enzyme in melanin biosynthesis, which plays an important role in multiple physiological and pathological pathways. For example, it can control the dopamine toxicity, and consequently, influencing the inducion and development process of many important neurodegenerative diseases, such as Parkinson's disease [1,2]. Recent studies also showed that its activity is closely related to the incidence of melanoma [3]. Moreover, tyrosinase can promote the development and defense function of insect and plays a vital role in melanin formation, wound healing and resistance to parasites and skin keratinization physiological processes [4–7]. Addationally, the browning of fruits and vegetables has a direct relationship with tyrosinase-involved activity [8–10]. Therefore, the research and development of highly effective and more safe tyrosinase inhibitors has become increasingly important in medication, cosmetic industry, agriculture as well as food industry.

Recently, the X-ray overall structure of tyrosinase have been respectively determined or predicted by the groups of Sugiyama, Vaya, Fishman, and Dijkstra (Fig. 1) [11–14]. As shown in Fig. 1, the active structure of tyrosinase contains a narrow “gap” and two center copper ions, which were separated by the “gap” and respectively coordinated with three different amino acids. In the reduced state, the two copper ions were linked by one oxygen atom; but in the oxidized state, these two copper ions were linked by two oxygen atoms, such a state is easy to offer one oxygen atom to oxidize substrate *L*-dopamine. Further analysis indicated that this narrow “gap” is lipophilic. These information give a meaningful direction for the structure-based design and development of more

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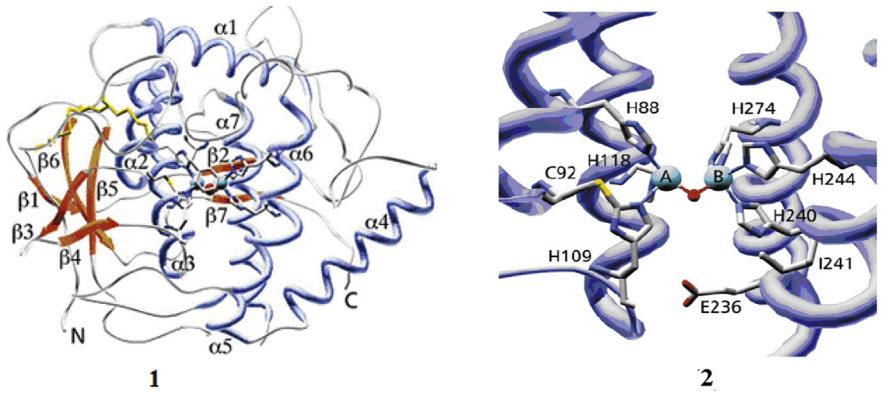

Fig. 1. **(1)** Crystal structure of tyrosinase; **(2)** Enlarged picture for active structure of tyrosinase.

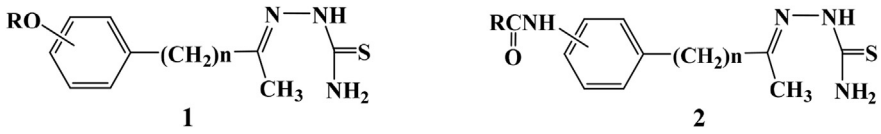

Fig. 2. Structures of 4-alkoxy- and 4-acyloxyphenylethylenethiosemicarbazone analogues (**1**) and 1-(1-(4-amidophenyl)ethylidene)thiosemicarbazone analogues (**2**).

effective tyrosinase inhibitors.

It was reported that, 4-alkoxy-/4-acyloxyphenylethylenethiosemicarbazone analogues (Fig. 2) [15], and 1-(1-(4-amidophenyl)ethylidene)thiosemicarbazone analogues (Fig. 2) [16] could perform high activities against tyrosinase. In the view of their molecular structures, we found that the thiosemicarbazone group is core unit for these two kinds of compounds.

By analyzing these reported representative structures of thiosemicarbazone compounds [15–20], in general, they could be divided into two parts (Fig. 3): the hydrophilic part (thiosemicarbazone-group part) and the lipophilic part (the –R part).

Since the narrow "gap" of tyrosinase is lipophilic, the increase of the hydrophobicity of the -R part of the inhibitor molecules would be favorable for them to entry the narrow "gap" of tyrosinase, and consequently, increasing the chance of thiosemicarbazone part in inhibitor molecules to combine with cooper ion enter. Based on the structural and biochemical information of tyrosinase and in continuation of our interest in developing the novel benzylidene-thiosemicarbazides as the potent tyrosinase inhibitors [15,16], we herein designed and synthesized several new series of structure-based thiosemicarbazone compounds bearing various substituted-lipophilic part, including substituted-benzaldehyde, substituted-phenylalkan-1-one and their biphenyl-type thiosemicarbazone analogues (Fig. 4), with the aim to find new tyrosinase inhibitors with more efficient inhibitory activities and lower toxicities.

2. Results and discussion

2.1. Chemistry

The synthetic route of target compounds was showed in Scheme 1. Briefly, to probe the effect of the nature, the chain length and the chain space volume of lipophilic moiety on tyrosinase inhibitory activity, compounds **3a-j** were firstly synthesized by condensation

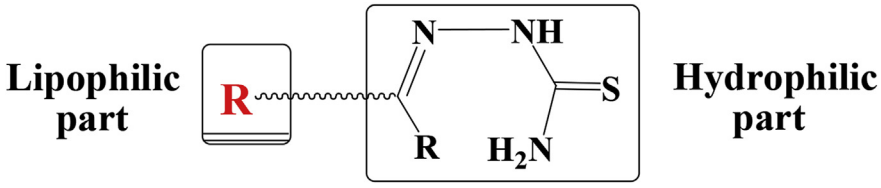

Fig. 3. Hydrophilic part and the lipophilic part of thiosemicarbazone compounds.

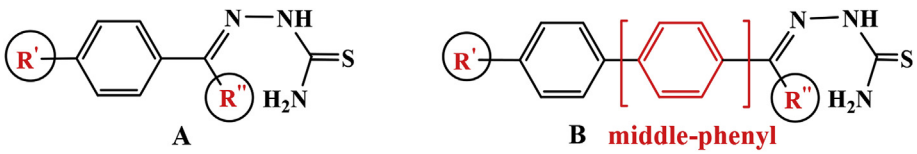

Fig. 4. The basic framework of tyrosinase inhibitors involved in this study.