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Molecular docking and QSAR analyses of aromatic heterocycle thiosemicarbazone analogues for finding novel tyrosinase inhibitors

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ABSTRACT

A collection of 36 thiosemicarbazone analogues possessed a broad span of tyrosinase inhibitory activities was designed and obtained. Robust and reliable CoMFA and CoMSIA models were gained to predict the structure–activity relationship and the new modifier direction. Inhibitory activities of the compounds were found to greatly depend upon molecular shape, size, and charge. The sterically bulky group at the C-4 position of the thiophene ring contributed a high capacity for biological activity. Some bulky substituents at the C1-position and C12-position, and electron-negative groups at the C3-position, helped to improve the activity of these analogues. The molecular docking results provided visual evidence for QSAR analysis and detailed information about binding mode, affinity, and the principal mechanism between the ligands and tyrosinase. Based on these, a prospective structure modification and optimization of the most potent compound, **T32**, was suggested for further research.

1. Introduction

Tyrosinase (EC 1.14.18.1), a metalloenzyme with dinuclear copper in the active site, is a key enzyme in the biosynthesis of melanin pigment [1]. Melanin plays an essential role in the protection against UV injury and skin cancer under normal physiological conditions. However, excessive melanin production and accumulation caused by abnormal tyrosinase activity is responsible for not only the undesired enzymatic browning of fruits and vegetables [2] but also for the formation of various dermatological disorders, such as freckles [3], melasma [4], ephelide [5], and senile lentigines [4]. Moreover, excessive tyrosinase activity has been linked to the neurodegeneration associated with Parkinson's and other degenerative diseases [6]. Thus, the relevance of tyrosinase is extensively highlighted and there is an increasing interest among researchers to pursue efficient and feasible tyrosinase inhibitors.

To date, a large number of naturally occurring and synthesized aromatic molecules including aromatic alcohols [7,8], aromatic acids [9,10] and aromatic aldehydes [5,11] have been reported as tyrosinase inhibitors. Unfortunately, these agents are not ideal enough due to their unsatisfied activity and undesirable side effects [12]. These years, aromatic thiosemicarbazone analogues have been receiving considerable attention in the area of medicinal chemistry because of their promising biological implications and remarkable pharmacological properties [13]. Various thiosemicarbazone analogues have been used in the treatment of antimicrobial [14], anti-HIV-1 [15], anticancer [16] as well as potential tyrosinase inhibitors [11,17–19]. However, most of these reports preferred compounds containing aromatic benzene moiety [20]. Reports on thiosemicarbazone derivatives containing aromatic heterocycle groups normally occurring in natural products are scarce. A series of aromatic heterocycle thiosemicarbazone analogues with notable tyrosinase inhibitory activity and low toxicity was suggested in our previous research as a probable new kind of potential tyrosinase inhibitors [21–24]. It was possible to significantly increase the inhibitory activity with a modifier by introducing an appropriate functional group at its thiophene ring [24]; however, more research is still necessary to find out how the functional structure and inhibitory mechanisms affect the inhibitory

Abbreviations: 3D-QSAR, three-dimensional quantitative structure–activity relationship; CoMFA, comparative molecular field analysis; CoMSIA, comparative molecular similarity indices analysis; PLS, Partial Least Squares; L-DOPA, L-3,4-dihydroxyphenylalanine; pIC_{50}, $-logIC_{50}$; q^2, cross-validated correlation coefficient; LOO, leave-one-out; ONC, optimum number of components; r^2, squared correlation coefficient; *SEE*, standard error estimate.

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activities and what other modification and optimization should be done to the known inhibitors for more activity and fewer side effects. In this study, a collection of fourteen newly synthesized (**T01**-**T09**, **T13**, **T32**-**T36**) as well as twenty-two previously reported (**T10**-**T12** [23], **T14**-**T25** [24], **and T26-T32** [25]) thiosemicarbazone heterocycle analogues and their tyrosinase inhibitory activities were designed and obtained. A three-dimensional quantitative structure-activity relationship (3D-QSAR) study using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) was performed to predict the structure–activity relationship and the new modifier direction. Partial least squares (PLS) analysis [26] with a cross-validation procedure was employed to select the relevant components from the large set of CoMFA data to obtain the best QSAR equation. The acquired CoMFA and CoMSIA contour maps were used as visible guides to design the new and more potent tyrosinase inhibitory compounds. In addition, molecular docking was employed to investigate the binding mode and interaction mechanism between the inhibitors and tyrosinase.

2. Materials and methods

2.1. Chemistry

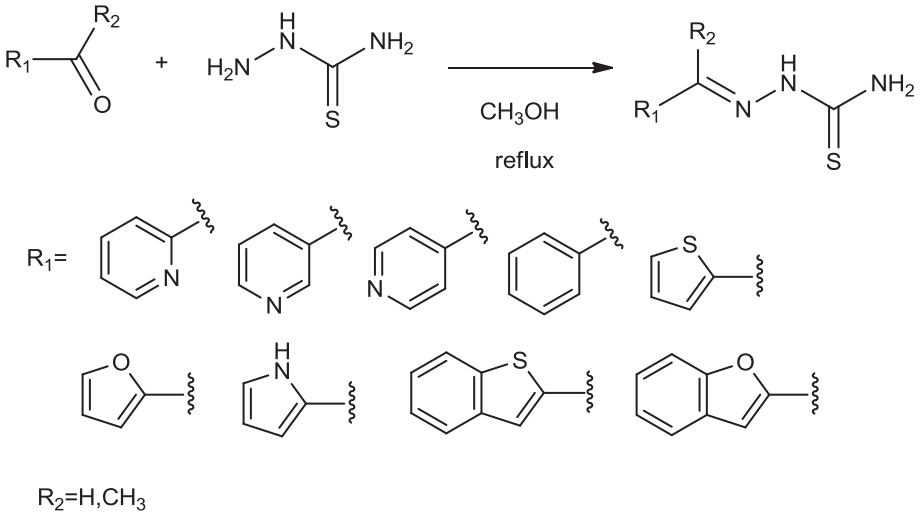
Synthesis route of target analogues **T01**-**T09** and **T13** was described in Scheme 1; Synthesis route of analogues **T32**-**T36** was described in Scheme 2, as references described [27,28].

The synthetic products were purified by recrystallization with ethanol and identified by ESI-MS, ^{1}H NMR and ^{13}C NMR analyses. ESI-MS data were recorded on a Bruker ESQUIRE-LC (Germany), ^{1}H NMR and ^{13}C NMR data were acquired on a 400 MHz NMR spectrometer (DD2-400) from Agilent (USA).

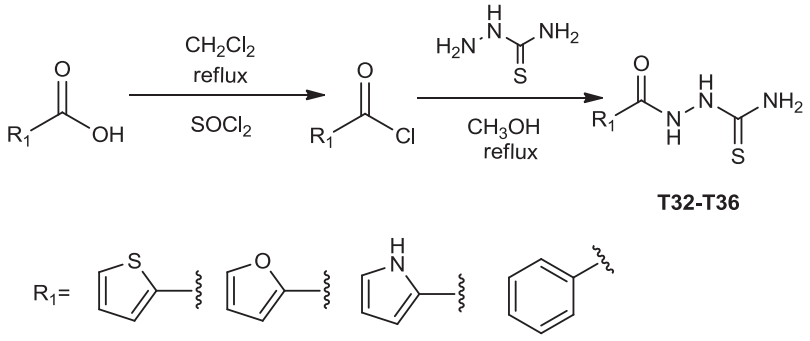
2-Pyridine carboxaldehyde thiosemicarbazone, **T01**: white solid, yield 85.2%, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H, NH), 8.56 (s, 2H, NH2), 7.13 (s, 1H, CH), 8.65 (s, 1H, pyridine-H), 7.85 (s, 1H, pyridine-H), 7.64 (s, 1H, pyridine-H), 7.79 (s, 1H, pyridine-H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 178.55 (1C, C=S), 152.27 (1C, C=N), 153.65 (1C, pyridine-C), 149.18 (1C, pyridine-C), 126.29 (1C, pyridine-C), 136.15 (1C, pyridine-C), 120.04 (1C, pyridine-C). MS (ESI): m/z 179.0 $[M-H]^-$.

3-Pyridine carboxaldehyde thiosemicarbazone, **T02**: white solid, yield 89.4%, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H, NH), 8.46 (s, 2H, NH2), 8.34 (s, 1H, CH), 9.07 (s, 1H, pyridine-H), 8.69 (s, 1H, pyridine-H), 7.58 (s, 1H, pyridine-H), 8.30 (s, 1H, pyridine-H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 178.55 (1C, C=S), 143.33 (1C, C=N), 130.43 (1C, pyridine-C), 149.06 (1C, pyridine-C), 151.97 (1C, pyridine-C), 123.95 (1C, pyridine-C), 133.74 (1C, pyridine-C). MS (ESI): m/z 179.0 $[M-H]^-$.

4-Pyridine carboxaldehyde thiosemicarbazone, **T03**: white solid, yield 88.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H, NH), 8.56 (s, 2H, NH2), 8.60 (s, 1H, CH), 8.66 (s, 1H, pyridine-H), 7.98 (s, 1H, pyridine-H), 7.98 (s, 1H, pyridine-H), 8.66 (s, 1H, pyridine-H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 178.55 (1C, C=S), 146.88 (1C, C=N), 144.39 (1C, pyridine-C), 120.41 (1C, pyridine-C), 149.46



Scheme 1. Synthetic route of analogues T01-T09 and T13.



Scheme 2. Synthetic route of analogues T32-T36.