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Investigating the binding mechanism of (4-Cyanophenyl)glycine derivatives as reversible LSD1 by 3D-QSAR, molecular docking and molecular dynamics simulations

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ABSTRACT

Lysine specific demethylase 1 (LSD1) have been regard as an important drug target on the therapy of cancer and leukemia. However, the development of effective reversible LSD1 inhibitors was facing many challenges. In this work, we carried out a molecular modeling study on (4-Cyanophenyl)glycine derivatives as reversible LSD1 inhibitors using 3D-QSAR, molecular docking and molecular dynamics simulations. Molecular docking study revealed the possible binding mechanism of these inhibitors with LSD1. We used comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) to generate 3D-QSAR models. The results showed that our CoMFA model had q^2 of 0.785, $r^2 = 0.994$ and r^2_{pred} of 0.92, while the best CoMSIA model had q^2 of 0.746, $r^2 = 0.985$ and r^2_{pred} of 0.86. Molecular dynamics simulations validated the rationality of docking results and predicted the detailed interactions between the ligands and LSD1. An important hydrogen bond network was discovered though MD simulation. Some key residues (FAD, Asp555, Gln358, Tyr761, Lys661 and Trp695) were pointed out after the binding free energy calculation using MM-PBSA method. We hope these result could provide useful information for our further design of potent and selective LSD1 inhibitors.

1. Introduction

Lysine specific demethylase 1 (LSD1) was the first identified histone lysine demethylase, and it could catalyze the demethylation process of histone lysine residues, specially H3K4me1/2 and H3K9me1/2 [1]. It was reported that the methylation of H3K4 and H3K9 was associated with gene activation, and removal of methyl group would result in transcriptional repression. Besides, the substrate of LSD1 could also be p53, E2F transcription factor 1 (E2F1) and DNA methyltransferases (DNMTs) [2–4]. In this way, LSD1 could further influence the function of downstream cells. Many studies have proved that the overexpression of LSD1 will lead to a series of diseases, such as cancer and leukemia [5,6]. Therefore, the developments of effective and selective LSD1 inhibitor have become an important goal for medicinal chemistry scientists.

LSD1 belongs to the FAD-dependent amine oxidase family, and was homology protein with monoamine oxidase A (MAO-A) and B (MAO-B). Based on this, some MAO inhibitors were initially used for LSD1 (Fig. 1A and B), and these compounds could inhibit LSD1 by covalently binding to FAD [7,8]. As the poor activity of these compounds, optimization was performed and finally got a series of effective irreversible inhibitors (Fig. 1C and D) [9,10]. Meanwhile, some small molecules were also found have LSD1 inhibitory activity (Fig. 1E–G) [11–13]. But their activity could not achieve the level of irreversible inhibitors, which prompted us to have a deep insight into the binding mechanism of LSD1 inhibitors and find key interactions between inhibitors and LSD1 for our further drug design.

Computer-aided drug design have become a frequently used method for the novel drug discovery in recent years, including three-dimensional quantitative structure-activity relationship (3D-QSAR), molecular docking and molecular dynamics (MD) simulations methods [14]. 3D-QSAR study could help to find the important

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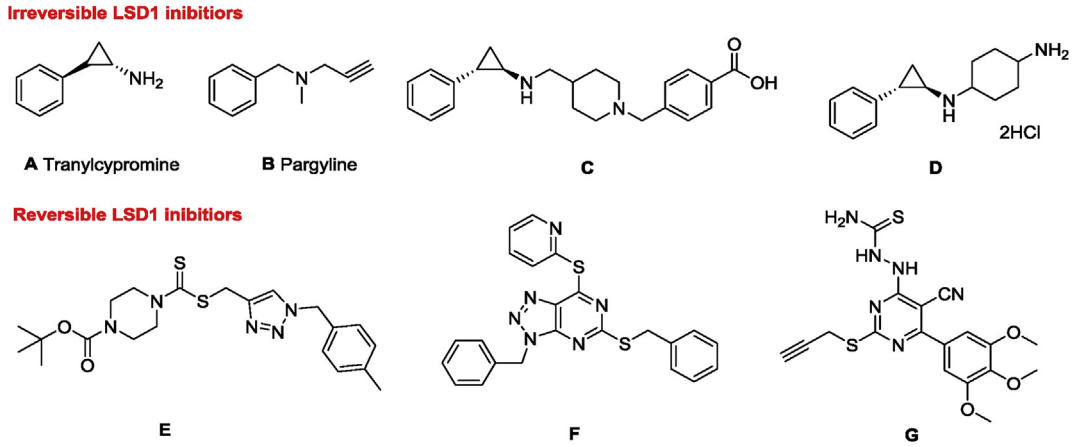

Fig. 1. Structures of some reported LSD1 inhibitors.

structural features affecting the activity and understand interaction characteristics between drug molecule and target [15]. Molecular docking was a powerful approach to predict the optimized conformation of a ligand at the binding site of a receptor and clarify the receptor-ligand interaction [16]. Meanwhile, MD simulations could analyze the conformational changes of ligand molecule and find key residues for the binding process [17]. Hence, the combination of 3D-QASR, molecular docking and molecular dynamics simulations might be an effective way to analyze the detailed binding mode between the inhibitor and receptor [18–20].

According to a recent study, a series of (4-Cyanophenyl)glycine derivatives were identified as reversible LSD1 inhibitors. These compounds showed potent activity against LSD1, while IC_{50} value of the most active compound was 0.083 μM [21]. And these compounds also exhibited promising activity toward two AML cell lines in cellular assays. To investigate which compound was competitively bind to the substrate pocket of LSD1 and would exhibit promising activity toward AML cell lines as well as find key residues during the binding process, a combination of 3D-QSAR, molecular docking and molecular dynamics simulations were performed on these (4-Cyanophenyl)glycine derivatives, and 3D-QSAR models were generated using comparative molecular field analysis (CoMFA) [22] and comparative molecular similarity indices analysis (CoMSIA) method [23].

2. Methods and materials

2.1. Data sets and biological activities

The molecular docking and 3D-QSAR studies were performed using Sybyl X-2.0 software [24]. In this study, all the 29 studied molecules and their IC_{50} values were taken from the literature [21]. The three-dimensional structures of all compounds were built and energy minimized with Gasteir-Huckel charge in the Tripos force filed [25]. The studied compounds were divided into a training set and a test set which contained 22 compounds and 7 compounds, respectively. The IC_{50} value of each compound was converted into pIC_{50} value (-log IC_{50}). The structures and activities of all the studied compounds were shown in Table 1.

2.2. Molecular docking

Molecular docking study was carried out to investigate the probable binding mode of studied compounds and find some important residues for binding. The crystal structure of LSD1 was retrieved from Protein Data Bank (PDB ID: 2V1D). Before the docking study, the protonation states of protein and ligands were calculated using PROPKA 3.1 [26]. The protein structure was prepared by adding hydrogen atoms, repairing side chains, adding charges and taking an energy minimization in the Tripos force filed. The three-dimensional structures of all studied compounds were also prepared though conformational search. Finally, the prepared ligands were docked into the substrate pocket of LSD1. Each compound remained 20 best-scored binding poses for our further analysis.

2.3. Molecular alignment

The molecular alignment played a key role in the generation of 3D-QSAR models, and the active conformation determination of compounds was its most important step. After molecular docking, all the other studied compounds were aligned to the best docked conformation of compound **29** as it was the most potent compound. The (4-Cyanophenyl)glycine fragment was set as common substructure for alignment. The structure of compound **29** and the alignment result were shown in Fig. 2.

2.4. 3D-QSAR studies

The CoMFA and CoMSIA descriptors were derived by using a 3D cube lattice with grid spacing of 2 Å beyond the aligned molecules in all directions. For the CoMFA analysis, models of steric and electrostatic fields were based on both Lennard-Jones and Coulombic potentials. The steric and electrostatic fields were calculated at each grid point using a sp^3 carbon probe atom with a charge of +1.0, a van der Waals radius of 1.52 Å [27]. The truncation for both the steric and the electrostatic energies was set to 30 kcal/mol.

For the CoMSIA models, besides steric and electrostatic fields, the hydrophobic, hydrogen bond donor and hydrogen bond acceptor fields could also be calculated using an sp^3 carbon probe atom of a +1 charge, a van der Waals radius of 1 Å, hydrophobicity of +1, and hydrogen bond donor and acceptor properties of +1 [27]. Gaussian function was used for evaluating the mutual distance between the probe atom and each molecule atom [28]. In addition, the value of attenuation factor α was set to 0.3.

The partial least square (PLS) regression method was utilized to conduct our CoMFA and CoMSIA analysis. We used leave-one-out (LOO) method to calculate the cross-validation correlation coefficient (q^2) and optimum number of components (N). A reliable 3D-