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Molecular dynamics simulation of the interaction between protein tyrosine phosphatase 1B and aryl diketoacid derivatives

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ABSTRACT

The protein tyrosine phosphatase 1B (PTP-1B) is acknowledged as an outstanding therapeutic target for the treatment of diabetes, obesity and cancer. In this work, six aryl diketoacid compounds have been studied on the basis of molecular dynamics simulations. Hydrogen bonds, binding energies and conformation changes of the WPD loop have been analyzed. The results indicated that their activation model falls into two parts: the target region of the monomeric aryl diketoacid compounds is the active site, whereas the target region of the dimeric aryl diketoacid compounds is the WPD loop or the R loop. The van der Waals interactions exhibit stronger effects than the short-range electrostatic interactions. The van der Waals interaction energy and the IC50 values exhibit an approximately exponential relationship. Furthermore, the van der Waals interactions cooperate with the hydrogen bond interactions. This study provides a more thorough understanding of the PTP-1B inhibitor binding processes.

1. Introduction

Protein tyrosine phosphatases (PTPs) are a large family of enzymes that catalyze the conversion of phosphorylated tyrosine of protein into tyrosine and inorganic phosphate [1]. PTPs play an important role in biological processes, and they are a crucial modulator in the range of cellular processes such as cell growth, differentiation and metabolism [2–4]. Among PTPs, protein tyrosine phosphatase 1B (PTP-1B) has been found to be a negative regulator in both insulin and leptin signaling [5,6]. For example, PTP-1B-deficient mice display enhanced insulin sensitivity and improved glycemic control and resistance to a high-fat diet, which induces obesity [7,8]. Therefore, PTP-1B inhibitors have been considered as a promising drug candidate for the treatment of Type II diabetes, insulin resistance and obesity [9–12].

PTP-1B contains N-terminal and C-terminal domains. The N-terminal domain contains catalytic regions [13]. The C-terminal domain contributes to the location of the enzyme at the cytoplasmic face of the endoplasmic reticulum and influences the N-terminal domain by causing a global conformational change of PTP-1B molecules that allows the formation of direct contacts between the catalytic domain and the phosphorylated substrates [14]. Interestingly, the catalytic domain contains two aryl phosphate-binding sites: a highly conserved active site (His214-Arg221) and a lowly conserved non-catalytic site B (Arg24 and Arg254) (Fig. 1), which is located adjacent to the active site [15]. In general, the most efficient inhibition is accomplished when the inhibitor occupies the active site. Therefore, the inhibitor should possess polar groups and be anionically charged at physiologic pH. At the same time, the inhibitor molecule is stably anchored through the formation of hydrogen bonds between particular amino acid residues and the functional groups of inhibitors within the active site. However, the polar groups will reduce the ability of the PTP-1B inhibitors to cross the cell membrane and access the cytosolic PTP-1B [16].

The WPD loop plays a role in the specificity and the affinity of the inhibitor. WPD (Thr177-Pro185) and R (Val113-Ser118) loops cover the active site when the inhibitor binds to the substrate. In the native form, no inhibitor binds to the PTP-1B; the WPD loop is in an open conformation, and the active site is easily accessible to the substrate. When the inhibitor is bound with the active site, the WPD loop closes over the active site, and the WPD loop and the active site subsequently form a tightly binding pocket for the substrate. To be specific for PTP-1B, the inhibitor should reduce the mobility of the WPD loop toward a more rigid conformation, which inhibits the closure of the WPD loop and prevents the substrate from binding [17,18]. Unfortunately, the discovered inhibitors exhibit poor selectivity toward PTP-1B.

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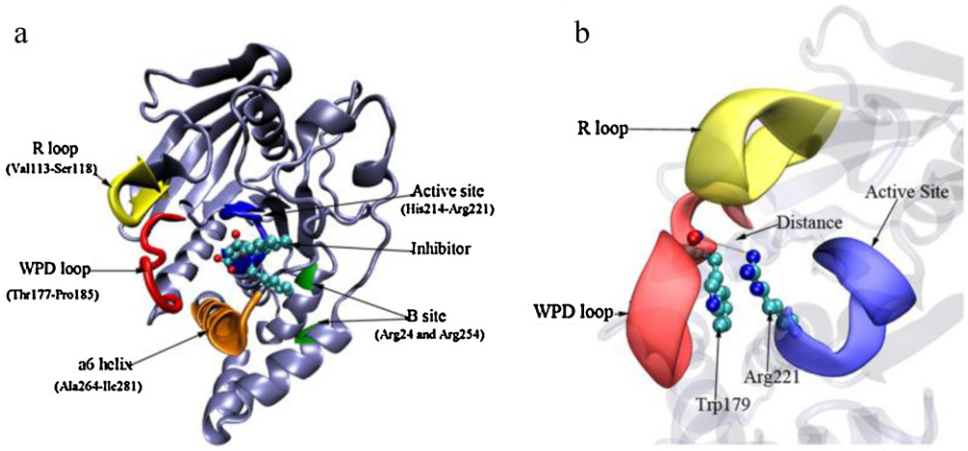

Fig. 1. (a) The three-dimensional structure of PTP-1B with highlight regions. (b) The distance of the backbone carbonyl oxygen of Trp179 and the nitrogen of the guanidinium moiety of Arg221 in PTP-1B.

Excellent work has been conducted on this topic over the past two decades. Many compounds have been studied and have been proven to be potential inhibitors. Vanadate [19–21], for example, was the first and most extensively investigated PTP1B inhibitor. Selectivity is a challenging issue in the design of PTP-1B inhibitors. In 1997, Zhang and his colleagues discovered a second binding active site near the conserved primary active site [15]. This binding site is not as conserved and can be exploited to design PTP-1B inhibitors with high selectivities. Since then, numerous bidentate compounds have been studied and have been proven to be potential and selective PTP-1B inhibitors [17,22–31]. However, these compounds contain negatively charged nonhydrolyzable phosphotyrosine (pTyr) mimetics and have poor membrane permeability, which results in their inability to readily enter the cell. Consequently, the identification of compounds with good bioavailability is still a major challenge in this field.

Recently, aryl diketoacids have been reported by Liu et al. to be potential noncompetitive, active site-directed and selective PTP-1B inhibitors [32]. The significance of these compounds stems from the dimeric aryl diketoacid lacking any formal charge, being cell-permeable and also exhibiting PTP-1B inhibitory activity. These properties may solve the bioavailability problem in pharmaceutical applications. Regrettably, little research has been conducted on these PTP-1B inhibitors. This work is intended to fill this gap through analysis of the interaction models of these compounds via molecular dynamics (MD) simulations. Hydrogen bonds, binding energies and conformation changes of the WPD loop are analyzed in this work.

2. Methods

2.1. Simulation models

Six aryl diketoacid compounds are adopted as the object of study (see Table 1). Three of them (LZP4, LZP38 and LZP25) are monomeric aryl diketoacid compounds that exhibit inhibitory activity for PTP1B. Three corresponding dimers (LZP6, LZP38 and LZP40) linked with the piperazine show an improvement in the inhibitory activity [32]. The atom label follows the nomenclature of the standard GROMACS96 43a2 force field. The geometry of six aryl diketoacid compounds is optimized using the Gaussian03 [33] program at the level of B3LYP/6-31G(d) [17,27].

The crystal structures of PTP-1B-LZP25 Complex (PDB ID: 3EB1 [32]) and LZP6-PTP-1B Complex (PDB ID: 3EAX [32]) were downloaded from the Protein Data Bank [34]. Because the crystal structure of 3EAX (LZP6-PTP-1B) is a high-resolution (1.9 Å) X-ray structure, we selected it for the generation of the initial models. Crystallographic water molecules and ligands in 3EAX were removed. Six aryl diketoacid compounds were subsequently docked into the binding pocket using the AutoDock4.2 program [35]. The binding model with lowest binding free energy for each inhibitor is selected as the best model. The binding positions for the six inhibitors are listed in Supporting information (Fig. S1). The best models generated here served as initial structures for subsequent molecular dynamics simulations.

2.2. Molecular dynamics simulations

The molecular dynamics (MD) simulations were performed using the GROMACS program (version 4.0.5) with the GROMACS96 43a2 force field [36]. The molecular topology file and the force-field parameters for the inhibitors were generated by the program PRODRG online [37]. PRODRG is an automated topology generation tool that has been widely used in the study of protein–ligand systems [29,31,38,39]. The charges of the inhibitors generated by this server have also been validated in similar compounds [29]. The generated charges of six inhibitors are listed in Supporting information (Tables SI–SII). Each model was solvated with explicit simple point charge (SPC) water embedded in a 70 Å × 70 Å × 70 Å box. The total charge of the system was −1. To achieve charge neutrality in the system, one sodium ion was added in place of one water molecule in the box.

The systems were then subjected to a steepest-descent energy minimization until they reached a tolerance of 1000 kJ/mol. All bonds that contained hydrogen bonds were constrained using the LINCS algorithm [40]. The Nose–Hoover and Parrinello–Rahman algorithms were used for the temperature and pressure coupling. The value of the isothermal compressibility was set to 4.5×10^{-5} bar^{-1} for water simulations. The electrostatic interaction energy was calculated using the particle-mesh Ewald (PME) algorithm [41], with an interpolation order of 4 and a grid spacing of 1.2 Å. The cut-off of van der Waals (vdW) interaction was 10 Å.

Finally, a 20 ns MD simulation was performed for each system under a temperature of 300 K and a pressure of 1 bar with a coupling time constant of 2.0 ps. The time step was 2 fs, and the trajectories were collected every 1 ps. The last 5 ns were used for further analyses.