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Aminotransferases Screening of Nitro-D-Arginine Using Molecular Modeling

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Abstract. This study is intended to screen the potential aminotransferases using molecular modeling technique. In detail, the sybyl-x software was employed to simulate the second step of catalysis process of nitro-D-arginine (D-NNA) by aminotransferases whose structural data were from Protein Data Bank (PDB). Results showed the most suitable candidate aminotransferase was human mitochondrial aspartate aminotransferase in the range of our research, which might aid to shortening the drug developing cycle and increasing the efficiency of lead compound discovery.

Keywords: molecular modeling, aminotransferase screen, nitro-D-arginine

1. Introduction

Molecular modeling is widely used in drug developing, material design and other fields [1]. As a powerful tool, molecular modeling provides the exploration guideline for the drug design in a simulation way, calculating the biomolecular interactions on the computer with saving time and money. There are many molecular modeling softwares were developed such as Affinity, Dock, DDT, AutoDock, DOCK, 3D-DOCK, ZDOCK, GRAMM, DOT, Modified, and FTDOCK [2, 3]. For example, DOCK software developed by Kuntz group, has the capacity of identification for the low-energy binding modes of a small molecule, or ligand, within the active site of a macromolecule, or receptor, whose structure is known[4, 5].

Studies reported that nitro-D-arginine could be converted into nitro-L-arginine as an inhibitor of nitric oxide synthase by chiral switch [6-9]. D- amino acid could be catalyzed into α-keto acid by the D- amino acids oxidase, which mainly distributed in the kidney in mammals. It was speculated that α-keto acids were converted to nitro-L-arginine by aminotransferase [7].

In this paper, the molecular docking software Sybyl was employed to simulate the molecular docking for the possible conversion of nitro-D-arginine to nitro-L-arginine, and screen the transaminase based on the scoring function.

2. Methods

The 3D data of transaminase structure were from Protein Data Bank (PDB, http://www.rcsb.org), which collects the 3D shapes of proteins, nucleic acids, and complex assemblies[1]. The transaminase was selected as the target protein molecule (Table 1).

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Table 1: The main transaminase selected

PDB ID	*Candidate Aminotransferase*
5AX8	human mitochondrial aspartate aminotransferase
3IHJ	Human alanine aminotransferase 2
3DYD	Human Tyrosine Aminotransferase
2BYJ	Ornithine aminotransferase mutant Y85I
3E77	Human phosphorserine aminotransferase
3II0	human Glutamate oxaloacetate transaminase 1
4KYO	Alanine-glyoxylate aminotransferase variant K390A

The small ligand molecules were removed from the structure of the aminotransferase using software sybyl-x. For example, the PLP were deleted from the PDB data of 5AX8 (Fig. 1). Then the aminotransferase were analyzed to dock with α-keto acid.

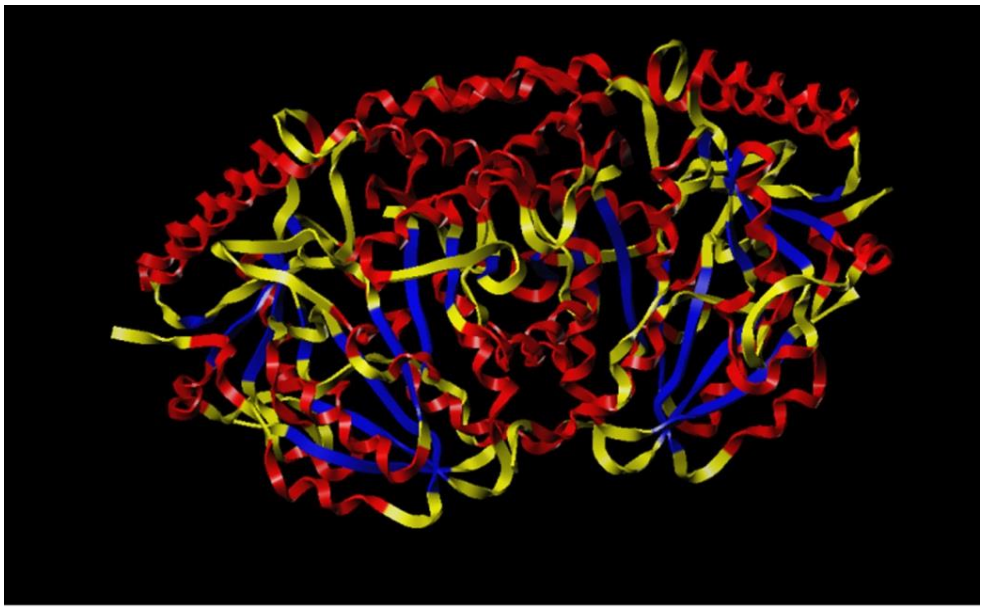

Fig. 1: human mitochondrial aspartate aminotransferase (5AX8)

α-keto acid were prepared by chemical paint tools in Sybyl, and the hydrogen atom was added to the protein structures (Fig. 2). The rigid rood and rotational bond were saved for the flexible docking.

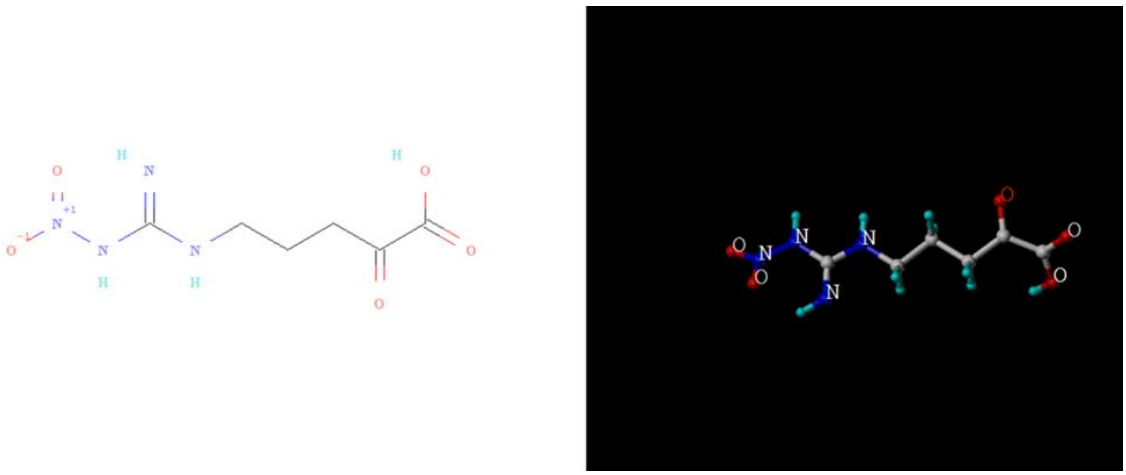

Fig. 2: the molecular model of α-keto acid

In molecular docking, small molecule ligands corresponding to the receptor are needed to be preprocessed. Generally, the changed-adding and hydrogasification processing on the terminal should be performed beforehand, and then minimized the molecular structure energy using powell energy gradient algorithm, with the convergence limit of 0.5 cal/mol. The Tripos force field and atom charge were iterated

using Gasteiger-Huckel, and the other parameters were setup as the default values of Sybyl software for the mini-energy structure of molecular docking.

The ligand molecular were also processed by adding hydrogen and parameters setup as the proteins molecular processing and saved as the mol2 format.

3. Results and Discussions

The docking experiment for transaminase and nitro-D-arginine were carried using Sybyl software.

Table 2: The results of molecular docking

Name	*Total_Score*	*Crash*	*Polar*	*D_SCORE*	*PMF_SCORE*	*CHEMSCORE*	*CSCORE*
NRG_001	8.6406	-0.7921	8.1595	-78.6878	-87.9116	-26.337	3
NRG_002	8.1465	-0.9949	7.528	-81.9974	-99.2282	-21.6335	3
NRG_003	7.9776	-1.0021	6.9329	-100.463	-71.0198	-22.376	3
NRG_004	7.9502	-0.3757	6.547	-88.6708	-102.874	-18.6506	2
NRG_005	7.7346	-0.7818	6.8886	-101.209	-75.096	-21.4337	3
NRG_006	7.2551	-1.3402	7.3879	-76.4041	-89.7335	-24.4206	2
NRG_007	7.2543	-1.5509	7.2714	-88.6045	-72.4366	-20.134	0
NRG_008	7.0521	-1.1924	5.956	-102.68	-72.6075	-19.7567	2
NRG_009	7.0299	-0.5803	5.7346	-80.4304	-74.8378	-17.8354	0
NRG_010	6.8278	-0.6317	5.6184	-80.7332	-77.6624	-17.4975	0
NRG_011	6.7106	-1.3753	6.2685	-80.8766	-74.2781	-19.0144	0
NRG_012	6.7097	-1.6915	6.2622	-95.3702	-74.4473	-15.3024	1
NRG_013	6.6759	-1.8697	6.0955	-109.848	-68.8009	-18.4744	2
NRG_014	6.631	-1.2177	5.3637	-94.19	-68.5063	-20.1126	2
NRG_015	6.6236	-0.4761	5.4376	-81.2247	-99.6563	-15.549	1
NRG_016	6.6195	-1.1871	5.5621	-104.382	-69.4228	-22.1755	3
NRG_017	6.5417	-0.8144	7.846	-73.6594	-95.2494	-24.1915	2
NRG_018	6.515	-0.8882	6.2464	-85.4758	-96.7722	-20.105	1
NRG_019	6.5119	-1.2859	6.6463	-74.5796	-86.6566	-22.6092	2
NRG_020	6.5003	-0.7946	6.2276	-81.8358	-96.8135	-19.6592	1

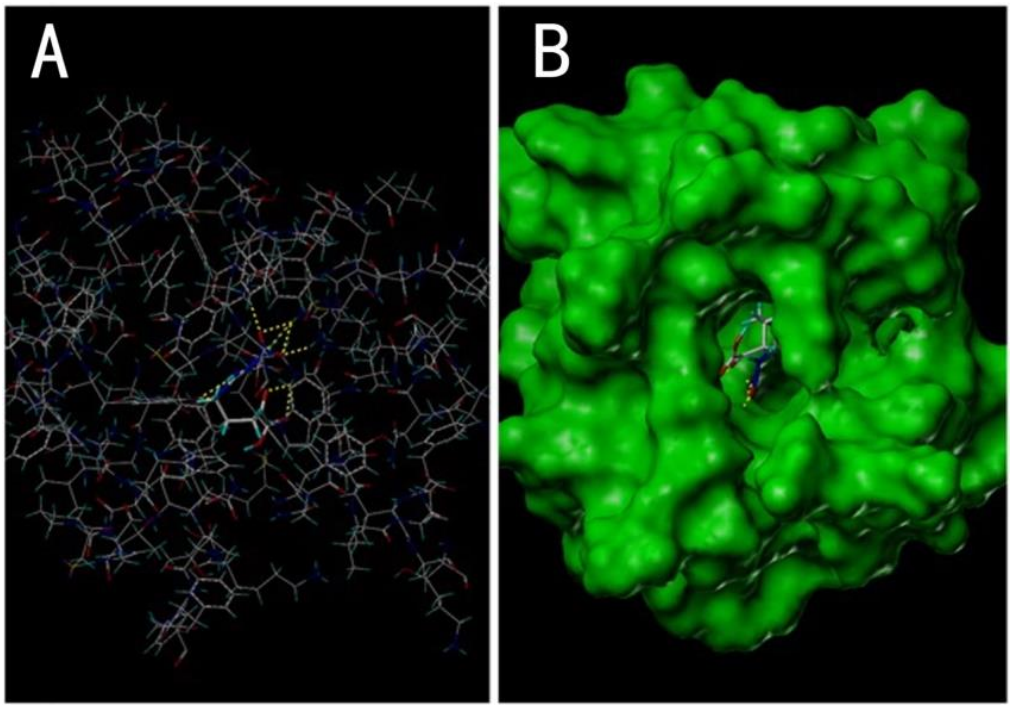

Fig. 3: The docking image of transaminase K and nitro-D-arginine. (A) Original structure of molecular docking model; (B) Structure model of rendering for the molecular

Depended on the molecular modeling simulation and analysis (Table 2), in the second stage of the catalysis reaction of N^G-nitro-D-Arginine into enantiomers nitro-L-Arginine, the most suitable candidate aminotransferase was calculated out to be human mitochondrial aspartate aminotransferase (Fig. 3) in the range of our research.

4. Acknowledgements

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