Molecular docking study of designed N-myristoyl transferase inhibitors

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Abstract: N-myristoyl transferase has a key role in the myristoylation of vital proteins and is necessary for the growth and synthesis of material for the survival of various fungi. Due to the difference in the structure of fungal and mammalian N-myristoyl transferase, the crystal structure of the N-myristoyl transferase originating from *Candida albicans* was used as the target molecule. The present *in silico* study aims to design compounds, benzofuran derivatives, and simulate the interactions of the compounds and the amino acid sequences of the active center N-myristoyl transferases from *Candida albicans* using the molecular docking method. The highest number of significant binding interactions is realized by the derivative **4.** Affinity toward the N-myristoyl transferase active site was very similar to the co-crystallized ligand, and important hydrogen interactions were retained. Based on the obtained results of molecular docking, it can be concluded that derivative **4** has the potential to inhibit N-myristoyl transferase, on which future research of its antifungal activity can be based.

Keywords: N-myristoyl transferase, molecular docking, benzofuran derivatives

1. Introduction

N-myristoyl transferase (NMT) is a member of the GNAT (Guanine nucleotide-binding protein) or G-protein superfamily and consists of an N-terminal and C-terminal region. The N-terminal region forms the myristoyl-CoA binding site while the C-terminal region forms the major part of the peptide binding site [1]. N-myristoyl transferase is a ubiquitous enzyme in eukaryotes that catalyzes the transfer of a myristoyl group from myristoyl-CoA to the N-terminal glycine of a protein substrate. Myristoylation occurs in two steps: methionine aminopeptidase removes the methionine initiator residue on the peptide substrate. Then, the resulting peptide with a terminal

glycine moiety becomes the substrate for NMT activity (Figure 1). Genetic experiments have shown that many fungal species such as *Candida albicans* and *Cryptococcus neoformans* cannot survive without NMT [2].

In recent years, infections caused by pathogenic fungi are becoming more common, especially in immunocompromised patients. *Candida albicans* is the most frequently identified *Candida* species and is one of the leading causes of hospital-acquired infections. Currently, conventional antifungal agents have a very limited spectrum of action with an inadequate pharmacokinetic profile and serious interactions with other drugs. Hence, research and development of new drugs with a more attractive mode of action are being pursued [3].

The purpose of the present *in silico* study was to design benzofuran derivatives, based on the results of SAR (structure-activity relationship) studies, and then to simulate their binding interactions with the active site of N-myristoyl transferases using the molecular docking method.

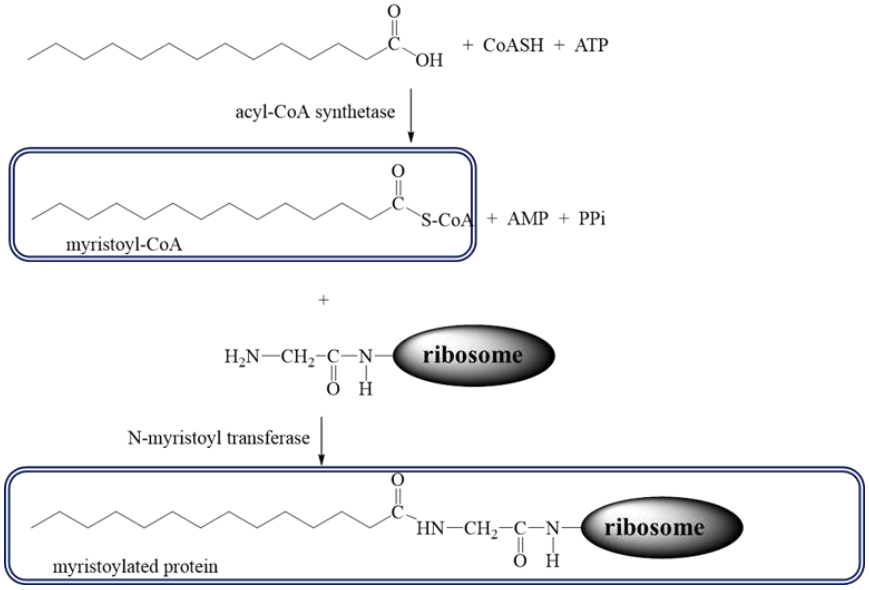

Figure 1. Mechanism of action N-myristoyl transferase.

2. Materials and methods

Optimizing energy of the design compounds was carried out using the program Chem3D Ultra 7.0.[4]. The crystal structure of N-myristoyl transferase in a complex with a non-peptide inhibitor (PDB ID: 1IYL) was downloaded from the Protein Data Bank. The preparation of the target molecule was performed in the Discovery Studio Visualizer 17.2.0.16349 [5], by removing units B, C, and D, whereas unit A was used in this molecular docking study. A focused semi-flexible molecular docking method was carried out using the AutoDockVina software [6]. The search area was set as a grid box size of 30 x 28 x 32 points and a spacing of 0.375 Å, based on the position of the co-crystallized ligand. The best fitted conformation of the design compounds was visualized using Discovery Studio Visualizer and PyMol 2.4.1. [7].

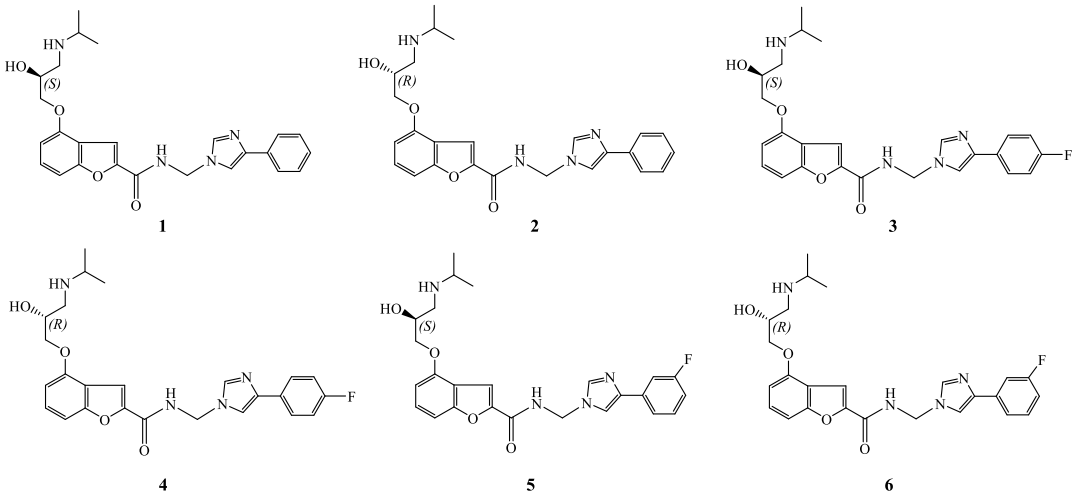

Figure 2. The structures of the design compounds.

3. Results and discussion

N-myristoyl transferase plays an important role in the myristoylation of vital proteins and is necessary for the growth and synthesis of material for the survival of various fungi. Due to the difference in the active sites of fungal and mammalian N-myristoyl transferase, and the difference in the binding manner of the potential inhibitor, the crystal structure of the N-myristoyl transferase originating from *Candida albicans* was used as the target molecule in this research.

The free binding energy values of all six designed compounds were negative, indicating that all compounds (**1**-**6**) spontaneously bind to the target enzyme (-9.2 kcal/mol, -9.3 kcal/mol, -9.4 kcal/mol, -9.5 kcal/mol, -9.4 kcal/mol, and -9.3 kcal/mol, respectively). The binding potency, in addition to the Gibbs free energy of binding, is influenced by the number and type of significant interactions that investigated compounds establish with the residues of the N-myristoyl transferase active site. The results of the molecular docking indicate the largest number of formed interactions were hydrophobic in nature, with all compounds forming interactions with Leu394, Tyr225, and Tyr354. The highest number of key interactions was realized by the derivative **4** (Figure 3). The phenyl core of derivative **4** formed hydrophobic interactions including π-alkyl type with Leu394 and π-π T shaped with residue Tyr354, while residue Leu415 participates in the formation of significant π-σ interaction with triazole heterocycle of this compound. Triazole heterocycle also formed π-π stacked interaction with Tyr225. Affinity toward the N-myristoyl transferase active site was very similar to co-crystallized ligand and important hydrogen bonds were retained. Namely, the amide linker group of derivative **4** formed a conventional hydrogen bond with Tyr225 as an H-acceptor and also formed an additional π-donor hydrogen bond. The obtained complex was additionally stabilized by the formation of a π-σ interaction of the residue Tyr225 with the side chain and a π-π T-shaped interaction with the benzofuran core of the tested compound. On the basis of the Gibbs free energy of binding, derivative **4** forms a more stable complex with N-

myristoyl transferase (-9.5 kcal/mol), compared to other design compounds, which makes it particularly interesting for future research.

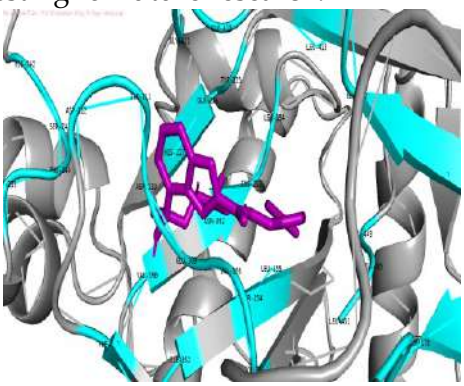

Figure 3. Molecular docking of derivative **4** into the active site of N-myristoyl transferase.

3. Conclusions

According to obtained results of molecular docking, it can be concluded that derivative 4 has the potential of inhibiting N-myristoyl transferase, on which future research of its antifungal activity can be based.

Acknowledgment

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