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In silico Discovery of a New Potent Inhibitor for Sterol 14-alpha Demethylase as a Promising Antifungal Drug against *Aspergillus fumigatus* Infection

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Abstract: *Aspergillus fumigatus* is a dangerous opportunistic pathogen that causes severe consequences for human beings when its conidia are inhaled. Several inhibitory drugs have recently been suggested to eradicate these fungi by inhibiting the cytochrome P450 sterol 14-alpha demethylase B (CYP51B). These drugs are designed to exhibit high specificity to the heme that is incorporated in the active site of this enzyme. Though effective binding with heme can be achieved, administration of these drugs can be accompanied by variable risks to the user's health. Series of *in silico* screenings were conducted to find out more eligible drug-like compounds to inhibit CYP51B-heme with fewer side effects on patients. Using stringent ZINCPharmer restrictions, seventeen compounds were found to have efficient binding to the heme group of CYP51B. Their effectiveness against CYP51B was tested using molecular docking, drug-likeness prediction, and molecular dynamics (MD) simulation. One compound (ZINC000015774018 or molecule-8) was found to inhibit the heme group with better drug-likeness than that found in the other sixteen drug-like compounds. MD simulations showed that this ligand introduced stabilized interactions with the targeted protein upon interacting with its heme and amino acid residues. Thus it may be used as a potent antifungal inhibitor against *A. fumigatus*.

Keywords: *Aspergillus fumigatus*; drug; heme; molecular docking; treatment.

1. Introduction

Aspergillus fumigatus is a pathogenic filamentous fungus that triggers allergic, acute or chronic diseases in both humans and animals. The inhalation of the conidial balls of *A. fumigatus* is the mortal cause among all known pulmonary aspergillosis, which is typically recognized in the form of aspergilloma. Globally, millions of predisposed people acquire pulmonary and allergies to *A. fumigatus*. A recent estimation suggested over a half million deaths and three million individuals being infected with *A. fumigatus* per year [1]. Pulmonary aspergillosis is a serious infection and is frequently connected with several harmful symptoms, such as asthma, nasal allergies, and aggravations of tuberculosis. This serious condition of Aspergillus results from the asexual reproduction of the fungus, which generates billions of conidial spores that humans consistently inhale. Additionally, recent researches have

highlighted the growing incidence of these fungal infections of the cerebrospinal nervous system, with *Aspergillus* with the primary etiological agents acquired by the respiratory system.

Regardless of the recent suggestions in preventing pulmonary aspergillosis, the prevalence of fungal infections continues to increase, especially in the recent decades in which the ratio of immunocompromised patients has been elevated [2]. In *A. fumigatus*, a crucial enzyme in the sterol biosynthesis is recognized, called lanosterol 14-α-demethylase B (CYP51B). It is involved in removing the lanosterol 14-methyl group to provide the necessary intermediates in ergosterol biosynthesis in the fungal membrane. Thus, the inhibition of CYP51B prevents the transformation of lanosterol to ergosterol [3]. The biosynthesis of ergosterol is mandatory in broad fungal metabolic activities, such as membrane integrity and permeability, cell cycle progression, and cell morphology [4]. Thus, the selective inhibition of this enzyme is extremely prerequisite to ensure a specific therapeutic index [5]. Though several active amino acid residues were recognized in CYP51B, the most important portion in the active site of CYP51B is the heme group. It is widely acknowledged that the heme group is the cornerstone on which CYP51B is largely based in the most metabolic reactions in which this enzyme is involved. Thus, the affinity of any antifungal compound to CYP51B should essentially be determined on binding to the heme group in CYP51B [6]. However, several clinical antifungal agents have been developed with various functions on fungal organisms, such as polyenes, echinocandins, and azoles. Polyenes dispose of ergosterol from cellular membranes; echinocandins can destroy the cell wall, while azole-based compounds can halt the biosynthesis of ergosterol of CYP51B enzyme [7]. Although azole-based drugs are one of the most functional antifungal agents [8], the utilization of each one of these developed drugs still has many constraints related to side effects and pharmacokinetic profile [9]. However, the treatment efficiency with these azole-based ligands remains unacceptably low, and the recovery rate largely depends on how quickly the fungal infection is diagnosed and treated [10]. A recent generation of azole drugs has been developed to inhibit CYP51 in many fungal species [11]. One of the most potent drugs in these recently developed drugs is VT-1598, which has been devised to bind specifically with the heme group of CYP51B [12]. However, it is unknown how this ligand is effective against the emergence of *A. fumigatus* [13]. Thus, this ligand has not been validated to eradicate *A. fumigatus* as further comparative *in silico* and *in vitro* experiments are required to approve this sort of inhibitory compound. However, the clinical administration of such drugs is not adequate to conquer the increasing fungal infections [14].

For this reason, the present situation makes it entirely inevitable to find out a novel chemical compound possesses better antifungal activity than that found in other suggested drugs. The necessity for such a novel compound with such specific antifungal impact is urgent to increase the possibility of recovery and reduce the side effects of the commonly used antifungal medications. Considering all these data, this study has performed a series of the state-of-the-art *in silico* computations to find out more appropriate ligands to act as better CYP51B inhibitors. This study aimed to suggest new possible antifungal compounds to act as promising antifungal drugs against the proliferation of *A. fumigatus* with lower side effects on patients.

2. Materials and Methods

A schematic diagram detailing the main tools employed in the study is shown in Figure 1.