ANTIFUNGAL ACTIVITY OF FLUORESCENT MIKONAZOLE DERIVATIVES

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Among different microbial infections fungal infestations form a separate group of disorders that stands out for its specific treatment methodologies due to the distinctive nature of a pathogen. Such diseases are called mycoses and have either respiratory or systemic manifestations [1]. Mycoses are usually observed among immunocompromised patients outcome and due to the recent rise of HIV infection, they emerge as a growing problem [2, 3]. Thus, an increasing number of confirmed fungal infestations induces the development of new antifungal drugs and tools for mycoses diagnostics. The most popular antifungal drugs are based on different azoles and are aided to inhibit specific fungal cytochromes P450 [4]. The majority of such azoles have a conservative scaffold which origins from 1-(2-(2,4-dichlorophenyl)-2-on)ethylimidazole substituent. On the other hand fluorescent analogs of bioactive compounds are widely used in biochemical researches for analyzing binding sites, cellular transport aspects and fluorescence polarization assays [5, 6]. Among fluorescent compounds boron-containing dyes are popular because of their good optical properties and small molecular volume [7]. Herein we perform a molecular docking (AutodockVina) study on (S)-mikonazole-based structures where the 2,4-diphenyl- substituent in the conservative fragment is replaced with various boron-containing fluorophores (BODIPY, BDAA, BOPHY, boranil and acetylnaphtholate complexes) to value their propensity in resembling (S)-mikonazole behavior on the example of 14 alpha-demethylase (4lxj) from *S. cerevisiae* yeasts. After preparation, the protein structure was relaxed using GROMOS96 43B1 force field. Ligand geometries were optimized using UFF method. Computed free binding energy (E_{bind}) for mikonazole is -9.9 kcal/mol and it is further used as a reference value. Simulations show that proposed fluorescent mikonazole derivatives do not significantly loose affinity towards the tested enzyme. The calculated E_{bind} for BDAA and BODIPY derivatives are from -8.7 kcal/mol to -10.5 kcal/mol with proper orientation in the enzyme active site. BOPHY and other tested boron moieties either have high affinity (highest E_{bind} -10.6 kcal/mol) but they appeared too large and their localization is distorted up to the impossibility of interaction with the enzyme heme. The most effective binding is observed for (2-BODIPY)mikonazole with the average distance between azole moiety and enzyme heme iron atom equal to 3.6 Å. It makes tested fluorescent mikonazole derivatives a perspective starting point for the development of new fluorescent tools for microbial application and fungi studying. In our further works, more comprehensive design, synthesis and *in vitro* testing of mentioned above derivatives are planned.

References

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