BODIPY-LABELED ISONIAZID DERIVATIVES AS TUBERCULOSIS PRODRUGS

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Today tuberculosis (TB) continues to be one of the major reasons for morbidity and mortality causing an estimated 10 million new cases and 1.5 million deaths per year. The emergence of multi-drug resistant and extensive-drug resistant strains is a growing problem fueling the TB epidemics [1]. Among anti-TB drugs isoniazid (INH) is found to be one of the most effective. It is a prodrug forming reactive species after interaction with KatG (RCSB 1sj2) enzyme. INH is rather hydrophilic (MarvinSketch LogP -0,69) and traps into the cell by passive diffusion [2]. Thus, the stage of permeating a hydrophobic cell membrane slows down the total rate of its intracellular accumulation. In recent works, pronounced anti-TB activity was shown for some N2-acylated INHs (NAINH) [3]. The presence of aliphatic moiety is supposed to promote cell membrane permeation by increasing total molecular hydrophobicity. For such derivatives, the mechanism of action is thought to be the same with INH but there is still no published evidence. Therefore, to clarify NAINH's ability to bind in the KatG active site we made molecular docking studies (AutodockVina) on a set of homologous NAINHs containing linear aliphatic substituents up to n-undecyl- [4]. Also we propose new fluorescent boron-dipyrromethene (BODIPY) based NAINHs as potential anti-TB agents. After preparation, the protein structure was allowed to relax using AMBER force field. Ligand geometries were optimized in ORCA program (PBE, def2-SVP, CPCM(Water)) [5]. Simulations show that all of NAINH with linear aliphatic chains able to take proper orientation in the KatG active site with free binding energies (E_{bind}) from -5.9 kcal/mol to -6.6 kcal/mol. The proximity of E_{bind} values for NAINH and INH (-6.1 kcal/mol) implicitly indicates that high NAINH anti-TB effect is likely for specifications in cellular trafficking influenced by physical properties changes (e.g. for undecylated NAINH LogP 3.27) rather than for more effective binding with KatG. The E_{bind} for considered BODIPY-NAINH ranges from -9.0 kcal/mol to -9.7 kcal/mol due to the formation of additional binding sites between protein and BODIPY moiety. Thus for N2-(3-(8-BODIPY)-propionylNAINH (E_{bind} -9.6 kcal/mol) hydrogen bonding with Arg104 and halogen bonding (F-O) with Ser315 additionally contributes to the final ligand-protein complex energy. It makes BODIPY-NAINH perspective derivatives for development. In our further works, we plan to consider the mechanism of NAINH action. Design, synthesis and microbiological evaluation of mentioned above, as well as a new BODIPY-NAINH, also will be accomplished.

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References

1. World Health Organization. Global Tuberculosis Report. World Health Organization, 2019. P. 297.
2. Bardou F., Raynaud C., Ramos C. et al. Mechanism of Isoniazid Uptake in Mycobacterium Tuberculosis // Microbiol. 1998. Vol. 144. P. 2539-2544.
3. Vila-Viçosa D., Victor B.L., Ramos J. et al. Insights on the Mechanism of Action of INH-C_{10} as an Antitubercular Prodrug // Mol. Pharm. 2017. Vol. 14. P. 4597-4605.
4. Trott O., Plson A.J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading // J. Comput. Chem. 2010. Vol. 31. P. 455-461.
5. F. Neese Software update: the ORCA program system, version 4.0 // Wiley Interdiscip. Rev. Comput. Mol. Sci. 2017. Vol. 8. P. e1327.