ABSTRACT

SYNTHESIS OF NEW IVACAFTOR DERIVATIVES WITH ENHANCED PHYSICOCHEMICAL PROPERTIES FOR AN IMPROVED CYSTIC FIBROSIS COMBINATION THERAPY

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Cystic fibrosis, CF, is one of the most common life-shortening genetic diseases among Caucasian population. It is a recessive genetic disease that is mainly caused by different types of mutations affecting the gene encoding for the cystic fibrosis transmembrane conductance regulator, CFTR, protein. CFTR is a multifunctional protein found in multiple organs in the human body, acting mainly as a transepithelial channel which regulates the flow of chloride and bicarbonate ions across epithelial membranes. A malfunctioning CFTR protein would lead to the accumulation of a thick viscous mucous layer blocking pancreatic ducts, intestines and airways which is the primary reason of death. The treatment of cystic fibrosis remained symptomatic until the development of small molecule therapy. Small molecule therapy depends on the development of small pharmacological agents that can bind to the mutated CFTR protein restoring its function. Pharmacological agents can act through different mechanisms and be mainly classified to; correctors and potentiators. Correctors can bind to the misfolded protein trapped inside the nucleus to correct its folding and rescue it to the plasma membrane, while potentiators can only bind to the CFTR channel located at the plasma membrane to help restoring its function. The release of the first drugs that tackles the main root of the disease was in 2012, Kalydeco®, followed by Orkambi® in 2015. Kalydeco is a personalized drug that is composed of Ivacaftor, potentiator, targeting a small percentage of CF patients carrying G551D mutation, ~5%. On the other hand, Orkambi is composed of a combination of a corrector, Lumacaftor, and a potentiator, Ivacaftor. Being a combination therapy, Orkambi can target the majority of CF patients, those carrying F508del mutation. CF patients treated with Orkambi experienced an enhancement in their quality of life, but with a modest effect. This limited effect was proved to be due to an inhibitory action exerted by Ivacaftor on Lumacaftor. The high lipophilicity of Ivacaftor has a destabilizing effect on the lipid bilayer of the plasma membrane. This membrane disruption causes a decreased abundance of the corrected protein leading to an inhibitory effect on the lumacaftor mediated correction of the CFTR protein. The main aim of this study is the synthesis of less lipophilic derivatives of Ivacaftor followed by their biological testing to allow the development of a better combination therapy.