

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 genetic disease that is caused by different 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 the airways which is the primary reason of death. The treatment of cystic fibrosis remained symptomatic until the development of small molecule therapy which includes small pharmacological agents that can bind to the mutated CFTR protein restoring its function. They can be 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 bind to the CFTR channel located at the plasma membrane and restore its function. The first drugs that tackles the main root of the disease was Kalydeco®, followed by Orkambi®. 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 causes membrane disruption leading to a decreased abundance of the lumacaftor corrected 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 an enhanced combination therapy.

Biography

Salma Elmallah is a recent PhD holder (Nov., 2019). She is a lecturer of medicinal and organic chemistry at the Arab Academy for Science and Technology. Her passion and area of expertise is drug synthesis and design. Throughout her graduate studies, she built a great knowledge regarding the manipulation of different pathways for drug synthesis. Her main research interest is cystic fibrosis disease and the development of an effective therapy. Her work was very fruitful in this field where different derivatives of cystic fibrosis drugs, Ivacaftor and Lumacaftor, were developed. Biological testing, these derivatives were proved to have better activity with fewer side effects than original drugs. Salma has participated in many international conferences either as an invited speaker or presenting a poster. She was first prize winner in Ryerson symposium for chemistry and biology. Salma is always very enthusiastic to learn and acquire knowledge.

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