TEZACAFTOR – SYNTHESIS OPTIMIZATION OF THE FIRST INTERMEDIATES

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Cystic fibrosis (CF) is an autosomal recessive disease that currently affects approximately 75,000 individuals in the world's population. It is a disease caused by mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator). Two types of drugs (correctors and potentiators) have been developed to treat cystic fibrosis by modulation the function of the defective CFTR protein. Tezacaftor, (*R*)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-*N*-(1-[(2*R*)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropane-2-yl)-1*H*-indol-5-yl)cyclopropane-1-carboxamide is a white to off-white powder, which is practically insoluble in water, belonging to the group CFTR of correctors. Tezacaftor is prepared by forming an amide bond between the carboxylic acid chloride fragment and the corresponding amine. This work is focused on optimizing of individual steps of tezacaftor synthesis, especially on i) bromination of 3-fluoro-4-nitroaniline, which is the starting material of the amine fragment; and ii) ester formation, the first step in the synthesis of a carboxylic acid fragment. Several bromination methods were tested using Br_2, *N*-bromosuccinimide (NBS), and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as brominating agents. 1,1'-Carbonyldiimidazole (CDI), *N*, *N*'-dicyclohexylcarbodiimide (DCC), methyl iodide, sulfuric acid, and *p*-toluenesulfonic acid were used to form the ester. Satisfactory results were obtained with bromination using both DBDMH and NBS (yield 68 %, purity 93 %). In the case of esterification, the best results were obtained using MeI (AUC >> 99 %) and H_2SO_4 (AUC = 97 %).

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