LEAD-OPTIMIZATION PROCESS AND CHARCTERIZATION OF THE DISSOCIATIVE EFFECT APPLIED TO NEW DIMER DISRUPTERS OF HUMAN THYMYDILATE SYNTASE

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ABSTRACT

Human thymidylate synthase (*h*TS) is a ubiquitous enzyme involved in the biosynthesis of DNA. Its primary role is the catalysis of dUMP to dTMP through reductive methylation that converts the coenzyme 5,10 mTHF to DHF [1]. Nowadays, *h*TS represents a validated target in chemotherapy. Among all the drugs already approved for the therapy the most important belong to the class of antimetabolites like 5-Fluorouracil (5-FU), methotrexate (MTX) and raltitrexed (RTX). These drugs have as main target the active site of the enzyme. Unfortunately, the continuous use of these drugs generates the emerging of drug resistance that leads to higher level of *h*TS in cancer cells.

During the past few years, it has been proved that the active form (dimeric) of *h*TS is in equilibrium with its inactive form (monomeric) [2] and that this equilibrium is sensitive to the monomeric interface binding ligands. These evidences have brought new perspectives to find non-canonical ways to inhibit the enzyme without increasing *h*TS levels in cancer cells and a promising perspective of reducing the emergence of drug resistance. Recently new class of inhibitors, named dimer disrupters (Ddis), able to interact at the enzyme interface of the dimer causing the shifting of the equilibrium toward the monomeric form has been developed [3]. This study delivered more than 200 compounds with the thiophenylacetamide scaffold. Among them, compound E7 has shown the ability to dissociate the *h*TS protein against the recombinant protein, in vitro and in vivo showing an efficacy higher than the 5-FU [2] in pancreatic mice model. Other inhibitors have shown interesting properties like AIC-A016. Despite their interesting activity, they show low solubility. In this context, the main focus of this work has been the optimization of the most active compounds in order to increase the solubility, the activity and the capacity of destabilizing the dimer causing the inactivation of the protein. For this purpose, we started a computational approach to identify the best candidates for the synthesis. A synthesis for the "top scores" candidates has been developed and the compounds have been synthetized and characterized. Then, biological assays are under development to understand if the optimization process has brought an increase of the efficacy both on the protein and on the cells.

REFERENCES

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