Novel aminoarylthiazole derivatives as correctors of the chloride transport defect in cystic fibrosis: computer assisted drug design, synthesis and biological evaluation

Liessi N[1], Cichero E[2], Pesce E[3], D'Ursi P[4], Salis A[1], Pedemonte N[3], Damonte G[1,5], Galietta LJV[3], Fossa P[2], Millo E[1,5]

[1]Center of Excellence for Biomedical Research (CEBR), University of Genoa, Genoa, Italy, [2]Department of Pharmacy, Section of Medicinal Chemistry, University of Genoa, Genoa, Italy, [3]Istituto Giannina Gaslini, Genoa, Italy, [4]Institute for Biomedical Technologies e National Research Council (ITB-CNR), Segrate (MI), Italy, [5]Department of Experimental Medicine, Section of Biochemistry, University of Genoa, Genoa, Italy. (FFC#7/2015) [doi.org/bwjx]

Keyword: CFTR, corrector, aminoarylthiazoles, potentiator, VX809

Background. CF is caused by mutations that abolish the function of CFTR, a protein that is needed to transport chloride and bicarbonate across cell membrane in the epithelial cells. The most frequent mutation, F508del requires a specific pharmacological treatment. Such defects can be addressed with small molecules, known as correctors and potentiators. In previous studies, we identified a class of compounds called aminoarylthiazoles (AATs) that potentially correct the CF basic defect.

Hypothesis and objectives. The main objective of our project is to identify new AATs which could be efficiently able to correct the CFTR protein defect caused by F508del. By using an integrated approach (bioinformatics, chemical synthesis, and functional assays) we will aim at developing drug- like compounds with improved activity on mutant CFTR.

Essential methods. We have manually synthetized molecules called aminoarylthiazoles (AATs) according to the Hantzsch synthesis based on structural information arising from their possible binding site on CFTR protein. Using functional assays we will test the ability of novel AATs to recover the expression and activity of mutant CFTR.

Results. In the other hand, our previous data on AATs have revealed the possibility to develop correctors and/or potentiators compounds and some of their also show a strong synergic effect when combined with VX809. Notably, our studies allowed to better explore the structure-activity relationship exhibited within AATs and the reference corrector VX809, giving useful information pointing out the most relevant residues involved in the ligand binding. Lastly the results have provided novel information on AATs, and led to the identification of some molecules, with a particular ability to rescue ΔF508CFTR.

Spin-off for research and clinical purposes. Our findings reveal the possibility to generate libraries of molecules particularly suited for the potentiation of F508del-CFTR. Identification of candidate drugs for the correction of the basic defect in CF is of high relevance to develop treatments able to revert or arrest the progression of the disease.

Acknowledgment. FFC#7/2015: funded by FFC, supported by Delegazione FFC di Vicenza

References

1. Rogan et al. Chest. 2001,139, 1480–1490. https://doi.org/10.1378/chest.10-2077 PMid:21652558

2. Pedemonte et al. The Journal of Biological Chemistry 2011, 286: 15215-15226.

https://doi.org/10.1074/jbc.M110.184267 PMid:21383017 PMCid:PMC3083174

3. Pesce et al. European Journal of Medicinal Chemistry 2015, 99, 14-35. https://doi.org/10.1016/j.ejmech.2015.05.030 PMid:26041577