Rescuing CFTR Protein Function: 1,3,4-oxadiazoles versus 1,2,4-oxadiazoles as readthrough inducing drugs

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In Cystic fibrosis (CF) disease nonsense mutations in the CFTR gene cause the absence of the CFTR protein expression and a more severe form of the disease. About 10% of patient affected by CF show a nonsense mutation. A potential treatment of this alteration is to promote translational readthrough of premature termination codons (PTCs) by translational readthrough inducing drugs such as Ataluren (1). We reported a rationale for Ataluren promoted readthrough of PTCs by computational approach and GFP-reporter cell-based assay (2) and the observed enhancement of readthrough activity by some Ataluren derivatives (3, 4).

In this context we aimed to compare the 1,2,4-oxadiazole core of Ataluren with a slightly different scaffold, the 1,3,4-oxadiazole core. By a validated protocol consisting of computational screening, synthesis and biological tests we identified, a new small molecule with 1,3,4-oxadiazole core showing high readthrough activity. Moreover, we evaluated quantitatively the CFTR functionality after treatment with our new lead in CF model systems and in cells expressing a *nonsense*-CFTR-mRNA. Finally, we studied the supramolecular interactions among readthrough inducing drugs and CFTR mRNA to assess the biological target and hypothesized mechanism and further we calculated and compared the ADME properties of our new lead to Ataluren.

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