Discovery and synthesis of novel inhibitors of the UPF1 helicase required for nonsense-mediated mRNA decay (NMD)

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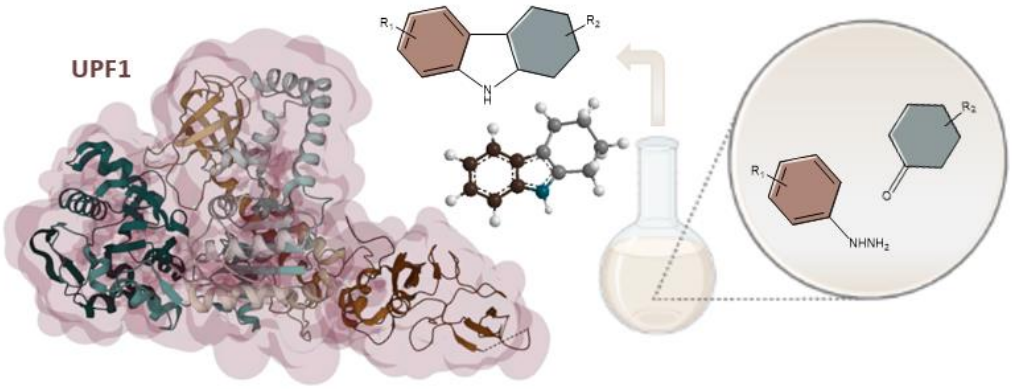
Nonsense mRNA decay (NMD) recognizes and eliminates mRNA that contain a premature translation termination codon (PTC). The NMD pathway consists of a trimetric complex of hUPF proteins (UPF1, UPF2 and UPF3). In contrast, the ATP-dependent UPF1 helicase deserves special attention, as it performs the main regulatory functions in the NMD machinery.[1] The activity of the pathway is observed in the pathophysiology of human genetic diseases, including malignancies.[2] For this reason, the UPF1 protein is an important molecular target in anti-cancer therapy. It should be emphasized that the mechanistic aspects of the NMD pathway are not fully understood. The presented approach focuses on the synthesis of potential UPF1 inhibitors - small molecule chemicals selected by analyzing the results of a computer simulation. Using the Fischer indolization method, a number of heterocyclic derivatives based on the structural scaffold of *2,3,4,9-tetrahydro-1H-carbazole* were obtained. The synthesized chemical compounds are potential UPF1 inhibitors. *In vitro* evaluation of active derivative ligands will be checked using thermal shift assay (TSA) and cellular thermal shift assay (CETSA).



[1] Kalathiya, U.; Padariya, M.; Pawlicka, K.; Verma, C. S.; Houston, D.; Hupp, T. R.; Alfaro, J. A. *Insights into the Effects of Cancer Associated Mutations at the UPF2 and ATP-Binding Sites of NMD Master Regulator: UPF1*. Int. J. Mol. Sci., 20, 5644 (**2019**)
[2] Nogueira, G.; Fernandes, R.; García-Moreno, J.F. et al. *Nonsense-mediated RNA decay and its bipolar function in cancer*. Mol Cancer., 20, 72 (**2021**)