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RESCUING P53 BY NEW TRANSLATIONAL READTHROUGH INDUCING DRUGS

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Nonsense mutations represent a distinct category of mutations, characterized by converting an amino acid coding triplet into a premature termination codon (PTC). This results in a notable reduction in cytosolic mRNA levels, ultimately leading to the premature halting of translation and the production of truncated and non-functional proteins. A substantial number of genetic disease (11%) and hereditary tumor (12%) is attributable to nonsense mutations. In this respect, TP53 represents one of the most frequently mutated genes[1]. The protein encoded by TP53 is p53, a transcription factor designated as "the guardian of the genome" due to its role in maintaining the integrity of the cell genome. p53 performs many functions within the cell, including regulating cell cycle progression, DNA repair, apoptosis, and senescence. It is estimated that over half of all human cancers exhibit mutations in TP53, with 10% of cases resulting from nonsense mutations. This highlights the urgent need to develop innovative therapeutic strategies[2]. One strategy in nonsense mutation treatment is based on the pharmacological induction of translational readthrough (RT). This process involves suppressing a stop codon using translational readthrough-inducing drugs (TRIDs)[3]. In the present work, we developed a novel pharmacophore model using a ligand-based approach to identify potential TRIDs capable of restoring the expression of a complete p53 protein. Following the synthesis of these new compounds, their capacity to induce translational readthrough was evaluated using a Firefly luciferase (FLuc) assay in HeLa cells with a nonsense mutation. The best-performing molecules were evaluated for their effectiveness in producing full-length p53 protein.

References

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