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Optimizing the mRNA Binding Affinity of Antisense Oligonucleotides with Simple Nucleobase Modifications

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Antisense therapy has emerged as a powerful strategy for treating genetic disorders—particularly rare "orphan" diseases—as well as viral infections and, more recently, certain cancers.[1] Antisense oligonucleotide (ASO) therapeutics rely on high-affinity, sequence-specific hybridization to target mRNAs and modulate gene expression via RNase H recruitment, splice-site alteration, or steric blockade of ribosome assembly[2], thereby suppressing or altering production of disease-related proteins and mitigating pathological processes. Chemical modifications—such as 2'–O–methylation, locked nucleic acids, and phosphorothioate backbones[3]—are routinely employed to enhance stability and binding strength; however, their effects on hybridization thermodynamics and kinetics remain highly context-dependent and difficult to predict experimentally.

An integrated quantum-mechanical and molecular-dynamics approach has been undertaken to dissect, at atomic resolution, the influence of minimal nucleobase substituents on ASO–mRNA binding affinity. Density functional theory calculations quantify the impact of introduced substituents at key positions of pyrimidine and purine rings on hydrogen–bonding energies and base-stacking interactions. Complementary long, explicit-solvent MD simulations combined with free-energy profiling reveal how each substituent alters duplex conformational flexibility and solvent-mediated contacts.

Preliminary insights suggest that even small, site-specific nucleobase modifications can meaningfully modulate binding affinity: some substituents enhance base-pairing and stacking interactions while promoting local duplex rigidity, whereas others introduce additional bonding potential but encounter solvent competition, leading to more moderate net effects. These emerging structure–activity trends provide a qualitative roadmap for prioritizing minimal nucleobase alterations in ASO design, pending quantitative validation.

Future work will expand this QM/MD framework to introduce minimal substituents across additional ASO regions—including the sugar and backbone—and to evaluate their impact on RNase H recruitment and other mechanisms of action. Insights thus gained will be applied to design mixed-chemistry oligonucleotides targeting clinically relevant transcripts, broadening the strategy toward next-generation antisense therapeutics with optimized activity and specificity.

[1] A. M. Quemener, L. Bachelot, A. Forestier, E. Donnou-Fournet, D. Gilot, M. Galibert, WIREs RNA 2020, 11, e1594, DOI: 10.1002/wrna.1594.

[2] C. Rinaldi, M. J. A. Wood, Nat Rev Neurol 2018, 14, 9, DOI: 10.1038/nrneurol.2017.148.

[3] T. C. Roberts, R. Langer, M. J. A. Wood, Nat Rev Drug Discov 2020, 19, 673, DOI: 10.1038/s41573-020-0075-7.

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