Novel Dioxane- and Morpholino Nucleotide Analouges with Improved Off-Target Profiles in siRNAs

Significance: The authors describe the synthesis of novel dioxane- and morpholino-based nucleotide precursors. These nucleotides were incorporated at position 7 of an antisense strand leading to improved in vitro off-target profiles due to destabilization of the seed region.

Comment: Interestingly, the corresponding (2S, 2R) isomers of 1 and 2 also led to improved off-target profiles. However, significantly lower in vivo potencies were observed, potentially due to the inability of these nucleosides to undergo Watson–Crick base paring.