A. HOFMEISTER* ET AL. (SANOFI, FRANKFURT AM MAIN, GERMANY)

Small Interfering RNAs Containing Dioxane- and Morpholino-Derived Nucleotide Analogues Show Improved Off-Target Profiles and Chirality-Dependent In Vivo Knock-Down

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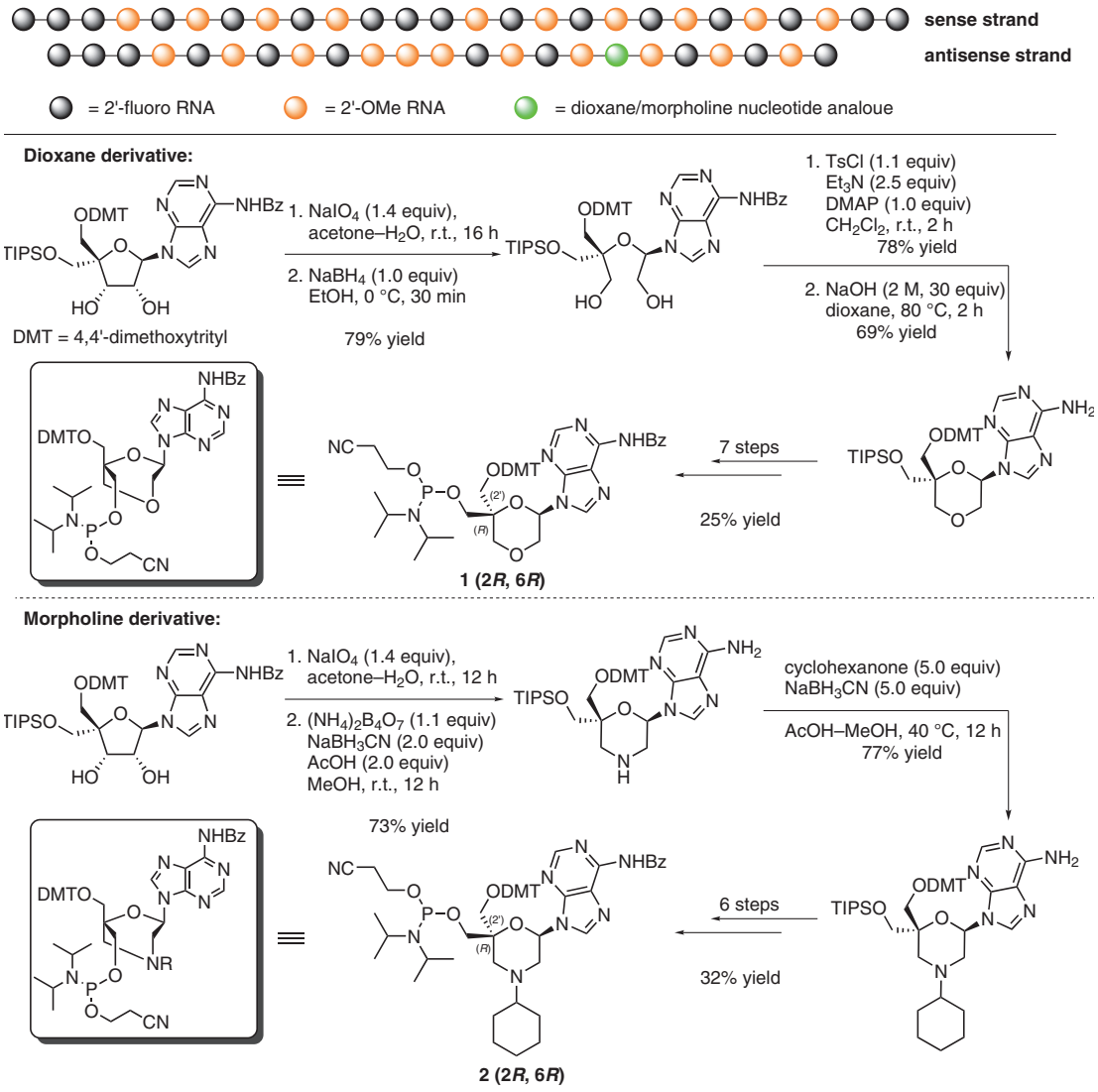
Novel Dioxane- and Morpholino Nucleotide Analogues with Improved Off-Target Profiles in siRNAs



Significance: The authors describe the synthesis of novel dioxane- and morpholine-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 (2*S*, 2*R*) 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.

SYNFACTS Contributors: Antonia F. Stepan (Roche), Danica Rankic (Pfizer), Ferdinand H. Lutter (Janssen Pharmaceutica)
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Innovative Drug Discovery and Development

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Synfact of the Month

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