ABSTRACT

The growing use of nucleic acids in contemporary life science has sparked a renewed interest in synthetic nucleic acid derivatives with compelling recognition profiles. This is, among other things, of paramount importance for nucleic acids in medicine, where strong and faithful recognition of complementary targets is crucial for the efficacy and safety of most nucleic acid-based drugs.

The first half of this thesis presents our work with extending the Hoogsteen face of nucleobases with a set of aromatic auxiliaries for enlarging π-π stacking—the key driving force in nucleic acid hybridization. In a systematic study that compared different simple scaffolds on 2′-deoxyuridine (**T1**—**T5**), we identified a *C*-connected 1,4-disubstituted triazole linkage (**T1**) as the best moiety for optimal stacking (CHAPTER 4). A subsequent study with polar auxiliaries **T6** and **T7** indicated that more hydrophilic 5-substituents are better accommodated in the major groove and allows favorable electrostatic contacts in the major groove to obtain extraordinary high binding affinity to RNA (CHAPTER 5). A study launched to compare different aromatic groups on 2′-deoxycytidine (**C1**—**C4**) showed that the conformational profile of the 1-phenylpyrazol-3-yl moiety (**C2**) makes it an ideal partner for **T1** in allowing high-affinity RNA recognition of complementary polypurine sequences (CHAPTER 6). We have also attached a phenyltriazole moiety to 7-deazapurine nucleosides (**A1** and **G1**), and successfully synthesized the **A1** nucleoside (CHAPTER 7).

The second half of this thesis presents our work with double-headed nucleotides, which have the makings for dual Watson–Crick contacts with a target strand. First, we have successfully prepared β-D-arabino-configured 1′,2′-double-headed nucleosides containing guanine ($\mathbf{U_G}$ and $\mathbf{G_T}$). While the synthesis of the $\mathbf{G_T}$ phosphoramidite turned out to be challenging, monomer $\mathbf{U_G}$ was successfully prepared and incorporated into oligonucleotides, where it was found to effectively behave as a 5′-dUG dinucleotide, but with enhanced affinity to complementary DNA targets (CHAPTER 9). In addition, we have prepared arabinouridines containing 2,6-diaminopurine ($\mathbf{U_D}$) and hypoxanthine ($\mathbf{U_I}$) bases, and we show that $\mathbf{U_D}$ significantly improved mismatch discrimination in duplexes compared to the canonical adenin base (CHAPTER 10). Finally, we have discovered a new synthetically appealing route to double-headed nucleotides on a 2-homoribose scaffold. We envision that this strategy allows convenient access to the full array of different base compositions by divergent synthesis (CHAPTER 11).