Abstract

My work titled "**A new GC Binder for sequence-selective DNA recognition**" mainly focuses on the synthesis of pyrrolo[2,3-*b*]pyridones as part of a larger modular system of heterocyclic ligands, designed to bind DNA in a sequence selective manner in the major groove. It is the first reported synthesis of such a scaffold. This biarylic system has been designed to form a triplex with GC base pair forming three simultaneous hydrogen bonds. Extensive molecular modeling was done leading to an optimized design of a modular system with perfect complementarity to the Hoogsteen site inside DNA's major groove.

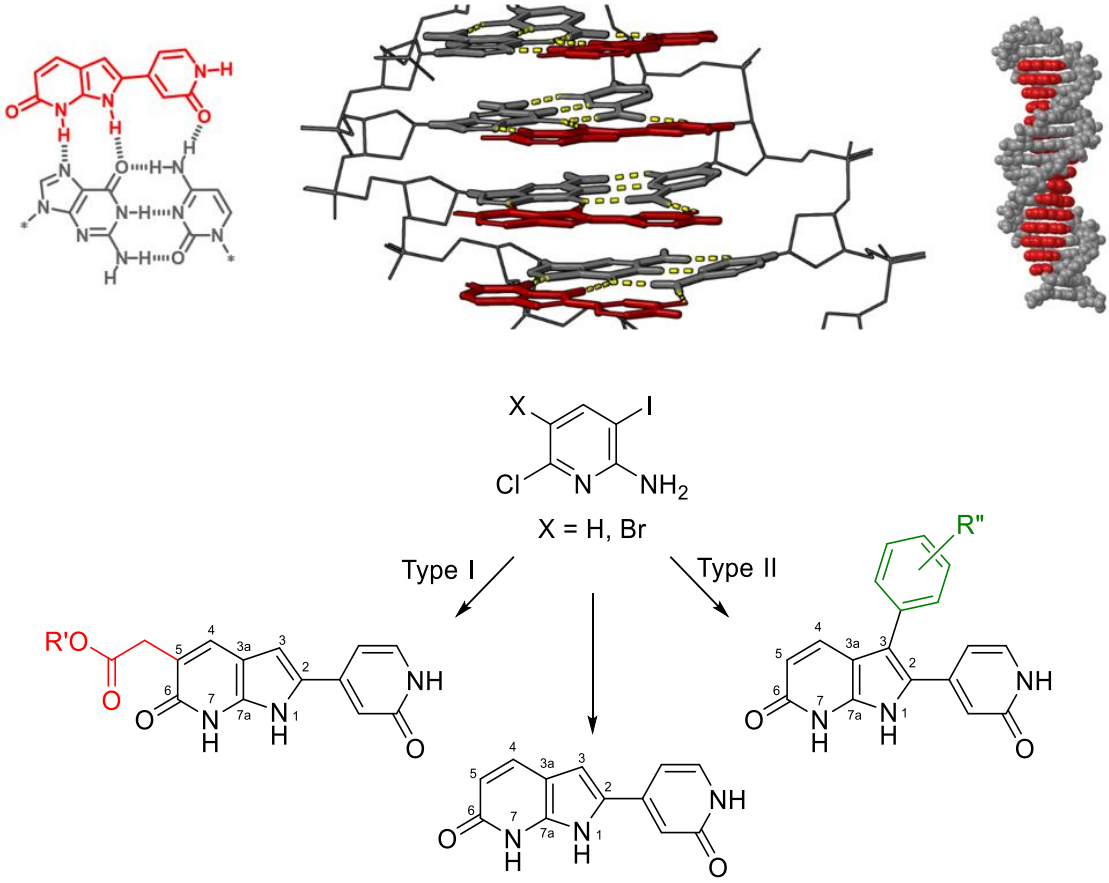

Figure 1. (top left) Biarylic pyrrolopyridone-pyridone GC binder forming a base triplet with the GC base pair. (top middle) Snapshot from a molecular modeling structure (MacroModel 10.7, OPLS-2005, water, GB/SA) showing four GC binders addressing a set of consecutive GC base pairs via three hydrogen bonds each. (top right) Molecular modeling structure of 16 GC binders hydrogen bonded and stacked to a 20 bp GC B-DNA filling up the entire major groove (MacroModel 10.7, OPLS-2005, water, GB/SA). (below) Divergent synthesis of pyrrolo[2,3-b]pyridone scaffold and its functional derivatives (Type I and II).

A flexible synthetic access to this binding motif consisting of a pyridone connected to a fused pyrrolo[2,3-*b*]pyridone, is presented. A wide range of functional elements have been introduced by minor modifications of the synthetic strategy. These functionalizations are necessary for two important purposes.

For DNA recognition, the base pair binder was modified (Type I) in such a way that it can be attached to a DNA-compatible backbone with self-repeating units. In this regard, a short C2 spacer was introduced at the 5- position of the pyrrolopyridone nucleus (Fig. 1).

For establishing correct hydrogen bonding capability, the base triplet formation with an isolated GC base pair must be proven. In the absence of the powerful π-stacking contributions, this must be done in highly nonpolar solvents because polar solvents (even DMSO) will strongly interfere with the three new weak hydrogen bonds. This is a major drawback in the design of all artificial base pair binders; even pyrrolo[2,3-*b*]pyridone scaffold is not soluble enough in $CDCl_3$ due to the presence of both pyridone amides. Without disturbing the hydrogen bonding recognition site of the binder, a modification (Type II) was envisaged on the back of the pyrrole ring. Solubilizing nonpolar substituents were installed on 3- position of the nucleus (Fig. 1). These derivatives were conveniently prepared by introducing minor changes in the established synthetic route.