The Molecular Recognition of DNA by Novel Heterocycles

Thesis by

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…for my parents…
…for B.S.E.…

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Abstract

With a rapid movement toward personalized genetic medicine, tailoring treatment to individual patient needs based each one's genetic code is becoming an important goal. The ability to develop small molecules capable of reprogramming the cellular machinery at the genetic level is one approach to the difficult challenge of treating diseases that result from aberrant gene expression. Inspired by the architecture of the natural products netropsin and distamycin, polyamides are capable of binding the DNA minor groove with high affinity and fidelity. Originally composed of 5-membered heterocyclic carboxamides, polyamides have evolved in both form and function. A search has been initiated to develop new DNA specific oligomers that have different electronic and geometric properties. Alteration of these properties may lead to a new class of compounds, capable of targeting DNA sequences that have previously been shown to be difficult to recognize. Second-generation compounds containing novel heterocyclic recognition elements, within the context of both 5-membered heterocyclic carboxamides and fused 6-5 benzimidazole analogues, have recently been developed. These molecules have successful DNA recognition profiles as well as favorable cell uptake properties, important considerations when searching for effective pharmacophores. These new classes of rationally designed oligomers offer one approach to the challenging problem of regulating gene expression.

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