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"Fluorescent nucleoside analogues with new properties"

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Abstract

Fluorescent nucleoside analogues (FNAs) are powerful probes for studying the structure and dynamics of nucleic acids, which are vital to understanding RNA function, DNA damage repair, nucleic acid–protein interactions, regulatory mechanisms for gene expression, and other aspects of nucleic acid function. Existing FNAs are prone to quenching by base pairing and stacking, are clustered at the blue–green end of the visible spectrum, and have limited brightness as compared with conventional fluorophores. Studies of nucleic acid function would benefit greatly from overcoming these limitations. We have designed, synthesized, and studied a series of fluorescent pyrimidine analogues, aiming to address these limitations and develop a detailed understanding of the relationships between chemical structure and fluorescent responses to local environment in nucleic acids. Included in this series is a tricyclic cytidine analogue DEAtC that is nearly non-fluorescent as a nucleoside, but responds to matched base pairing and stacking with a fluorescence turn-on. A chlorinated tricyclic cytidine 8-Cl-tCO reports on local environment by changes in the vibrational fine structure of its emission spectra. To address the problem of limited brightness, we have design and synthesized a new NFA that we call ABN, which has a conjugated push–pull system similar to those found in bright fluorophores such as rhodamines. ABN is the brightest known FNA when present in duplex nucleic acids, and it is readily detected in single-molecule fluorescence measurements using both 1-photon and 2-photon excitation. Collectively, these FNAs offer new capabilities for biophysical studies on nucleic acids. Comparisons of their structure and properties help to reveal mechanisms for fluorescence changes in response to local environment in nucleic acids.

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