PNA for Use in Small-Molecule Libraries Derived by Combinatorial Solid-Phase Synthesis: Reaction Optimization

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Peptide nucleic acids (PNAs) are highly resilient molecules that are resistant to nucleases and proteases. As formidable nucleic acid mimics, peptide nucleic acids can hybridize with complementary sequences of DNA or RNA. Unlike DNA and RNA, PNAs are supported by a polyamide backbone held together by peptide bonds. Here, a streamlined process for constructing and assembling peptide nucleic acids is optimized for the purpose of producing molecular tags for small molecule libraries that are synthesized through combinatorial solid phase synthesis (SPS). Combinatorial SPS allows for the facile construction of a diverse small molecule library. However, combinatorial SPS produces a mixture of compounds that is difficult to separate. PNAs provide a means for encoding each unique small molecule to give a mixture that is separated with far greater ease. Currently, the synthesis of PNAs is not feasible enough to employ in library encoding, so optimization is necessary to maximize yield and purity while simultaneously promoting ease of synthesis. In the current work, optimization for yield, purity, and diversity was achieved through synthesis of PNA oligomers that could be coupled with one another with a single coupling step to produce larger oligomers suited for tagging purposes. A preliminary synthesis of a three-membered collection of trimeric codons was performed and validated using mass spectrometry. This indicates the feasibility of constructing a library of PNA codons. Thus, this project puts forth a facile scheme for synthesizing versatile, modular tags for use in combinatorial SPS as well as other potential applications in medical research.