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Synthesis of Pyrrole-Imidazole Polyamide

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Abstract: One simple and versatile method is established for the synthesis of DNA recognition molecules—polyamides containing alternating N-methylpyrrole and N-methylimidazole without necessitating NH_2- group protection.

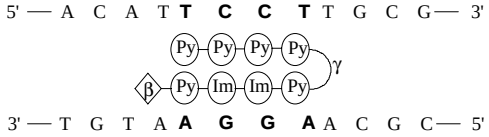
Keywords: Polyamides, DNA recognition molecules, pyrroles and imidazoles.

Small molecules that target specific predetermined DNA sequences have the potential to control gene expression[1]. Realization of the high affinity binding and specific recognition of DNA sequences by organic molecules is one of the focuses of biological chemistry. The natural products netropsin and distamycin are N-methylpyrrole containing di- and tripeptides, with binding specificity at sites of successive A·T or T·A base pairs of DNA in the minor groove[2]. Recently, N-methylimidazole is introduced into polyamides for the recognition of G·C or C·G base pairs[3]. This is a basis for recognition of four Watson-Crick base pairs of B-DNA; it provided impetus to develop an ensemble of motifs, which recognize a broad range of DNA sequence.

Our interest is focused on synthesis of polyamides containing N-methylpyrrole (Py) and N-methylimidazole (Im) that have high affinity and specificity for recognition of DNA comparable to naturally occurring molecules. In this article, the binding sequence (5'-TCCT-3') of natural calicheamicin γ with DNA is chosen as the target site for designing a novel polyamide.

In designed polyamide, antiparallel pairing of Py/Py recognizes a T·A base pair; Py/Im targets a C·G base pair[1]. The γ-aminobutyric acid (γ) will facilitate the formation of γ-turn and the β-alanine (β) will increase the affinity of polyamide to DNA [2].

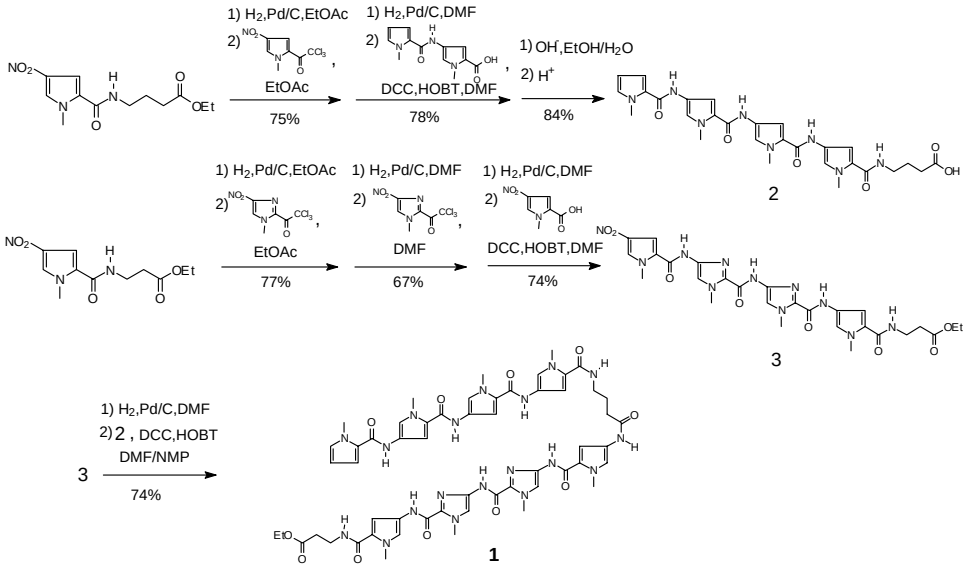
Figure 1. Schematic binding model of hairpin polyamide with 5'-TCCT-3'



The polyamide PyPyPyPyγPyImImPyβOEt (1) was conveniently constructed by the chloroform and DCC/HOBT coupling reaction. By using the chloroform

reaction, $NO_2PyPy\gamma OEt$ (I) and $NO_2ImImPy\beta OEt$ (II) were obtained in good yields. The PyPyCOOH and $NO_2PyCOOH$ were introduced to (I), (II) by DCC/HOBT coupling reaction to give $PyPyPyPy\gamma OEt$ (III) and $NO_2PyImImPy\beta OEt$ (3), respectively. After saponification and neutralization, (III) was transformed into $PyPyPyPy\gamma COOH$ (2). Hydrogenating the sub-chain (3) and coupling with another sub-chain (2) activated by DCC/HOBT, the target product (1) was achieved in satisfactory yield. The structure of this eight-ring polyamide (1) was confirmed by a combination of ^{1}H-NMR, ^{13}C-NMR, IR and MALDI-TOF-MS.

Scheme 1. Synthetic route of eight-ring polyamide



Conclusion

This procedure is a facile and versatile method for synthesis of various polyamides-DNA recognition molecules without necessitating NH_2- group protection. The biological activities will be tested in due course.

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