# Shape Selective Recognition of the DNA

#### Minor Groove by Hairpin Polyamides

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For my Parents

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iv

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#### Abstract

Polyamides composed of N-methylpyrrole (Py), N-methylimidazole (Im), and 3-hydroxy-N-methylpyrrole (Hp) crescent-shaped ligands are that bind predetermined DNA sequences with affinities and specificities rivaling naturally Inherent limitations of the thymine-selective Hp residue, occurring proteins. including reduced affinity, diminished stability in aqueous solution, and loss of specificity in N-terminal pairings, have restricted the array of DNA sequences that can be specifically targeted with polyamides. The work described in this thesis addresses two major areas of research: the development of fluorescent conjugates of minor groove-binding polyamides as tools for genomic analysis and expansion of the minor groove recognition code by designing internal and N-terminal replacements for Hp.

Fluorophore-polyamide conjugates were designed using different fluorescent probes, different sites of probe attachment with respect to the polyamide, and different chemical linkers separating the above moieties. Ring conjugates, connecting tetramethylrhodamine or cyanine probes to the N-methyl position of Py rings exhibited reasonable affinities and specificities for the cognate DNA sequences, and displayed fluorescent enhancement upon association with the minor groove. The cyanine conjugates, though less quenched than their TMR counterparts, also demonstrated the capacity for fluorescence resonance energy transfer (FRET). The advantages offered by polyamides relative to oligonucleotidebased probes for DNA detection suggest that polyamides might be useful tools for genomic analysis.

The utility of polyamides as diagnostic tools or as therapeutic agents would be greatly enhanced by the development of novel thymine-specific residues. Efforts toward this end have employed two general design strategies for Hp replacement. One approach has sought to remove the hydroxyl recognition element in favor of purely shape selective discrimination of the T•A base pair, while other efforts have examined alternative hydroxy-substituted aromatic scaffolds that possess greater stability than Hp. Both of these approaches are discussed in the context of Nterminal, internal, and multiple recognition of T•A base pairs.

#### **Table of Contents**

		Page
Acknowledge	ements	iv
Abstract		vii
Table of Cor	ntents	ix
List of Figure	es and Tables	xi
Chapter 1	Introduction to DNA Recognition by Minor Groove-Binding Polyamides	1
Chapter 2	Design and Synthesis of Fluorophore-Polyamide Conjugates	20
Chapter 3	Sequence Specific Detection of DNA Using Self-Quenched Fluorophore-Polyamide Conjugates	56
Chapter 3A	Sequence Specific Fluorescence Detection of Double Strand DNA	58
Chapter 3B	Progress towards Applications Using Fluorophore- Polyamide Conjugates in Genomic Analysis	81
Chapter 4	Fluorescence Resonance Energy Transfer (FRET) by Minor Groove-Associated Cyanine-Polyamide Conjugates	108

Chapter 5	Shape Selective Recognition of T•A Base Pairs by Hairpin	
	Polyamides Containing Novel N-Terminal Pairings1	28

Chapter 5A	Shape Selective Recognition of T•A Base Pairs by
	Hairpin Polyamides Containing N-Terminal 3-Methoxy
	(and 3-Chloro) Thiophene Residues131
Chapter 5B	Further Progress toward the Development of Novel

N-Terminal Recognition Motifs	15	56
	10	

Chapter 6	Internal Residues for Thymine Discrimination by Minor	
	Groove-Binding Polyamides	169

# List of Figures and Tables

Chapter 1		page
Figure 1.1	Structural features of the DNA double helix	3
Figure 1.2	Naturally occurring ligands for DNA	5
Figure 1.3	The molecular details of minor groove recognition by	
	polyamides	6
Figure 1.4	Hydrogen-bonding model of the hairpin motif illustrating the	
	pairing rules	8
Figure 1.5	Biological applications and implications for polyamide motifs	10
Figure 1.6	N-Terminal aromatic residues for specific DNA recognition	11
Figure 1.7	Novel heterocycles for thymine-selective recognition of the	
	minor groove	12
Figure 1.8	Bicyclic aromatic heterocycles for minor groove discrimination	13

Figure 2.1	Applications of polyamide conjugates	23
Figure 2.2	Modification strategies for synthesis of hairpin polyamide	
	conjugates	24
Figure 2.3	Synthesis of N-(Fmocaminopropyl)pyrrole building block	25
Figure 2.4	Synthesis of N-(Phthalimidopropyl)pyrrole building bock	27
Figure 2.5	Synthesis of cyanine-hairpin polyamide conjugates	28
Figure 2.6	Synthesis of fluorophore conjugates containing C-terminal	
	$\beta$ -tails using PAM resin	30

Figure 2.7	Synthesis of C-terminal fluorophore conjugates using	
	Oxime resin	.32
Figure 2.8	Synthesis of tail fluorophore conjugates using hydrazine resin	34
Figure 2.9	Synthesis of self-quenched TMR-hairpin polyamide conjugates	.36
Figure 2.10	Chemical structures of self-quenched TMR-polyamide	
	Conjugates	.37

Figure 3.1	Binding models for self-quenched TMR-hairpin conjugates	60
Figure 3.2	Chemical structures of TMR-hairpin polyamide conjugates	
	and control compounds	61
Figure 3.3	Ball-and-stick representations of hairpin conjugates bound to	
	match duplex DNA sequences	62
Figure 3.4	Spectroscopic properties of TMR-hairpin conjugates	65
Figure 3.5	TMR-polyamide conjugate microplate experiments	67
Figure 3.6	Non-Watson-Crick base pair recognition by TMR-polyamide	
	conjugates	71
Figure 3.7	X-ray co-crystal structure of nucleosome core particle-	
	polyamide complex	82
Figure 3.8	DNA recognition properties of TMR-hairpin polyamide	
	conjugates	83
Figure 3.9	Chemical structures of different classes of fluorophore-	
	polyamide conjugates	84

0 1
0
0
)1
)1
3
6
7
<b>)</b> 9
1
3
63
3
6
5

Table 3.4	Trinucleotide repeat sequences associated with	
	human diseases	89
Table 3.5	Properties of TMR- and fluorescein-hairpin polyamide conjugates	
	examined in microplate titrations with $\lambda$ DNA	96

Figure 4.1	Molecular processes underlying FRET illustrated for fluorophore-
	polyamide conjugates111
Figure 4.2	Previous efforts to demonstrate polyamide-based FRET114
Figure 4.3	Model systems for examination of FRET by polyamide
	conjugates116
Figure 4.4	Chemical structures of cyanine-polyamide conjugates117
Figure 4.5	Normalized absorption emission spectra for cyanine-
	polyamide conjugates118
Figure 4.6	Cyanine-polyamide conjugates exhibit fluorescent
	enhancement when bound to DNA120
Figure 4.7	Demonstration of FRET by minor groove-associated cyanine-
	polyamide conjugates122
Figure 4.8	Optimization of condition for polyamide-based FRET123

Table 4.1Physical properties of cyanine-hairpin polyamide conjugates......119

Figure 5.1	Proposed binding models for hairpin polyamides with
	5'-TXTACA-3' site134
Figure 5.2	Experimental design for evaluation of novel N-terminal residues135
Figure 5.3	Synthesis of N-terminal thiophene building blocks
Figure 5.4	Synthesis of hairpin polyamides137
Figure 5.5	Quantitative DNase I footprint titration experiments for polyamides
	<b>1</b> , <b>2</b> , <b>6</b> , and <b>8</b> on pCW15 PCR product139
Figure 5.6	Hypothetical binding model explaining T•A selectivity for
	3-methoxythiophene-2-carboxamide residue143
Figure 5.7	The development of a second sequence specific N-terminal
	pairing expands the repertoire of sequences that can be targeted
	by hairpin polyamides158
Figure 5.8	Molecular models of N-terminal Hp replacements160
Figure 5.9	DNase I footprinting gels for 5- and 3-methylthiophene-2-
	carboxamide N-terminal residues162
Figure 5.10	3-Cyanothiophene-2-carboxamide residues and derivatives
	as N-terminal recognition elements163
Figure 5.11	Synthesis of 3-cyano and 3-amidino-thiophene cap building
	blocks and polyamides165
Figure 5.12	Nuclear localization of 3-chlorothiophene-containing
	polyamides166

Table 5.1	Equilibrium association constants	140
Table 5.2	Physical properties determined by molecular modeling	.141
Table 5.3	Comprehensive summary of equilibrium association constants	161
Table 5.4	Cellular localization of Ct-containing hairpin polyamides in a	
	panel of cell lines	167

Figure 6.1	Designed plasmids used to assess DNA binding properties of	
	hairpin polyamides targeting internal or multiple thymine bases17	73
Figure 6.2	Molecular rendering of a 3-fluoropyrrole-containing polyamide	
	bound in the minor groove of DNA17	74
Figure 6.3	Retrosynthetic analyses of 3-fluoropyrrole building block17	'6
Figure 6.4	Attempted routes to 3-fluoropyrrole building block using	
	nucleophilic methods of aromatic fluorination17	77
Figure 6.5	Synthetic schemes to fluoropyrrole using electrophilic	
	methods of aromatic fluorination18	30
Figure 6.6	Design of novel internal thiophene residues based upon	
	leads from <i>N-terminal</i> studies18	32
Figure 6.7	Molecular rendering of unfavorable backbone interactions that	
	could occur between internal 3-chloro- and 3-methoxy-thiophene	
	residues when bound in the minor groove of DNA18	34
Figure 6.8	Benzimidazole scaffolds as internal Hp replacements18	36

Table 6.1A	Observed association constants for N-terminal 3-substituted-	
	thiophene residues	183
Table 6.1B	Observed association constants for internal 3-substituted-	
	thiophene residues	183
Table 6.2	Observed association constants for Hp-, Tn-, and Hz-containing	
	hairpin polyamides	.187
Table 6.3	Observed association constants for multiple Hp-, Tn-, and Hz-	
	containing hairpin polyamides	188

Figure 7.1	Design of N-terminal dimers using "chimeric" mode of
	thymine recognition198
Figure 7.2	Plasmid design and model hairpin polyamides for
	characterization of novel N-terminal dimers196
Figure 7.3	Synthesis of novel N-terminal Ct-Hz dimeric building blocks197
Figure 7.4	Solid phase synthesis of hairpin polyamides containing novel
	N-terminal dimers198
Figure 7.5	Representative DNase I footprinting gels for hairpin
	polyamides containing novel N-terminal dimers
Figure 7.6	Inherent structural and geometric differences between
	classic five-member heterocycles for minor groove recognition
	and next generation bicyclic heterocycles20

Figure 7.7	Molecular overlays comparing Im-Hz and 3-Cyanothiophene-
	Hz terminal dimers to Im-Py202
Figure 7.8	New classes of N-terminal dimers for specific recognition of
	dinucleotide sequences within the context of hairpin polyamides204