Appendix

Synthetic Experiments toward Fluorinated Heterocycles

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A.1. Background

The incorporation of fluorine into pyrrole-imidazole polyamides as a recognition element in the DNA minor groove has been demonstrated at an internal position as well as in the N-terminal cap position. The pairing of α-fluoro-β-alanine side-by-side with β-alanine in the 2-β-2 hairpin motif produces little (1.4-fold) specificity for T•A over A•T.[1] In addition, there was a 30-fold decrease in binding affinity relative to the β/β pairing.[1] At the N-terminal cap position, 3-fluorothiophene has been paired across from Py in an eight-ring hairpin polyamide to produce 3-fold specificity for T•A over A•T.[2] Synthetic efforts towards an internal *N*-methyl-3-fluoropyrrole monomer have been reported.[3]

The second-generation fused heterocycles provide an additional scaffold for the incorporation of fluorine into polyamides. The fused heterocycle hydroxybenzimidazole paired with Py in an eight-ring hairpin polyamide recognizes T•A in the DNA minor groove.[4] The pyrrole-fluoropyrrole dimer **1** and the pyrrole-fluorobenzimidazole dimer **2** present the same atomic connectivity along the recognition surface of the polyamide (Figure A.1).[4] Therefore, the fluorobenzimidazole heterocycle was proposed as a synthetic target.

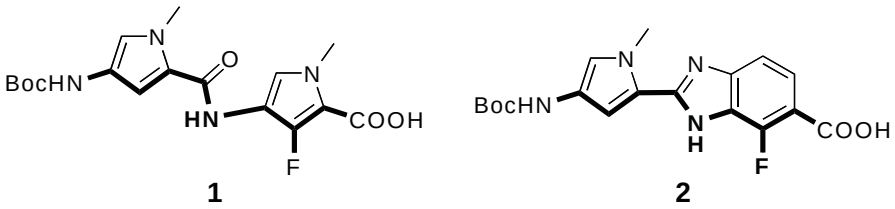

Figure A.1. The pyrrole-fluoropyrrole dimer **1** and the pyrrole-fluorobenzimidazole dimer **2** present the same atomic connectivity along the recognition edge.[4]

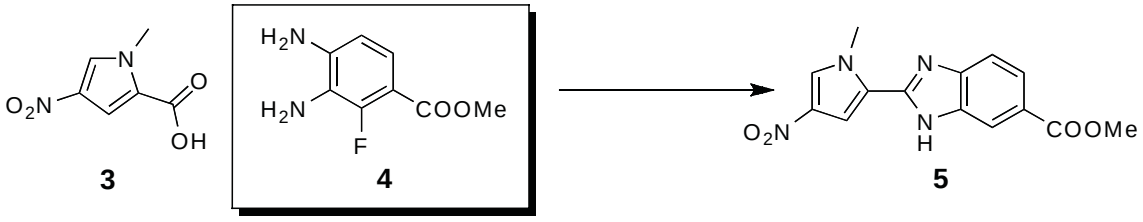

Figure A.2. Coupling of **3** and **4**, followed by condensation, was envisioned for the synthesis of the intermediate **5**.[4] Fluorodiamine **4** was the key synthetic target.

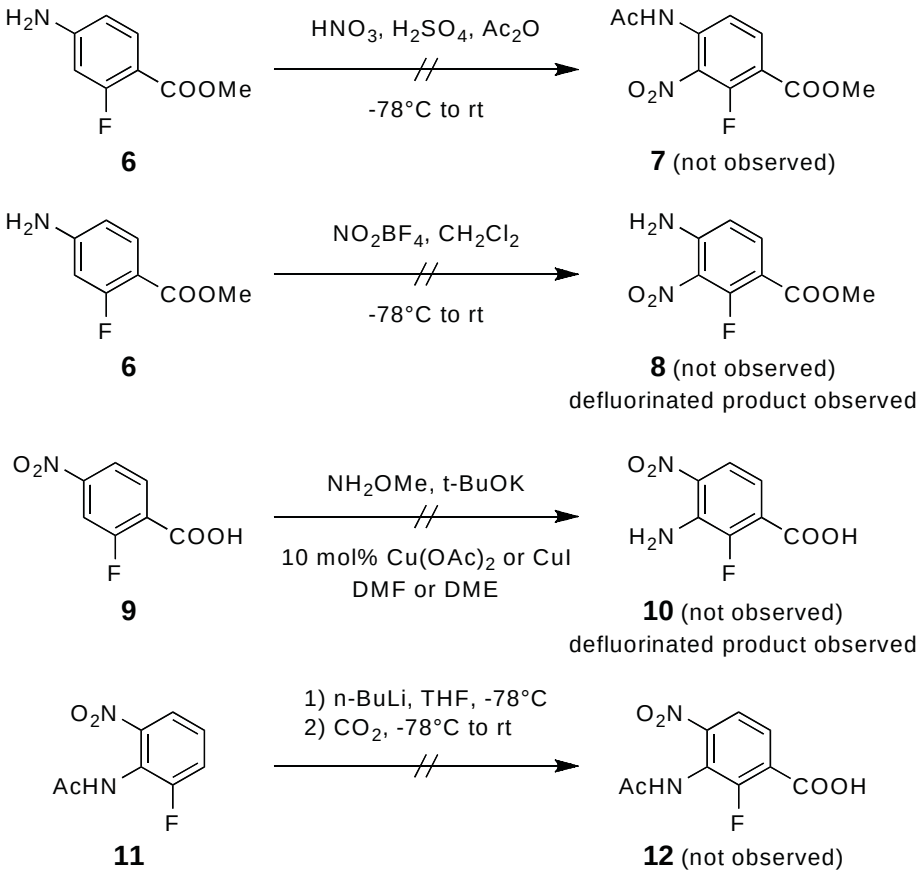

Figure A.3. Reactions attempted to achieve the desired tetrasubstitution of **4**.

A.2. Synthetic efforts

It was envisioned that pyrrole-fluorobenzimidazole dimer **2** could be synthesized by an HBTU coupling, followed by condensation, of NO_2-Py-COOH monomer **3** and fluorodiamine **4** to give compound **5** (Figure A.2).[4] The intermediate **5** could be reduced, Boc-protected, and saponified to give the Boc-protected amino acid **2** suitable for solid-phase coupling.[4] For this synthetic route, the fluorodiamine methyl ester **4** was the key synthetic target.

Figure A.3 illustrates reactions that were attempted to achieve the desired tetrasubstitution of synthetic target **4**. Two sets of nitration conditions were attempted on starting material **6**, which was available in three steps from commercially available 2-fluoro-4-nitrotoluene (Aldrich).[5-7] Nitric acid treatment did not yield nitration at the sterically hindered 3-position as in structure **7**. The use of nitronium tetrafluoroborate in an attempt to form structure **8** resulted in a defluorinated product, as no peaks were observed in the ^{19}F NMR spectrum. A copper-catalyzed direct amination with methoxylamine of starting material **9**[5] also resulted in a defluorinated product.[8] An attempt to use fluorine as a directing group in *ortho*-lithiation did not result in the synthesis of structure **12**.[9]

References

1. Floreancig, P. E.; Swalley, S. E.; Trauger, J. W.; Dervan, P. B., *J. Am. Chem. Soc.* **2000,** 122, 6342-6350.

2. Foister, S.; Marques, M. A.; Doss, R. M.; Dervan, P. B., *Bioorg. Med. Chem.* **2003,** 11, 4333-4340.

3. Foister, S. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 2004.

4. Renneberg, D.; Dervan, P. B., *J. Am. Chem. Soc.* **2003,** 125, 5707-5716.

5. Schmelkes, F. C.; Rubin, M., *J. Am. Chem. Soc.* **1944,** 66, 1631-1632.

6. Cary, J. M.; Moore, J. S., *Org. Lett.* **2002,** 4, 4663-4666.

7. Soundararajan, N.; Platz, M. S., *J. Org. Chem.* **1990,** 55, 2034-2044.

8. Seko, S.; Miyake, K.; Kawamura, N., *J. Chem. Soc.-Perkin Trans. 1* **1999**, 1437-1444.

9. Snieckus, V., *Chem. Rev.* **1990,** 90, 879-933.