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# SYNTHESIS OF 2-(5-AMIDINOBENZOXAZOL-2-YL)-5-(4-AMIDINOPHENYL)FURAN AND 2-(5-AMIDINOBENZOXAZOL-2-YL)-5-(4-AMIDINOPHENYL)THIPHENE TO TEST A DNA MINOR GROOVE DIMER BINDING MODEL

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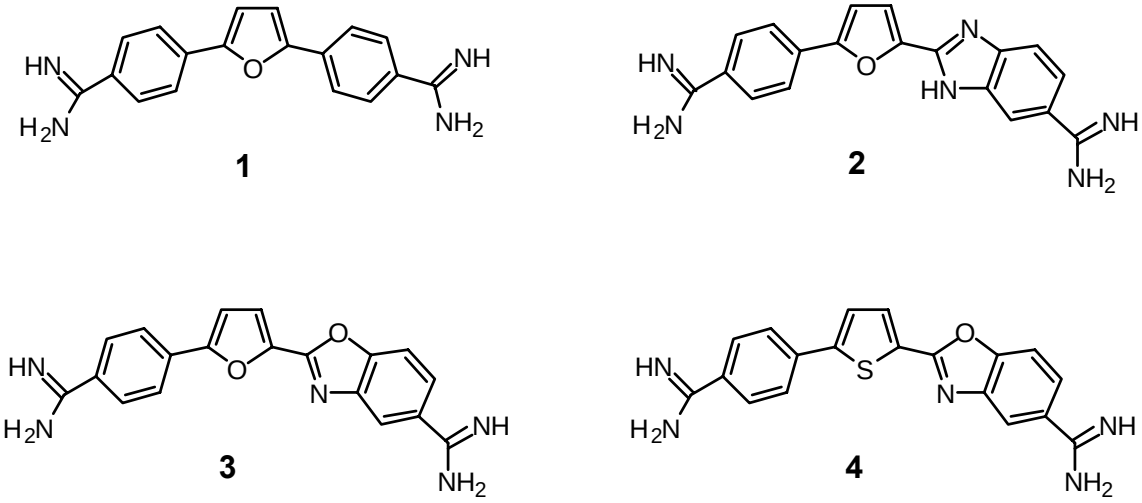
**Abstract** – Two new bis-amidines were synthesized, characterized and tested to probe the structural requirements for a DNA minor groove dimmer binding model.

## Introduction

Organic dications that bind to the DNA minor groove exhibit biological activities that range from effectiveness against opportunistic infections to anticancer properties.[1] They also serve as important models in the study of nucleic acid-small molecule interactions.[1] Biophysical studies with 2,5-bis(4-amidinophenyl)furan (**1**) (furamidine) indicate that factors such as electrostatic, hydrogen bonding, and van der Waals interactions as well the radius of curvature of the molecule are important contributors to the minor groove binding affinity of this type of dication.[2] Based on these studies and with the goal to increase the overall efficacy, decrease toxicity, and improve the minor groove binding affinity, our laboratory synthesized derivatives of furamidine with extended aromatic ring systems. 5-[2-(5-Amidinobenzimidazoyl)]-2-(4-amidinophenyl)furan hydrochloride (**2**) (where one of the phenyl rings has been replaced by benzimidazole in reference to furamidine) was synthesized and its properties studied.[3] Footprinting experiments identified an unusual mode of interaction of **2** with GC containing sequences.[4] NMR spectral and surface plasmon resonance studies indicate that two molecules of **2** bind as a side-by-side antiparallel stacked dimer in the DNA minor groove.[4-6] Since all other dicationic furan derivatives previously studied to bind in the minor groove as monomers and recognize AT regions of the DNA, the GC base-pair recognition and dimer-binding mode represents an important new interaction mode. In an

effort to understand what structural features of **2** are required for dimer formation and GC recognition, the synthesis of new analogs of **2** has been undertaken. In this report we describe the synthesis of two new bis-amidines. We have replaced the benzimidazole ring of **2** with a benzoxazole ring by synthesizing **3**, to test the importance benzimidazole hydrogen bond donor potential on dimer formation. In addition, we have prepared the analogous benzoxazole analog in which we have replaced the central furan ring with thiophene as can be seen in **4**.

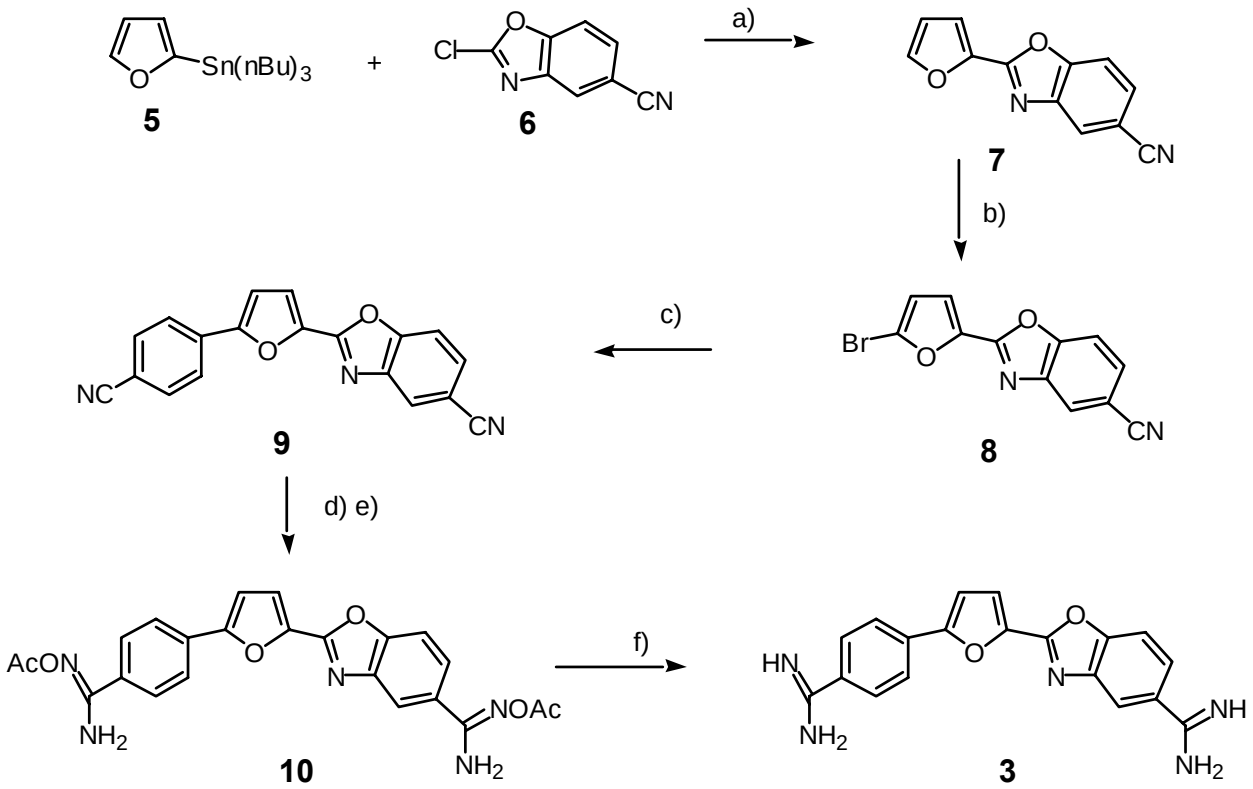
**Figure 1.**




**Results and Discussion**

The synthesis employed for **3** is outlined in Scheme 1. In the route which we have used a key step in making the triaryl system involves Stille coupling between a 2-(tri-n-butylstannyl)furan (**5**) and 2-chloro-5-cyanobenzoxazole (**6**). The synthesis of **6** has been previously described[7] and begins with the reduction of commercially available 4-cyano-2-nitrophenol to form 2-amino-4-cyanophenol. The reaction of 2-amino-4-cyanophenol with potassium *O*-ethylxanthate formed 5-cyanobenzoxazole-2-thione. Treatment of the thione with thionyl chloride yielded **6**. When **5** and **6** were allowed to react under Stille conditions[8] an 80% yield of the coupling product (**7)** was obtained. An attempt to achieve similar coupling using the Suzuki reaction between benzoxazole (**6)** and the appropriate furan pinacol boronate failed. NBS bromination[9] of **7** in DMF solution afforded the bromo derivative (**8)** in very good yield (92%). This bromofuran (**8)** was allowed to react with 4-cyanophenylboronic acid[10] to obtain the bis-nitrile (**9)**. This bis-nitrile was allowed to react with hydroxylamine to form the bis-amidoxime which was then converted into the bis-acetoamidoxime (**10)** by the action of acetic anhydride in acetic acid.[11] Hydrogenation of **10** cleanly gave the desired bis-amidine (**3)**.

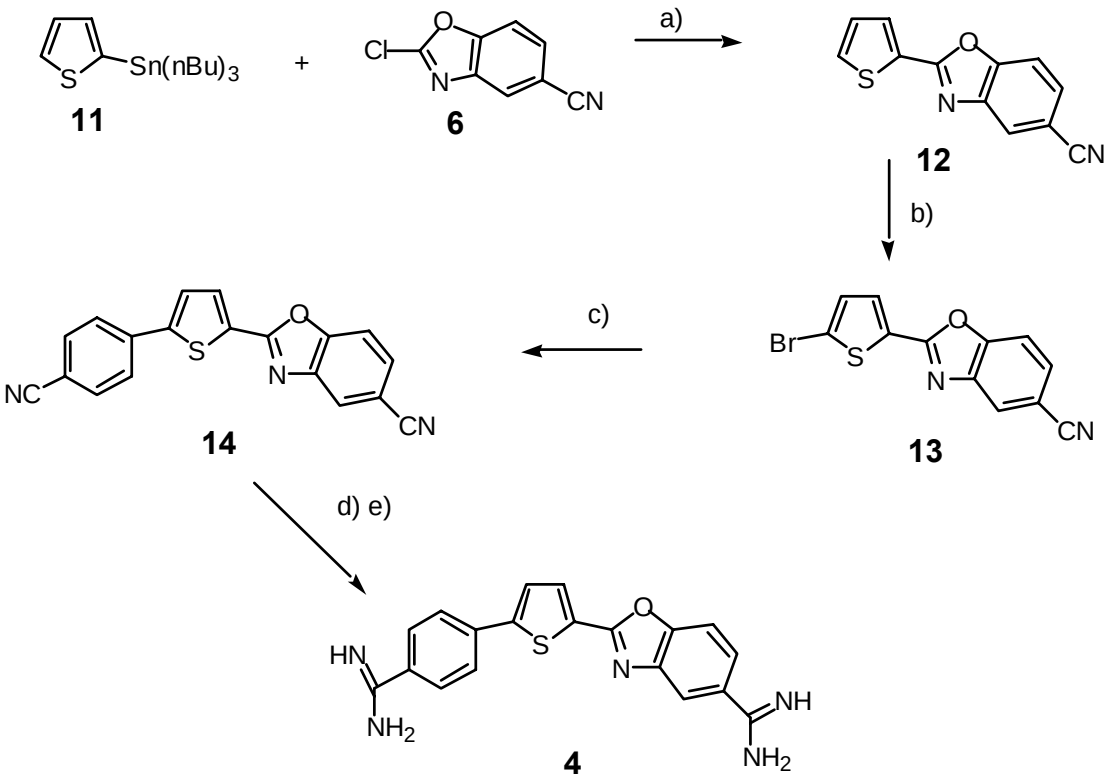
**Scheme 1**




a) $Pd(PPh_3)_4$ b) NBS, DMF c) 4-cyanophenylboronic acid, $Na_2CO_3$, $Pd(PPh_3)_4$
d) $NH_2OH$-HCl, KO-t-Bu, DMSO e) $Ac_2O$, AcOH f) $H_2$, Pd-C, HOAc

A similar approach for the preparation of the thiophene bis-amidine (**4**) is outlined in Scheme 2. In this case, 2-(tri-n-butylstannyl)thiophene (**11**) was allowed to react with **6** to yield **12**. NBS bromination was again used to selectively substitute the 2-position of the 5-membered ring heterocycle, however in this case the reaction did not go to completion and the mixture of bromination products, which could not be readily separated, was used directly in the Suzuki coupling step to give **13** in a 51% yield based on boronic acid. For the synthesis of **4** a Pinner sequence was used for conversion of the bis-nitrile to the bis-amidine.[12,13] The Pinner approach was used in this case to avoid the possible problem of catalyst poisoning due to the thiophene sulfur atom if the amidoxime strategy were employed.

**Scheme 2**




a) $Pd(PPh_3)_4$ b) NBS, DMF c) 4-cyanophenylboronic acid, $Na_2CO_3$, $Pd(PPh_3)_4$ d) HCl, EtOH e) $NH_3$, EtOH

The Stille coupling product for the furan analog (**7**) was obtained in an 80% yield while the thiophene one (**12**) was obtained in a 64% yield. The difference in yield may be attributed to the fact that the reaction conditions have not been optimized in either case (for example, this type of coupling has been reported[14] in a very good yield in DMF at 105 °C). NBS bromination leading to **8** and **13** was performed in DMF. In the furan case (**8**) an excellent yield of the bromo analog was obtained, however in the thiophene case (**13**), even under much longer reaction times, the reaction did not go to completion. NBS bromination of a related thiophene using DMF as solvent but under different conditions to that used in this work has been reported.[14] Also, the bromination of another related thiophene compound using chloroform-acetic acid as a solvent[15] has been described. In both cases the yields are very good. Therefore, it can be inferred that the reaction conditions for the thiophene bromination studied in this research has not been optimized. When the aryl bromides (**8**) and (**13**) were allowed to react with the 4-cyanophenylboronic acid in toluene with a catalytic amount of $Pd(PPh_3)_4$ at 100 °C or at reflux the expected Suzuki products were obtained. The percent yield from the Suzuki coupling reactions ranged

from 51% to 64%. There is not a significant difference between the yield of the coupling products using the bromide (**8**) or (**13**), which suggests that the furan and thiophene rings exhibit very similar reactivity under the Suzuki conditions used here.

In Table 1 data for the DNA binding affinities for **2**, **3** and **4** are compared. The results of Tm and biosensor-surface plasmon resonance (SPR) binding studies with polydA.dT and oligo1 show that the benzoxazole analogs (**3**) and (**4**) exhibit a lower binding affinity for the DNA minor groove at AT sequences than the benzimidazole parent molecule (**2**). This result suggests that the benzimidazole ring contributes a significant hydrogen bonding component to the minor groove affinity for these bis-amidine molecules. The SPR data for binding to oligo1 and oligo2 shows that **3** and **4** do not bind in the minor groove as a dimer. The absence of evidence for dimer formation by **3** and **4** demonstrates the importance of hydrogen bonding in the DNA-dimer formation of **2**. Further details of the biophysical interactions of **3**, **4** and related compounds will appear in due course.

Table 1. Comparison of DNA Binding Affinities for **2**, **3** and **4**. [a]

| Compound | ΔTm Poly dA.dT($^{o}$C) | Binding K Oligo1 [b] | Binding K Oligo2-1 [b] | Dimer binding |
|---|---|---|---|---|
| **2**[c] | 22.4 | $2.1\ 10^{7}$ | $2.0\ 10^{7}$ | strong |
| **3** | 13.3 | $3.5\ 10^{5}$ | $2.2\ 10^{5}$ | none |
| **4** | 17.0 | $7.4\ 10^{5}$ | $4.7\ 10^{5}$ | none |

a)For experimental details of measurements see refs. 3-6 b)

**Oligo1: 5'-CGAATTCG T C**
**GCTTAAGC C T**

**Oligo2-1: 5'-CTATGAC T C**
**GATACTG C T**

c) ref. 4.

**ACKNOWLEDGEMENT**

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**EXPERIMENTAL**

Melting points were recorded using a Melt-Temp apparatus and are uncorrected. $^{1}$H-NMR and $^{13}$C-NMR spectra were obtained on a Varian +300 and a VXR 400 spectrometer, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (J) are in hertz. MS spctral data were obtained by Georgia Institute of Technology, Atlanta, GA. Elemental analyses were performed by Atlantic Microlab Inc.

Norcross, GA. A few of the elemental analysis of the amidines synthesized in this work, shown fractional amounts of acetic acid and water. The fractional amounts of acetic acid and water could not be readily removed from the crystalline material due to the high polarity of these compounds. All chemicals and solvents were purchased from Aldrich Co. or Fisher Scientific with the exception of the boronic acids that were obtained from Frontier Scientific, Inc. All solvents were reagent grade.

**2-Chloro-5-cyanobenzoxazole (6)**

Hydrogenation of 4-cyano-2-nitrophenol (3.1 g, 19.0 mmol) in the presence of 10% Pd-C(150 mg) gave 2.3 g (90%) of 2-amino-4-cyanophenol, mp 153-154 °C (lit., [3] mp 153-156°C), and this compound was allowed to react with potassium *O*-ethylxanthate(3.04 g, 19 mmol) in pyridine(40 mL) to afford 1.68 g (73%) of 5-cyanobenzoxazole-2-thione. This thione (1.68 g, 9.5 mmol) was treated, without characterization with thionyl chloride under conditions described by Lok *et al*.[3] to yield 1.51 g (89%). $^1$H-NMR (DMSO-$d_6$) δ 8.39 (d, 1H, J = 1.5), 7.94 (dd, 1H, J = 9.0, 1.5), 8.00 (d, 1H, J = 9.0). The $^1$H-NMR spectral data are in accord with that reported by Lok *et al*.[3] The compound was used in the next step without further characterization.

**2-(5-Cyanobenzoxazol-2-yl)furan (7)**

A mixture of 2-(tri-*n*-butylstannyl)furan (1.79 g, 5 mmol), 2-chloro-5-cyanobenzoxazole (0.90 g, 5 mmol) and 100 mg of $Pd(PPh_3)_4$ in 30 mL of dioxane was heated, under nitrogen, at 100 °C overnight.[8] Work-up was performed as described by Kumar *et al*.[8] and purification was achieved by chromatography on silica gel with dichloromethane/methanol (95:5). After partial reduction of the volume of eluent the pure compound crystallized to give 0.84 g (80%) of 2-(5-cyanobenzoxazol-2-yl)furan, mp 189-191 °C. $^1$H-NMR (DMSO-$d_6$) δ 8.06 (d, 1H, J = 2.0), 7.73 (s, 1H), 7.66 (d, 1H, J = 2.0), 7.36 (d, 1H, J = 4.0), 7.26 (d, 1H, J = 1.0), 6.67 (dd, 1H, J = 4.0 and 1.0); $^{13}$C-NMR (DMSO-$d_6$) δ 119.6, 115.0, 109.2, 104.8, 104.1, 91.7, 87.1, 81.0, 78.6, 75.1, 74.3, 71.5; MS (EI) calcd mass for $C_{12}H_6N_2O_2$: 210.2; observed mass 210.1. Anal. Calcd. for $C_{12}H_6N_2O_2$ : C, 68.57; H, 2.88; N, 13.33. Found: C, 68.49; H, 2.93; N, 13.39.

**5-Bromo-2-(5-cyanobenzoxazol-2-yl)furan (8)**

2-(5-Cyanobenzoxazol-2-yl)furan (0.8 g, 3.8 mmol) was dissolved in 10 mL of DMF and 0.78 g (4.37 mmol) of NBS was added. The mixture was stirred overnight at room temperature.[9] Addition of ice water caused precipitation and the solid was collected by filtration, washed with ether and dried to yield the pure product at 92% yield (1.0 g), mp 210-212 °C. $^1$H-NMR (DMSO-$d_6$) δ 8.40 (d, 1H, J = 2), 8.00 (d, 1H, J = 8.0), 7.91 (dd, 1H, J = 8.0 and 2), 7.61 (d, 1H, J = 4), 7.01 (d, 1H, J = 4); $^{13}$C-NMR (DMSO-

*d*$_6$) δ 155.3, 152.2, 142.7, 141.5, 130.0, 127.8, 124.5, 118.9, 118.7, 115.3, 112.6, 108.0; HRMS (EI) calcd mass for $C_{12}H_5N_2O_2Br$: 289.084; observed mass 289.086. Anal. Calcd for $C_{12}H_5N_2O_2Br$: C, 49.86; H,1.74; N, 9.69. Found: C, 49.66; H, 1.77; N, 9.61.

**2-(5-CYANOBENZOXAZOL-2-YL)-5-(4-CYANOPHENYL)FURAN (9)**

To a solution of the above compound (1.0 g, 3.46 mmol) and $Pd(PPh_3)_4$ (0.20 g, 0.17 mmol) in 7 mL of toluene under a nitrogen atmosphere was added 3 mL of 2 M aqueous solution of $Na_2CO_3$ and (0.61 g, 4.15 mmol) of 4-cyanobenzeneboronic acid in 5 mL of methanol. The mixture was vigorously stirred at 80 °C overnight.[10] The mixture was cooled and extracted with dichloromethane. The organic layer was filtratered through a pad of celite and rinsed with dichloromethane. The filtrate was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. The compound was dispersed in ethanol and heated at reflux for 1 h; filtration gave pure product (0.65 g; 64%), mp 275-276 °C. $^1$H-NMR (DMSO-*d*$_6$) δ 8.35 (s, 1H), 8.04 (d, 2H, J = 8.4), 799 (d, 1H. J = 8), 7.95 (d, 2H, J = 8.4), 7.88 (d, 1H, J = 8), 7.69 (d, 1H, J = 4), 7.53 (d, 1H, J = 4); $^{13}$C-NMR (DMSO-*d*$_6$) δ 159.6, 158.5, 152.9, 139.3, 137.7, 132.2, 129.9, 128.8, 127.6, 123.2, 120.2, 118.8, 112.5, 14.9; HRMS (EI) calcd mass for $C_{19}H_9N_3O_2$: 311.294; observed mass 311.057.

**2-(5-Hydroxyamidinobenzoxazol-2-yl)-5-(4-hydroxyamidinophenyl)furan**

2-(5-Cyanobenzoxazol-2-yl)-5-(4-cyanophenyl)furan (0.40 g, 1.28 mmol), hydroxylamine hydrochloride (0.86 g, 12.4 mmol), potassium *t*-butoxide (1.40 g, 12.4 mmol) and 7 mL of DMSO were allowed to react under nitrogen according to the previously described method.[11] A pure fluorescent green product was obtained after washing with water, ether and drying in quantitative yield(0.49g); mp 208-210 °C. $^1$H-NMR (DMSO-*d*$_6$) δ 9.78 (s, 1H), 8.06 (s, 1H), 7.90 (d, 3H, J = 8), 7.83 (d, 3H, J = 8), 7.79 (s, 1H), 7.62 (d, 1H, J = 4), 7.37 (d, 1H, J = 4), 5.96-5.90 (s, 3H); $^{13}$C-NMR (DMSO-*d*$_6$) δ 156.0, 154.8, 150.5, 150.1, 149.8, 141.1, 140.8, 133.4, 130.7, 129.0, 125.8, 123.8, 123.1, 117.3, 116.4, 110.0, 108.8. Anal. Calcd for $C_{19}H_{15}N_5O_4$-0.7$H_2O$: C, 58.43; H, 4.25; N, 17.93. Found: C, 58.88; H, 4.04; N, 17.46.

**2-(5-Acetoxyamidinobenzoxazol-2-yl)-5-(4-acetoxyamidinophenyl)furan (11)**

The above amidoxime (0.48 g, 1.25mmol), was converted to the acetoxyamidino compound by treating with 5 mL of acetic acid and 0.5 mL( 6.5 mmol) of acetic anhydride, following the procedure described previously.[11] A green compound was obtained in 82% yield (0.48 g). It was used directly in the next step without further characterization.

**2-(5- Amidinobenzoxazol-2-yl)-5-(4-amidinophenyl)furan acetate salt (3)**

The above acetoxy compound (0.48 g, 1.04 mmol) was submitted to catalytic hydrogenation in acetic acid following the procedure previously reported[11] and afforded, after washing with water, ether and drying, 0.44 g (80%) of the pure compound, mp 245-246 °C. $^1$H-NMR (DMSO-$d_6$) δ 8.17 (s, 1H), 8.00 (d, 2H, J = 8), 7.89 (dd, 2H, J = 4), 7.81 (d, 2H, J = 8), 7.62 (d, 1H, J = 4), 7.36 (d, 1H, J = 4), 1.68 (s, 6H); it was not possible to get the $^{13}$C-NMR spectral data because the compound is very insoluble; MS (EI) calcd mass for $C_{19}H_{15}N_5O_2$: 345.4; observed mass 345.8. Anal. Calcd for $C_{19}H_{15}N_5O_2$-2.5 $CH_3COOH$-2.0$H_2O$: C, 54.23; H, 5.50; N, 13.18. Found: C, 54.32; H, 5.51; N, 12.91.

**2-(5-Cyanobenzoxazol-2-yl)thiophene (12)**

A mixture of 2-(tri-*n*-butylstannyl)thiophene (1.87 g, 5 mmol), 2-chloro-5-cyanobenzoxazole (0.90 g, 5 mmol) and 100 mg of $Pd(PPh_3)_4$ in 30 mL of toluene was heated under nitrogen at 100 °C overnight.[8] Work-up as described previously,[8] purification by chromatography on silica gel with dichloromethane/methanol (95:5), and partial concentration of the eluent gave pure crystals; 0.70 g (64%) of 2-(5-cyanobenzoxazol-2-yl)thiophene, mp 165-166 °C. $^1$H-NMR (DMSO-$d_6$) δ 8.03 (t, 1H, J = 2.0), 7.97 (dd, 1H, J = 2.0), 7.65 (d, 1H, J = 4.0, J = 2.0), 7.64 (d, 1H, J = 4.0), 7.26 (s, 1H), 7.23 (dd, 1H, J = 4.0, J = 2.0); $^{13}$C-NMR (DMSO-$d_6$) δ 161.0, 152.8, 142.6, 131.8, 131.3, 129.1, 128.6, 128.3, 124.2, 118.7, 111.7, 108.7; MS (EI) calcd mass for $C_{12}H_6N_2O_2$: 226.3; observed mass 226.7. Anal. Calcd for $C_{12}H_6N_2O_2$: C, 63.70; H, 2.67; N, 12.38. Found: C, 63.62; H, 2.76; N, 12.17.

**5-Bromo-2-(5-cyanobenzoxazol-2-yl)thiophene (13)**

The above compound (0.6 g, 2.65 mmol), 7 mL of DMF and 0.62 g (3.5 mmol) of NBS were mixed and allowed to react for 2 days at rt according the procedure reported before.[9] A mixture of starting material and product was obtained, which could not be readily separated. Therefore, the crude product was used in the next step without further purification.

**2-(5-Cyanobenzoxazol-2-yl)-5-(4-cyanophenyl)thiophene (14)**

To a solution of the above compound (0.28 g, 0.92 mmol) and $Pd(PPh_3)_4$ (100 mg, 0.085 mmol) in 4 mL of toluene, under a nitrogen atmosphere, was added 1.5 mL of 2 M aqueous solution of $Na_2CO_3$ and of 4-cyanobenzeneboronic acid (0.18 g, 1.22 mmol) in 3 mL of methanol.[10] The mixture was vigorously stirred at 80 °C overnight. After cooling, the mixture was extracted with dichloromethane. The organic layer was filtered through a pad of celite and rinsed with dichloromethane. The filtrate was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. The solid was dispersed

in ethanol and heated at reflux for 1 h; filtration gave 0.20 g (51%, based on the boronic acid) of product, mp 301-303°C. $^1$H-NMR (DMSO-$d_6$) δ 8.30 (s, 1H), 7.98-7.84 (br m, 8H); it was not possible to obtain the $^{13}$C-NMR spectrum because the compound is insoluble; HRMS (EI) calcd mass for $C_{19}H_9N_3OS$: 327.360; observed mass 327.037.

**2-(5-Amidinobenzoxazol-2-yl)-5-(4-amidinophenyl)thiophene hydrochloride salt (4)**

2-(5-Cyanobenzoxazol-2-yl)-5-(4-cyanophenyl)thiophene (0.15 g, 0.50 mmol) in 2 mL of anhydrous dioxane and 1 mL of dry ethanol was saturated with dry HCl gas at 5 °C. The suspension, in a closed vessel, was stirred for 3 weeks at rt. Filtration of the suspension after that period of time gave the imidate ester hydrochloride, which was suspended in 5 mL of dry ethanol and saturated with $NH_3$ gas at 5 °C. The mixture was stirred for 1 week at rt and the solvent was evaporated under reduced pressure. The free base was suspended in ethanol and saturated with anhydrous HCl,[13] stirred at rt for 4 h, filtered, washed with ether and dried to produce 0.15 g (83%) of pure yellow solid, mp > 338 °C. $^1$H-NMR (DMSO-$d_6$) δ 9.50 (s, 2H), 9.47(s, 2H), 9.24 (s, 2H), 9.22 (s, 2H), 8.29 (d, 1H, J = 2), 8.11-7.88 (m, 8H); it was not possible to obtain $^{13}$C-NMR spectral data because the compound is insoluble; MS(FAB) calcd mass for $C_{19}H_{15}N_5OS$ (M + H): 362.4; observed mass 362.1. Anal. Calcd for $C_{19}H_{15}N_5OS$-2HCl-1.5$H_2O$: C, 49.46; H, 4.37; N, 15.18. Found: C, 49.24; H, 4.36; N, 15.18.

## REFERENCES


1. R. R. Tidwell and D.W. Boykin, Dicationic DNA Minor Groove Binders as Antimicrobial Agents, in Small Molecule DNA and RNA Binders: From Synthesis to Nucleic Acid Complexes. Ed. by M. Demeunynck, C. Bailly, and W. D. Wilson, Wiley-VCH, New York, 2003, Vol. 2, pp. 416-460.
2. W. D. Wilson, F. Tanious, D. Ding, A. Kumar, D. W. Boykin, P. Colson, C. Houssier, and C. Bailly, *J. Am. Chem. Soc.*, 1998, **120**, 10310.
3. K. Hopkins, A. Kumar, M. Bajic, W.D. Wilson, B.C. Bender, D. R. McCurdy, R. R. Tidwell, and D. W. Boykin, *J. Med. Chem.*, 1998, **41**, 3872.
4. L. Wang, C. Bailly, A. Kumar, D. Ding, M. Bajic, D. W. Boykin, and D. W. Wilson, *Proc. Natl. Acad. Sci.*, 2000, **97**, 12.
5. L. Wang, C. Carrasco, A. Kumar, C.E. Stephens, C. Bailly, D. W. Boykin, and W. D. Wilson, *Biochemistry*, 2001,**40**, 2511.
6. L. Wang, A. Kumar, D. W. Boykin, C. Bailly, and W. D. Wilson, *J. Mol. Biol.*, 2002, **317**, 361.
7. R. Lok, R. E. Leone, and A. J. Williams, *J. Org. Chem.,* 1996, **61**, 3289.

8. A. Kumar, C. E. Stephens, and D. W. Boykin, *Heterocyclic Commun*., 1999, **5**, 301.
9. R. H. Mitchell, Y. H. Lai, and R. V. Williams, *J. Org. Chem.*, 1979, **44**, 4733.
10. W. J. Thompson and J. A. Gaudino, *J. Org. Chem*., 1984, **49**, 5237.
11. B. D. Judkins, D. G Allen, T. A. Cook, B. Evans, and T. E. Sardharwala, *Synth. Commun*., 1996, **26**, 4351.
12. G. Haeflinger and F. K. Kuske, *The Chemistry of Amidines and Imidates*, ed. by S. Patai, John Wiley and Sons Ltd., New York; 1991, Vol. *2*, pp. 339-366.
13. B. P. Das and D. W. Boykin, *J. Med. Chem.*, 1977, **20**, 1219.
14. A. Fazio, B. Grabrilel, G. Salerno, and S. Destri, *Tetrahedron*, 1999, **55**, 485.
15. R. M. Kellog, A.P. Schaap, E.T. Harper, and H. Wynberg, *J. Org. Chem.*, **1968**, 33, 2902.