An efficient synthesis of 5'-(4-cyanophenyl)-2,2'-bifuran-5-carbonitrile and analogues

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5'-(4-Cyanophenyl)-2,2'-bifuran-5-carbonitrile (**6a**) was prepared by two approaches. The first approach involves four steps, employs Stille coupling conditions utilising 2-tributylstannylfuran and 5-bromofuran-2-carboxaldehyde to furnish **3a** in excellent yield. Oxime formation of **3a** followed by acetic anhdride induced-dehydration gives the carbonitrile **4a**, which on treatment with *N*-bromosuccinimide furnished **5a**. A subsequent Suzuki coupling of **5a** with 4-cyanophenylboronic acid gave **6a** in good yield. The second approach used to prepare **6a** involves cyanation of bromo-compound **10a** with Cu(I)CN in DMF. Oligo-chalcophenes **7a–d** were obtained *via* hexabutylditin-mediated homocoupling of respective brominated precursors **5a–d**. Nitro-containing bichalcophenes **14** and **15** were obtained from the 1,4-dicarbonyl compound **13**.

Keywords: bichalcophenes, Stille coupling, Suzuki coupling, cyanation, homocoupling

There is a continuing interest in the development of new methodologies for the preparation of nitrile-containing compounds, precursors of diamidine-containing molecules, which exhibit broad-spectrum antimicrobial activity including effectiveness against different protozoan diseases.[1-4] Besides, bi- and oligo-chalcophenes (furans, thiophenes, *etc.*) continue to receive significant attention as advanced materials.[5] For example, 5,5'-diaryl-2,2'-bichalcophenes have luminescent,[6] electro-chemical,[7] and semiconducting[8] properties. Recently, we have reported a straightforward and high-yielding homocoupling approach to 5,5'-diaryl-2,2'-bichalcophenes, including cyano-substituted derivatives; this route only allows the synthesis of symmetrical bichalcophenes dinitrile of type **II**.[9] Given the specific recognition of G-quadruplex DNA by bichalcophene diamidines **I** and **II**[10] and for comparative synthetic pathways studies, we decided to synthesise several different triaryl/heteroaryl systems of nitrile- and nitro-containing bichalcophenes of type **I** (Fig. 1). This report also describes the synthesis and characterisation of four new oligochalcophene dinitriles by the hexaalkylditin-mediated homocoupling of their respective brominated precursors.

Results

The synthesis of 5'-(4-cyanophenyl)-2,2'-bifuran-5-carbonitrile (**6a**) is achieved in four steps starting from 2-tributylstannylfuran (**1a**) as outlined in Scheme 1. The first step in this approach employs Stille coupling conditions between **1a** and 5-bromofuran-2-carboxaldehyde (**2a**) in the presence of catalytic $Pd(PPh_3)_4$ using 1,4-dioxane as a solvent and heating at 90°C for 24 h to furnish **3a** in excellent yield. Conventional oxime formation of the 5-formyl-2,2'-bifuran (**3a**) with hydroxylamine hydrochloride followed by acetic anhydride induced-dehydration gives the corresponding carbonitrile **4a**. Bromination of **4a** with *N*-bromosuccinimide in DMF, furnished 5'-bromo-2,2'-bifuran-5-carbonitrile (**5a**) in 86% yield. A subsequent Suzuki coupling of **5a** with 4-cyanophenylboronic acid gave **6a** in good yield. In a similar way, a series of dinitriles **6b–d** was prepared employing the corresponding precursors. Oligo-chalcophenes **7a–d** were obtained *via* hexabutylditin-mediated homocoupling of respective brominated precursors **5a–d**. The conditions for homocoupling involved reaction of the 5'-bromo-2,2'-bichalcophene-5-carbonitrile (1 equivalent) with hexabutylditin (1 equiv) in the presence of catalytic $Pd(PPh_3)_4$ (~2 mol%) using refluxing toluene as solvent. After a period of 6 h, the insoluble product was filtered off and recrystallised from DMF to give the oligo-chalcophenes **7a–d** in 78–85% yield.

The second approach used to prepare 5'-(4-cyanophenyl)-2,2'-bifuran-5-carbonitrile (**6a**) is presented in Scheme 2. Stille coupling reaction of the readily available 5-bromo-2-(4-cyanophenyl)furan (**8**)[9] with 2-*n*-tributylstannylfuran gave the corresponding 5-(4-cyanophenyl)-2,2'-bifuran **9a** in good yield. Bromination of **9a** with *N*-bromosuccinimide in DMF, furnished 5-bromo-5'-(4-cyanophenyl)-2,2'-bifuran (**10a**) in 65% yield. Subsequent treatment of **10a** (1 equiv) with Cu(I)CN (2 equiv) furnished the anticipated dinitrile **6a** in 40% yield. In a similar way, the dinitrile **6c** was prepared employing the corresponding precursor **10b**, which is obtained from a Stille reaction of the readily available 5-(tributyltin)-2,2'-bithiophene[11] with 4-bromobenzonitrile.

Scheme 3 outlines the route used to prepare 2-(4-nitrophenyl)-5-(5-nitrothiophen-2-yl)-furan (**14**) and 2-(4-nitrophenyl)-5-(5-nitrothiophen-2-yl)-1*H*-pyrrole (**15**). In this approach, 1,4-dicarbonyl compound **13** was prepared by an anhydrous $ZnCl_2$ condensation reaction between 4-nitrophenacyl bromide and 2-acetyl-5-nitrothiophene in the presence of Et_3N.[12] An acid-catalysed dehydration reaction of compound **13** afforded the bichalcophene derivative **14** in 70% yield. The bichalcophene containing-pyrrole ring system **15**, was obtained by the Paal–Knorr pyrrole synthesis, on treatment of **13** with ammonium acetate and reflux in ethanol/acetic acid at 80°C.

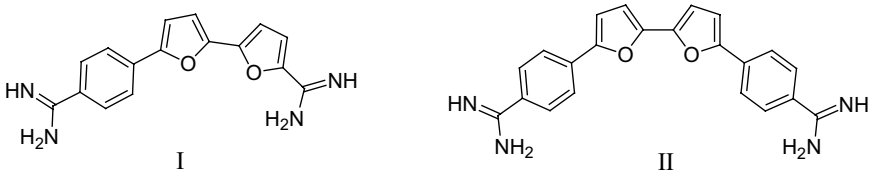

Figure 1

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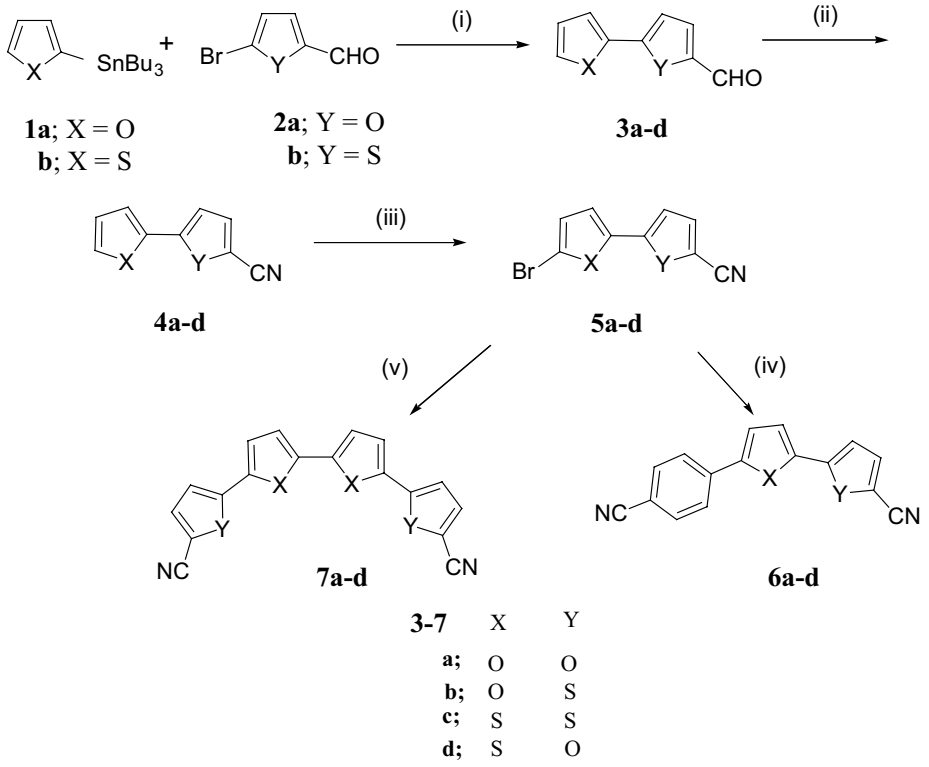
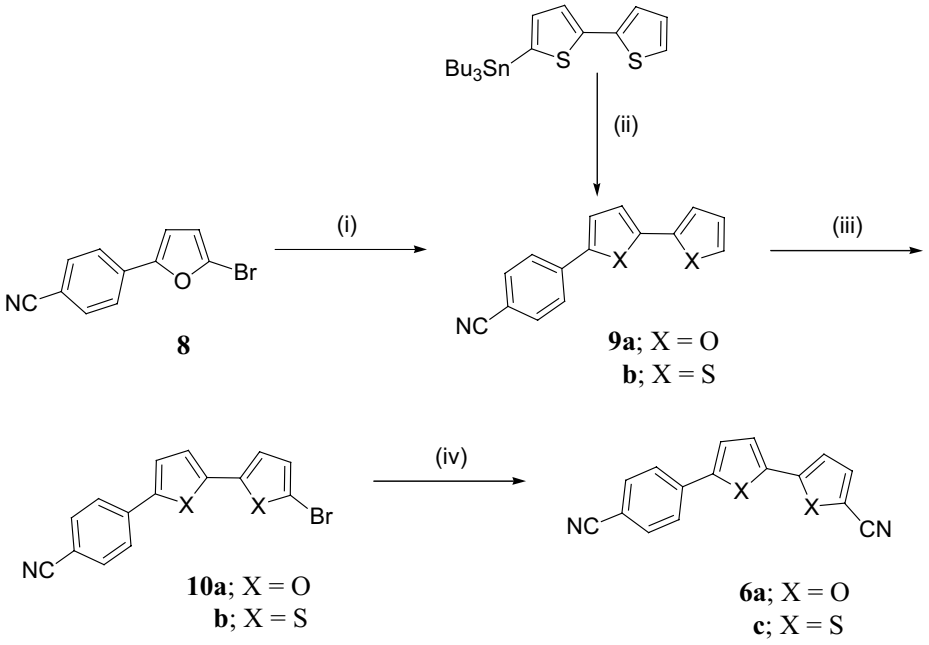


Scheme 1 Reagents and conditions: (i) $Pd(PPh_3)_4$, 1,4-dioxane, 80–90°C; (ii) (a) $NH_2OH.HCl/Na_2CO_3$, (b) Ac_2O; (iii) NBS, DMF; (iv) 4-cyanophenylboronic acid, $Pd(PPh_3)_4$, (v) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene, 120°C.



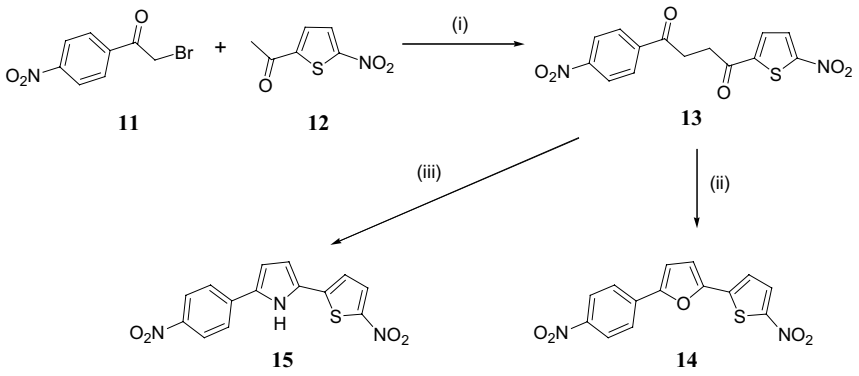
Scheme 2 Reagents and conditions: (i) 2-tributyltinfuran, $Pd(PPh_3)_4$; (ii) 4-bromobenzonitrile, $Pd(PPh_3)_4$ (iii) NBS, DMF; (iv) Cu(I)CN, DMF 140–150°C.

In conclusion, we have described straightforward synthetic approaches for new bichalcophene derivatives. For example 5'-(4-cyanophenyl)-2,2'-bifuran-5-carbonitrile (**6a**) and its analogue **6c** were prepared by two approaches. The first approach involves four higher-yielding steps starting from the commercially available 5-bromochalcophene-2-carboxaldehydes **2a**,**b**. The second approach used to prepare **6a**,**c** involves a moderate-yielding cyanation of **10a**,**b**. Oligo-chalcophenes **7a–d** were obtained in excellent yield by hexabutylditin-mediated homocoupling of the respective brominated precursors. Nitro-containing bichalcophenes **14** and **15** were obtained from the 1,4-dicarbonyl compound **13**. The use of these analogues in the synthesis of diamidines and analogues will be reported in due course.

Experimental

General

Melting points were recorded using a Thomas-Hoover (Uni-Melt) capillary melting point apparatus and are uncorrected. TLC analysis was carried out on silica gel 60 F_{254} precoated aluminum sheets and



Scheme 3 Reagents and conditions: (i) $ZnCl_2$; (ii) Ac_2O/c. H_2SO_4, rt; (iii) $CH_3CO_2NH_4$.

detected under UV light. ^1H and ^{13}C NMR spectra, were recorded employing a Varian Unity Plus 300 spectrometer at Georgia State University, and chemical shifts (δ) are in ppm relative to TMS as internal standard. Mass spectra were recorded on a VG analytical 70-SE spectrometer. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA) and are within ±0.4 of the theoretical values. All chemicals and solvents were purchased from Aldrich Co., Fisher Scientific and Lancaster. NBS was recrystallised from nitromethane prior to use. All solvents were reagent grade.

2,2′-Bifuran-5-carboxaldehyde **(3a)**: A mixture of 5-bromofuran-2-carboxaldehyde (8.7 g, 50 mmol), 2-tri-*n*-butylstannylfuran (17.9 g, 50 mmol), and tetrakis(triphenylphosphine) palladium (1.5 g) in dry dioxane (100 ml) was heated under nitrogen at 80–90°C for 24 h. The solvent was evaporated under reduced pressure and the resulting residue was dissolved in ethyl acetate. This solution was passed through celite to remove Pd. The solution was evaporated, and the residue was chromatographed on silica gel using hexanes/EtOAc (95 : 5) as an eluent to furnish compound **3a** in 83% yield, m.p. 49–49.5°C. ^1H NMR (DMSO-d_6); δ 6.67 (dd, J = 3.6, 1.5 Hz, 1H), 6.97 (d, J = 3.6 Hz, 1H), 7.04 (d, J = 3.6 Hz, 1H), 7.62 (d, J = 3.6 Hz, 1H), 7.88 (d, J = 1.5 Hz, 1H), 9.56 (s, 1H). ^{13}C NMR (DMSO-d_6); δ 177.5, 151.2, 150.1, 145.1, 144.0, 125.3, 112.4, 110.0, 107.9. MS (EI) *m/e* (rel. int.): 162 (M^+, 85), 105 (100), 77 (30), 51 (70). Anal. Calcd for $C_9H_6O_3$: C, 66.67; H, 3.73. Found. C, 66.4; H, 3.6.

5-(Furan-2-yl)thiophene-2-carboxaldehyde **(3b)**: The same procedure described for preparation of **3a** was used employing 5-bromothiophene-2-carboxaldehyde instead of 5-bromofuran-2-carboxaldehyde. Yield 81%, m.p. 38°C. ^1H NMR (DMSO-d_6); δ 6.67 (dd, J = 3.6, 1.5 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 7.55 (d, J = 4.2 Hz, 1H), 7.84 (d, J = 1.5 Hz, 1H), 7.99 (d, J = 4.2 Hz, 1H), 9.88 (s, 1H). ^{13}C NMR (DMSO-d_6); δ 183.9, 147.5, 144.6, 141.2, 141.1, 139.0, 123.8, 112.8, 109.6. MS (EI) *m/e* (rel. int.): 178 (M^+, 100), 149 (12), 121 (40), 77 (18). Anal. Calcd for $C_9H_6O_2S$: C, 60.66; H, 3.39. Found. C, 60.4; H, 3.5.

2,2′-Bithiophene-5-carboxaldehyde **(3c)**: The same procedure described for preparation of **3a** was used employing 5-bromothiophene-2-carboxaldehyde and 2-tri-*n*-butylstannylthiophene. Yield 85%, m.p. 46–46.5°C. ^1H NMR (DMSO-d_6); δ 7.15 (dd, J = 5.1, 3.9 Hz, 1H), 7.49 (d, J = 3.9 Hz, 1H), 7.56 (dd, J = 3.9, 1.2 Hz, 1H), 7.68 (dd, J = 5.1, 1.2 Hz, 1H), 7.96 (d, J = 3.9 Hz, 1H), 9.86 (s, 1H). ^{13}C NMR (DMSO-d_6); δ 183.8, 145.6, 141.1, 139.1, 135.1, 128.8, 128.3, 126.9, 125.1. MS (EI) *m/e* (rel. int.): 194 (M^+, 100), 165 (15), 121 (60). Anal. Calcd for $C_9H_6OS_2$: C, 55.64; H, 3.11. Found. C, 55.7; H, 3.2.

5-(Thiophen-2-yl)furan-2-carboxaldehyde **(3d)**: The same procedure described for preparation of **3a** was used employing 2-tri-*n*-butylstannylthiophene instead of 2-tri-*n*-butylstannylfuran. Yield 79%, m.p. 36°C. ^1H NMR (DMSO-d_6); δ 7.08 (d, J = 3.6 Hz, 1H), 7.20 (dd, J = 5.1, 3.9 Hz, 1H), 7.63 (d, J = 3.6 Hz, 1H), 7.67 (d, J = 3.9, 1.2 Hz, 1H), 7.75 (d, J = 5.1, 1.2 Hz, 1H), 9.54 (s, 1H). ^{13}C NMR (DMSO-d_6); δ 177.3, 154.0, 151.1, 130.9, 128.7, 126.9, 125.8, 115.1, 108.1. MS (EI) *m/e* (rel. int.): 178 (M^+, 70), 150 (10), 121 (57), 43 (100). Anal. Calcd for $C_9H_6O_2S$: C, 60.66; H, 3.39. Found. C, 60.7; H, 3.5.

2,2′-Bifuran-5-carbonitrile **(4a)**: To a stirred solution of **3a** (6.48 g, 40 mmol) in 75 ml of methanol was slowly added an aqueous solution (30 ml) of hydroxylamine hydrochloride (2.80 g, 40 mmol) and sodium carbonate (4.24 g, 40 mmol). The reaction mixture was allowed to reflux for 6 h. The solvent was evaporated, the precipitate was partitioned between water and ethyl acetate (200 ml), the organic layer was dried (Na_2SO_4), and then concentrated to dryness under reduced pressure. The crude oxime was allowed to reflux in acetic anhydride (40 ml) for 4 h. The solvent was evaporated and the precipitate was chromatographed on silica gel using hexanes/EtOAc (90 : 10) as an eluent to afford **4a** in 79% yield, m.p. 78.5–79°C. ^1H NMR (DMSO-d_6); δ 6.68 (dd, J = 3.3, 1.5 Hz, 1H), 6.95 (d, J = 3.6 Hz,1H), 7.02 (d, J = 3.3 Hz, 1H), 7.71 (d, J = 3.6 Hz, 1H), 7.86 (d, J = 1.5 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 150.0, 144.8, 143.6, 125.5, 123.7, 112.3, 111.8, 109.7, 106.7. MS (EI) *m/e* (rel. int.): 159 (M^+, 100), 130 (15), 103 (90), 76 (80), 51 (50). Anal. Calcd for $C_9H_5NO_2$: C, 67.92; H, 3.17. Found. C, 67.9; H, 3.2.

5-(Furan-2-yl)thiophene-2-carbonitrile **(4b)**: The same procedure described for preparation of **4a** was used starting with **3b**. Yield 75%, m.p. 81.5°C. ^1H NMR (DMSO-d_6); δ 6.66 (dd, J = 3.6, 1.8 Hz, 1H), 7.09 (d, J = 3.6 Hz, 1H), 7.50 (d, J = 4.2 Hz, 1H), 7.82 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 4.2 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 146.8, 144.4, 140.1, 139.8, 123.1, 114.3, 112.7, 109.2, 105.7. MS (EI) *m/e* (rel. int.): 175 (M^+, 100), 146 (75), 120 (10), 103 (12). Anal. Calcd for C_9H_5NOS: C, 61.70; H, 2.88. Found. C, 61.6; H, 2.9.

2,2′-Bithiophene-5-carbonitrile **(4c)**: The same procedure described for preparation of **4a** was used starting with **3c**. Yield 83%, m.p. 74–75°C (Lit.[13] melting point not reported). ^1H NMR (DMSO-d_6); δ 7.14 (dd, J = 5.1, 3.9 Hz, 1H), 7.44 (d, J = 3.9 Hz, 1H), 7.53 (dd, J = 3.9, 1.2 Hz, 1H), 7.68 (dd, J = 5.1, 1.2 Hz, 1H), 7.92 (d, J = 3.9 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 144.8, 140.9, 134.7, 129.5, 128.9, 127.6, 125.1, 114.9, 106.6. MS (EI) *m/e* (rel. int.): 191 (M^+, 100), 159 (10), 146 (13). Anal. Calcd for $C_9H_5NS_2$: C, 56.51; H, 2.63. Found. C, 56.7; H, 2.7.

5-(Thiophen-2-yl)furan-2-carbonitrile **(4d)**: The same procedure described for preparation of **4a** was used starting with **3d**. Yield 74%, m.p. 67–67.5°C. ^1H NMR (DMSO-d_6); δ 7.05 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 5.1, 3.9 Hz, 1H), 7.62 (dd, J = 3.9, 1.2 Hz, 1H), 7.69 (d, J = 3.6 Hz, 1H), 7.73 (dd, J = 5.1, 1.2 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 153.7, 130.3, 128.5, 128.4, 126.5, 125.8, 123.4, 111.9, 106.8. MS (EI) *m/e* (rel. int.): 175 (M^+, 100), 147 (40), 121 (22), 103 (15). Anal. Calcd for C_9H_5NOS: C, 61.70; H, 2.88. Found. C, 61.6; H, 2.8.

5′-Bromo-2,2′-bifuran-5-carbonitrile **(5a)**: To a solution of **4a** (4.77 g, 30 mmol) in DMF (20 ml) was added portionwise *N*-bromosuccinimide (5.34 g, 30 mmol) with stirring. The reaction mixture was stirred overnight, then poured onto cold water. The precipitate which formed was collected, washed with water and dried to give **5a** in 86% yield, m.p. 127–128°C. ^1H NMR (DMSO-d_6); δ 6.80 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 3.6 Hz, 1H), 7.06 (d, J = 3.6 Hz, 1H), 7.71 (d, J = 3.6 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 148.6, 145.5, 125.5, 124.0, 123.9, 114.4, 112.1, 111.7, 107.3. MS (EI) *m/e* (rel. int.): 237, 239 (M^+, 35, 30), 158 (20), 130 (100). Anal. Calcd for $C_9H_4BrNO_2$: C, 45.41; H, 1.69. Found. C, 45.1; H, 1.9.

5-(5-Bromofuran-2-yl)thiophene-2-carbonitrile **(5b)**: The same procedure described for preparation of **5a** was used starting with **4b**. Yield 90%, m.p. 109–109.5°C. ^1H NMR (DMSO-d_6); δ 6.78 (d, J = 3.6 Hz, 1H), 7.13 (d, J = 3.6 Hz, 1H), 7.50 (d, J = 4.2 Hz, 1H), 7.94 (d, J = 4.2 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 148.9, 140.1, 138.4, 123.4, 123.3, 114.7, 114.1, 111.7, 106.2. MS (EI) *m/e* (rel. int.): 253, 255 (M^+, 25, 23), 146 (100). Anal. Calcd for C_9H_4BrNOS: C, 42.54; H, 1.59. Found. C, 42.6; H, 1.6.

5′-Bromo-2,2′-bithiophene-5-carbonitrile **(5c)**: The same procedure described for preparation of **5a** was used starting with **4c**. Yield 95%, m.p. 158–159°C (Lit.[13] melting point not reported). ^1H NMR (DMSO-d_6); δ 7.26 (d, J = 3.9 Hz, 1H), 7.34 (d, J = 3.9 Hz, 1H),

7.41 (d, J = 3.9 Hz, 1H), 7.88 (d, J = 3.9 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 142.3, 139.6, 135.3, 131.6, 127.1, 124.7, 113.5, 112.8, 106.5. MS (EI) *m/e* (rel. int.): 269, 271 (M^+, 90, 93), 190 (46), 146 (100). Anal. Calcd for $C_9H_4BrNS_2$: C, 40.01; H, 1.49. Found. C, 39.7; H, 1.7.

5-(5-Bromothiophen-2-yl)furan-2-carbonitrile **(5d)**: The same procedure described for preparation of **5a** was used starting with **4d**. Yield 93%, m.p. 101–102°C. ^{1}H NMR (DMSO-d_6); δ 7.09 (d, J = 3.9 Hz, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 3.9 Hz, 1H), 7.70 (d, J = 4.8 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 152.2, 131.9, 127.1, 125.8, 124.8, 123.7, 113.8, 111.7, 107.4. MS (EI) *m/e* (rel. int.): 253, 255 (M^+, 60, 57), 146 (100). Anal. Calcd for C_9H_4BrNOS: C, 42.54; H, 1.59. Found. C, 42.8; H, 1.6.

5'-(4-Cyanophenyl)-2,2'-bifuran-5-carbonitrile **(6a)**
Method A
To a stirred solution of **5a** (4.74 g, 20 mmol), and tetrakis(triphenylphosphine) palladium (600 mg) in toluene (40 ml) under a nitrogen atmosphere was added 20 ml of a 1.5 M aqueous solution of Na_2CO_3 followed by 4-cyanophenylboronic acid (3.21 g, 22 mmol) in 5 ml of methanol. The vigorously stirred mixture was warmed to 80°C for 16 h. The solvent was evaporated, the precipitate was partitioned between methylene chloride (300 ml) and aqueous solution containing 15 ml of concentrated ammonia. The organic layer was dried (Na_2SO_4), and then concentrated to dryness under reduced pressure to afford **6a** in 74% yield, m.p. 194–195°C (DMF). ^{1}H NMR (DMSO-d_6); δ 7.17 (d, J = 3.6 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 7.43 (d, J = 3.6 Hz, 1H), 7.76 (d, J = 3.6 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H). ^{13}C NMR (DMSO-d_6); δ 152.3, 149.3, 144.3, 133.0, 132.9, 125.6, 124.3, 124.1, 118.7, 112.0, 111.8, 111.5, 110.0, 107.9. MS (EI) *m/e* (rel. int.); 260 (M^+, 100), 231 (15), 203 (25), 177 (25), 140 (10), 130 (55). Anal. Calcd for $C_{16}H_8N_2O_2$: C, 73.84; H, 3.09; N, 10.76. Found. C, 73.6; H, 3.2; N, 10.9.

Method B
A mixture of **10a** (740 mg, 2.35 mmol) and Cu(I)CN (423 mg, 4.7 mmol) in dry DMF (25 ml) was refluxed for 48 h. The reaction mixture was poured onto water/ammonia and extracted with methylene chloride. The extract was washed with water and brine, dried over Na_2SO_4, then passed on silica gel to give compound **6a** in 40% yield.

5-[5-(4-Cyanophenyl)-furan-2-yl]thiophene-2-carbonitrile **(6b)**: The same Suzuki coupling procedure described for preparation of **6a** was used starting with **5b**. Yield 76%, m.p. 187–188°C. ^{1}H NMR (DMSO-d_6); δ 7.22 (d, J = 3.6 Hz, 1H), 7.35 (d, J = 3.6 Hz, 1H), 7.62 (d, J = 3.9 Hz, 1H), 7.85–7.94 (m, 5H). ^{13}C NMR (DMSO-d_6); δ 151.8, 147.5, 139.5, 138.7, 132.8, 132.6, 123.9, 123.8, 118.3, 113.7, 111.5, 111.4, 109.8, 106.3. MS (EI) *m/e* (rel. int.); 276 (M^+, 100), 247 (12), 215 (5), 146 (28). Anal. Calcd for $C_{16}H_8N_2OS$: C, 69.55; H, 2.92. Found. C, 69.2; H, 3.15.

5'-(4-Cyanophenyl)-2,2'-bithiophene-5-carbonitrile **(6c)**
Method A
The same Suzuki coupling procedure described for preparation of **6a** was used starting with **5c**. Yield 70%, m.p. 231–233°C. ^{1}H NMR (DMSO-d_6); δ 7.50 (d, J = 3.9 Hz, 1H), 7.59 (d, J = 3.9 Hz, 1H), 7.73 (d, J = 3.9 Hz, 1H), 7.84–7.87 (m, 4H), 7.91 (d, J = 3.9 Hz, 1H). ^{13}C NMR (DMSO-d_6); δ 143.1, 142.3, 140.0, 136.9, 135.1, 132.9, 128.2, 127.4, 125.9, 124.9, 118.4, 113.8, 110.2, 106.6. MS (EI) *m/e* (rel. int.); 292 (M^+, 100), 267 (6), 146 (15). Anal. Calcd for $C_{16}H_8N_2S_2$: C, 65.73; H, 2.76. Found. C, 65.4; H, 2.95.

Method B
The cyanation procedure described for preparation of **6a** was used starting with **10b**. Yield 34%.

5-[5-(4-Cyanophenyl)-thiophen-2-yl]furan-2-carbonitrile **(6d)**: The same Suzuki coupling procedure described for preparation of **6a** was used starting with **5d**. Yield 75%, m.p. 216.5–218°C. ^{1}H NMR (DMSO-d_6); δ 7.09 (d, J = 3.9 Hz, 1H), 7.64–7.66 (m, 2H), 7.75 (d, J = 3.9 Hz, 1H), 7.84–7.88 (m, 4H). ^{13}C NMR (DMSO-d_6); δ 152.6, 142.5, 136.8, 132.7, 131.1, 127.5, 127.0, 125.7, 125.4, 123.7, 118.1, 111.3, 110.1, 107.5. MS (EI) *m/e* (rel. int.); 276 (M^+, 100), 247 (25), 222 (12). Anal. Calcd for $C_{16}H_8N_2OS$: C, 69.55; H, 2.92. Found. C, 69.5; H, 3.0.

[2,2';5',2";5",2"']Quaterfuran-5,5"'-dicarbonitrile **(7a)**: To a solution of **5a** (2.37 g, 10 mmol), and $Pd(PPh_3)_4$ (200 mg, 0.17 mmol) in toluene (40 ml) was added hexa-*n*-butylditin (5.8 g, 10 mmol). The reaction mixture was heated under N_2 at 120°C for 6 h, then cooled, and the precipitate was filtered and washed with hexanes. Recrystallisation from DMF gave compound **7a** in 83%, m.p. 248–250°C. ^{1}H NMR (DMSO-d_6); δ 7.02 (d, J = 3.9 Hz, 4H), 7.13 (d, J = 3.9 Hz, 2H), 7.65 (d, J = 3.9 Hz, 2H). ^{13}C NMR (DMSO-d_6); δ 148.8, 145.2, 143.2, 124.7, 123.9, 111.3, 111.1, 109.1, 107.2. MS (EI) *m/e* (rel. int.); 316 (M^+, 100), 260 (10), 203 (8), 177 (15), 158 (18). Anal. Calcd for $C_{18}H_8N_2O_4$: C, 68.36; H, 2.55. Found. C, 68.7; H, 2.7.

5,5'-Bis(5-cyanothiophen-2-yl)-2,2'-bifuran **(7b)**: The same procedure described for preparation of **7a** was used starting with **5b**. Yield 85%, m.p. 235–237°C. ^{1}H NMR (DMSO-d_6); δ 7.01 (d, J = 3.6 Hz, 2H), 7.21 (d, J = 3.6 Hz, 2H), 7.57 (d, J = 3.9 Hz, 2H), 7.92 (d, J = 3.9 Hz, 2H). MS (EI) *m/e* (rel. int.); 348 (M^+, 100), 319 (8), 212 (12), 174 (18), 136 (30). Anal. Calcd for $C_{18}H_8N_2O_2S_2$: C, 62.05; H, 2.31. Found. C, 62.4; H, 2.5.

[2,2';5',2";5",2"']Quaterthiophene-5,5"'-dicarbonitrile **(7c)**: The same procedure described for preparation of **7a** was used starting with **5c**. Yield 80%, m.p. 259–261°C. ^{1}H NMR (DMSO-d_6); δ 7.33–7.44 (m, 4H), 7.67 (d, J = 3.9 Hz, 2H), 7.86 (d, J = 3.9 Hz, 2H). MS (EI) *m/e* (rel. int.); 380 (M^+, 100), 348 (5), 310 (5), 190 (14). Anal. Calcd for $C_{18}H_8N_2S_4$: C, 56.81; H, 2.12. Found. C, 57.1; H, 2.1.

5,5'-Bis(5-cyanofuran-2-yl)-2,2'-bithiophene **(7d)**: The same procedure described for preparation of **7a** was used starting with **5d**. Yield 78%, m.p. 226–228°C. ^{1}H NMR (DMSO-d_6); δ 7.04 (d, J = 3.9 Hz, 2H), 7.44 (d, J = 4.2 Hz, 2H), 7.57 (d, J = 4.2 Hz, 2H), 7.63 (d, J = 3.9 Hz, 2H). ^{13}C NMR (DMSO-d_6); δ 152.4, 136.7, 129.3, 127.2, 125.7, 125.2, 123.5, 111.2, 107.2. MS (EI) *m/e* (rel. int.); 348 (M^+, 100), 319 (10), 291 (12), 266 (10), 174 (16). Anal. Calcd for $C_{18}H_8N_2O_2S_2$: C, 62.05; H, 2.31. Found. C, 62.4; H, 2.2.

5-(4-Cyanophenyl)-2,2'-bifuran (**9a**): Adopting Stille coupling conditions used for preparation of **3a** by employing compound **8** instead of 5-bromofuran-2-carboxaldehyde and heating temperature 100–110°C furnished compound **9a** in 79.5% yield, m.p. 104–105°C. ^{1}H NMR ($CDCl_3$); δ 6.51 (dd, J = 3.6, 1.8 Hz, 1H), 6.68 (d, J = 3.6 Hz, 1H), 6.69 (d, J = 3.6 Hz, 1H), 6.87 (d, J = 3.6 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$); δ 150.9, 147.5, 145.8, 142.4, 134.1, 132.5, 123.7, 118.9, 111.6, 110.1, 107.5, 106.3. MS (EI) *m/e* (rel. int.); 235 (M^+, 100), 206 (10), 178 (15). Anal. Calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95. Found. C, 76.35; H, 3.9; N, 5.9.

5-(4-Cyanophenyl)-2,2'-bithiophene **(9b)**: Adopting Stille coupling conditions used for preparation of **3a** by employing 4-bromobenzonitrile and 5-(2-*n*-tributyltin)-2,2'-bithiophene and heating temperature 100–110°C to furnish compound **9b** in 84.5% yield, m.p. 140–141°C. ^{1}H NMR ($CDCl_3$); δ 7.05 (dd, J = 4.8, 3.6 Hz, 1H), 7.18 (d, J = 3.9 Hz, 1H), 7.22 (dd, J = 3.6, 1.2 Hz, 1H), 7.27 (dd, J = 4.8, 1.2 Hz, 1H), 7.33 (d, J = 3.9 Hz, 1H), 7.65–7.68 (m, 4H). ^{13}C NMR ($CDCl_3$); δ 140.3, 139.0, 138.2, 136.6, 132.7, 128.0, 125.8, 125.6, 125.1, 124.8, 124.2, 118.8, 110.4. MS (EI) *m/e* (rel. int.); 268 (M^+ + 1, 100), 239 (20). Anal. Calcd for $C_{15}H_9NS_2$: C, 67.38; H, 3.39; N, 5.23. Found. C, 67.1; H, 3.5; N, 4.95.

5-(4-Cyanophenyl)-5'-bromo-2,2'-bifuran (**10a**): The same procedure described for preparation of **5a** was used starting with **9a**. Yield 65%, m.p. 127–128°C. ^{1}H NMR ($CDCl_3$); δ 6.42 (d, J = 3.6 Hz, 1H), 6.63 (d, J = 3.6 Hz, 1H), 6.68 (d, J = 3.6 Hz, 1H), 6.86 (d, J = 3.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$); δ 151.2, 147.6, 146.2, 134.0, 132.5, 124.0, 123.8, 122.3, 113.4, 110.4, 110.0, 108.4, 108.1. MS (EI) *m/e* (rel. int.); 314 (M^+, 40), 234 (10), 206 (100). Anal. Calcd for $C_{15}H_8BrNO_2$: C; 57.32, H; 2.56; N, 4.46. Found. C; 56.9, H; 2.55; N, 4.4.

5-(4-Cyanophenyl)-5'-bromo-2,2'-bithiophene **(10b)**: The same procedure described for preparation of **5a** was used starting with **9b**. Yield 68%, m.p. 175–176.5°C. ^{1}H NMR ($CDCl_3$); δ 6.98 (d, J = 3.9 Hz, 1H), 7.01 (d, J = 3.9 Hz, 1H), 7.12 (d, J = 3.9 Hz, 1H), 7.33 (d, J = 3.9 Hz, 1H), 7.66 (s, 4H). ^{13}C NMR ($CDCl_3$); δ 140.8, 138.1, 138.0, 137.9, 132.7, 130.8, 125.8, 125.7, 125.0, 124.3, 118.7, 111.9, 110.7. MS (EI) *m/e* (rel. int.); 347 (M^+ + 1, 100), 266 (8), 222 (40). Anal. Calcd for $C_{15}H_8BrNS_2$: C, 52.03; H, 2.33. Found. C, 51.9; H, 2.25.

1-(4-Nitrophenyl)-4-(5-nitrothiophen-2-yl)butane-1,4-dione **(13)**: Anhydrous $ZnCl_2$ (5.44 g, 40 mmol), was stirred in dry benzene (20 ml), dry Et_3N (2.2 g, 30 mmol) and *t*-BuOH (2.8 ml, 30 mmol) till homogenous (2 h). The 5-nitro-2-acetylthiophene (5.13 g, 30 mmol) followed by the 4-nitrophenacyl bromide (4.88 g, 20 mmol) were added. After stirring at room temperature for 4 days, the reaction mixture was quenched with 5% H_2SO_4, the resultant solid was filtered, washed with water, dried and purified by silica gel using hexanes/ethyl acetate (40: 60) as an eluent to furnish compound **13** in 45% yield, m.p. 153–154°C. ^{1}H NMR (DMSO-d_6);

δ 3.43–3.52 (m, 4H), 8.12 (d, *J* = 4.5 Hz, 1H), 8.21–8.25 (m, 3H), 8.35 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (DMSO-d_6); δ 197.6, 192.7, 155.2, 150.0, 147.5, 140.7, 132.1, 130.2, 129.4, 123.9, 32.9, 32.6. MS (EI) *m/e* (rel. int.); 334 (M^+, 8), 306 (80), 156 (27), 150 (100), 43 (84). Anal. Calcd for $C_{14}H_{10}N_2O_6S$: C, 50.30; H, 3.02. Found. C, 50.0; H, 3.2.

2-(4-Nitrophenyl)-5-(5-nitrothiophen-2-yl)furan **(14)**: To a stirred solution of 1,4-dicarbonyl compound **13** (1.0 g, 3 mmol) in acetic anhydride (5 ml) was added conc. H_2SO_4 (1 ml). After stirring at room temperature for 16 h, the reaction mixture was poured onto ice-water, the resultant solid was filtered off, washed with water, crystallised from ethanol to afford compound **14** in 70% yield, m.p. 257–259°C. ^{1}H NMR (DMSO-d_6); δ 7.42 (s, 1H), 7.48 (s, 1H), 7.62 (d, *J* = 3.9 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 2H), 8.14 (d, *J* = 3.9 Hz, 1H), 8.30 (d, *J* = 7.5 Hz, 2H). MS (EI) *m/e* (rel. int.); 316 (M^+, 100), 286 (18), 270 (18), 226 (25). Anal. Calcd for $C_{14}H_8N_2O_5S$: C, 53.16; H, 2.55. Found. C, 52.9; H, 2.8.

*2-(4-nitrophenyl)-5-(5-nitrothiophen-2-yl)-1*H*-pyrrole* **(15)**: A solution of compound **13** (1.0 g, 3.0 mmol) and ammonium acetate (1.15 g, 15 mmol) in glacial acetic acid (5 ml) and ethanol (10 ml) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature, and then poured onto ice-water. The resultant solid was collected by filtration, washed with water, and crystallised from acetone to give compound **15** in 41% yield, m.p. 251–253°C. ^{1}H NMR (DMSO-d_6); δ 6.92 (s, 1H), 6.99 (s, 1H), 7.58 (d, *J* = 4.5 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 8.12 (d, *J* = 4.5 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 2H), 12.08 (s, 1H). ^{13}C NMR (DMSO-d_6); δ 146.7, 145.2, 143.4, 137.3, 133.7, 131.4, 127.9, 124.7, 124.0, 121.9, 113.2, 112.3. MS (EI) *m/e* (rel. int.); 315 (M^+, 100), 285 (14), 269 (23), 223 (30). Anal. Calcd for $C_{14}H_9N_3O_4S$: C, 53.33; H, 2.88. Found. C, 53.15; H, 3.0.

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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*. M. Demeunynck, C. Bailly and W.D. Wilson, Eds. Wiley-VCH, New York, Vol. 2, 2003; 416.
2 W.D. Wilson, B. Nguyen, F.A. Tanious, A. Mathis, J.E. Hall, C.E. Stephens and D.W. Boykin, *Curr. Med. Chem. Anti-Cancer Agents*, 2005, **5**, 389.
3 M.N.C. Soeiro, E.M. de Souza, C.E. Stephens and D.W. Boykin, *Expert Opin. Invest. Drugs,* 2005, **14**, 957.
4 A.M. Mathis, J.L. Holman, L.M. Sturk, M.A. Ismail, D.W. Boykin, R.R Tidwell and J.E. Hall, *Antimicrob. Agents Chemother.,* 2006, **50**, 2185.
5 (a) B.S. Ong, Y. Wu, P. Liu and S. Gardner, *J. Am. Chem. Soc.,* 2004, **126**, 3378; (b) P.C. Chang, J. Lee, D. Huang, V. Subramanian, A.R. Murphy and J.M.J. Frechet, *Chem. Mater*., 2004, **16**, 4783; (c) R.P. Ortiz, M.C.R. Delgado, J. Casado, V. Hernandez, O.-K. Kim, H.Y. Woo and J.T.L. Navarrete, *J. Am. Chem. Soc.,* 2004, **126**, 13363.
6 (a) M.M.M. Raposo, A.M.C. Fonseca and G. Kirsch, *Tetrahedron,* 2004, **60**, 4071; (b) J.-S. Kim, H.K. Ahn and M. Ree, *Tetrahedron Lett.,* 2005, **46**, 277.
7 J.A.E.H. van Haare, M. van Boxtel and R.A.J. Janssen, *Chem. Mater.,* 1998, **10**, 1166.
8 (a) V. Marcon and G. Raos *J. Phys. Chem. B,* 2004, **108**, 18053; (b) H. Meng, Z. Bao, A.J. Lovinger, B.-C. Wang and A.M. Mujsce, *J. Am. Chem. Soc.,* 2001, **123**, 9214; (c) A. Yokooji, T. Satoh, M. Miura and M. Nomura, *Tetrahedron,* 2004, **60**, 6757; (d) S. Ando, J. Nishida, H. Tada, Y. Inoue, S. Tokito and Y. Yamashita, *J. Am. Chem. Soc.,* 2005, **127**, 5336.
9 M.A. Ismail, D.W. Boykin and C.E. Stephens, *Tetrahedron Lett.,* 2006, **47**, 795.
10 E.W. White, F. Tanious, M.A. Ismail, A.P. Reszka, S. Neidle, D.W. Boykin and D.W. Wilson, *Biophys. Chem.*, 2006, in the press.
11 S.S. Zhu and T.M. Swager, *J. Am. Chem. Soc.,* 1997, **119**, 12568.
12 N.M. Nevar, A.V. Kel'in and O.G. Kulinkovich, *Synthesis,* 2000, 1259.
13 P. Hapiot, F. Demanze, A. Yassar and F. Garnier, *J. Phys. Chem. B,* 1996, **100**, 8397.