Facile synthesis of Benzobisimidazole and Bibenzimidazole-based bisnitriles as potential precursors for DNA minor groove binders.

Abdelbasset A. Farahat* [a,b], Satori Iwamoto [a], Michael Roche [a], David W. Boykin [c].

[a] Master of Pharmaceutical Sciences Program, California Northstate University, 9700 W. Taron Dr., Elk Grove, California, 95757, [b] Faculty of Pharmacy, Mansoura University, Mansoura, Egypt 35516. [c] Chemistry Department, Georgia State University, Atlanta, GA, USA 30303.

* Corresponding author email: abdelbasset.farahat@cnsu.edu

Keywords

Benzobisimidazole, Bibenzimidazole, Bisnitriles, Suzuki coupling, DNA Minor groove.

Abstract

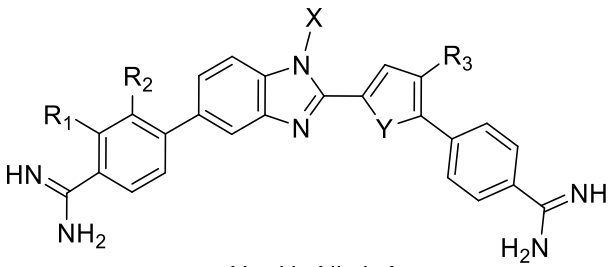
The synthesis of bisnitrile derivatives of benzobisimidazole and bibenzimidazole in a good yield is described in detail for the first time. Nucleophilic substitution of 1,5-difluoro-2,4-dinitrobenzene using different amines produced the intermediate diamines that were reduced using sodium borohydride/Pd(C) to produce the tetramines. These tetramines were allowed to couple with different aldehydes to produce the final benzimidazoles. In a different investigation, these bisnitrile derivatives will be used to make benzimidazole diamidines that could be used as potential mixed sequence minor groove binders.

Introduction

Benzobisimidazole and bibenzimidazole cores play an important role in the field of materials chemistry. These cores can be used in solar cells [1], organometallic polymers [2], catalysts in Suzuki reactions [3], and chemosensors for carbon dioxide [4]. While in the medicinal chemistry field, only limited reports have appeared involving benzobisimidazole and bibenzimidazoles cores which showed antitumor activity by inhibiting Topoisomerase II [5,6]. Heterocyclic diamidines, which can effectively enter human cells, and bind specifically to AT base pairs in the DNA duplex minor groove have been successfully used as nuclear and cell stains and as therapeutic agents, mainly against infectious diseases, [7-13]. Expanding the DNA sequence recognition ability of DNA minor groove binding diamidines to bind both AT and GC base pairs could also expand their therapeutic targets and have an impact on many indications, such as modulation of transcription factors biological activity [14,15]. Our group has considerable

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jhet.4353

success in the design of mixed sequence binding compounds through making *N*-alkylbenzimidazole thiophenes which are preorganized to fit the shape of the DNA minor groove and H-bond to the NH of GC base pairs that projects into the minor groove [16-20] (figure 1). In continuation of our effort to synthesize compounds that can specifically recognize GC base pairs, we report here the facile synthesis of new *N*-alkyl-benzobisimidazole and *N*-alkyl-bibenzimidazole-based bisnitrile intermediates to be used in a different investigation to synthesize benzimidazole diamidines that can be used in our drug discovery projects.

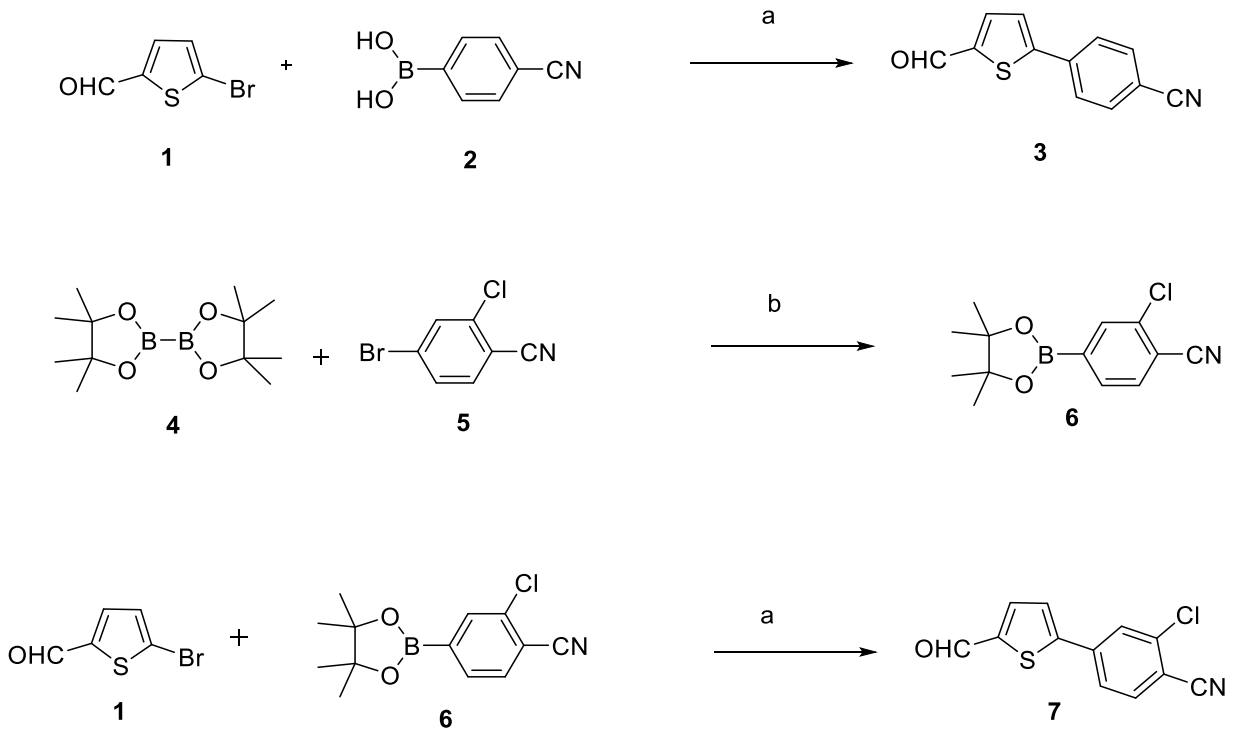


X = H, Alkyl, Ar
Y = S, Se
R_1 = H, Cl
R_2 = H, Me
R_3 = H, Me

Figure 1: Compounds recognize both AT and GC base pairs.

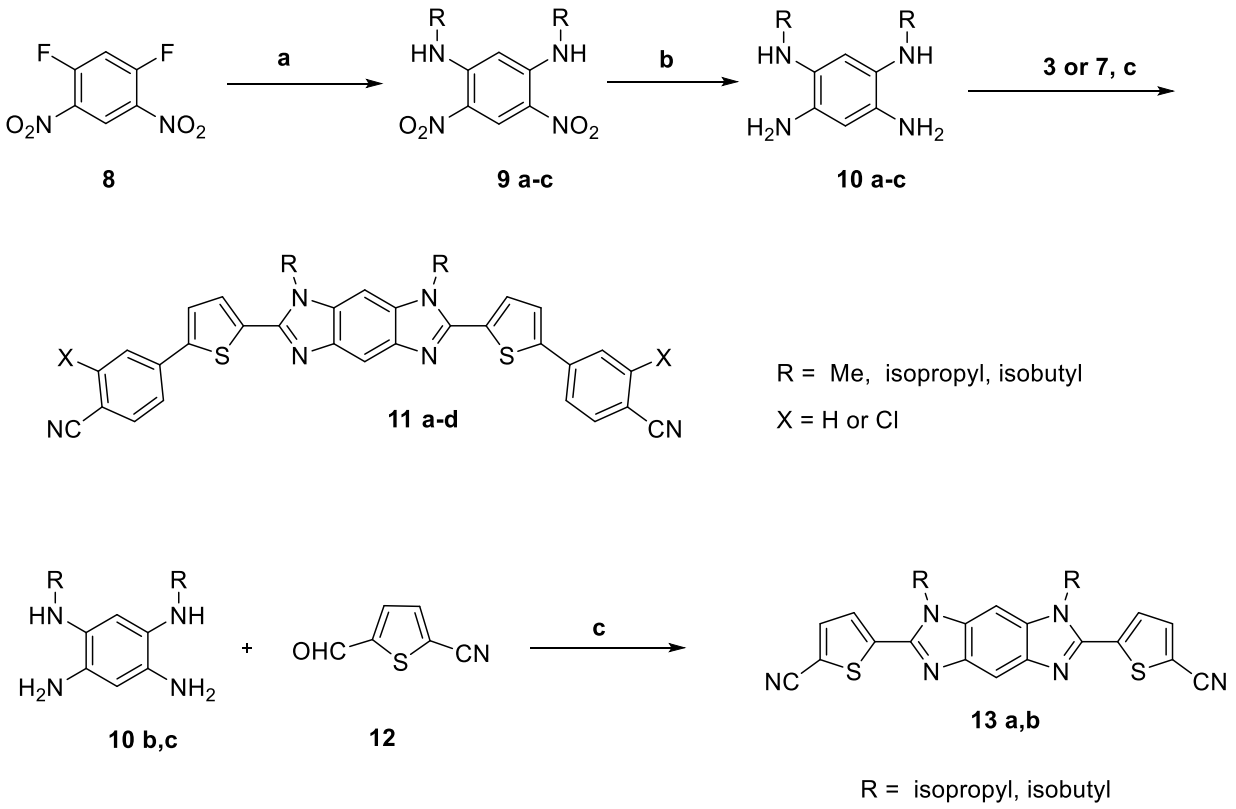
Results and discussion

Scheme 1 outlines the synthesis of the formyl thiophenes **3** and **7**. Compound **3** was made by applying Suzuki coupling conditions between the bromo derivative **1** and the boronic acid derivative 2. For the preparation of compound **7**, we started by making the boronic ester **6** via reaction of bis(pinacolato)diboron **4** with the bromo derivative **5**. Suzuki coupling using palladium (0) [21,22] was applied between the bromo compound **1** and the boronic ester **6** to produce the formyl intermediate **7** in good yield.



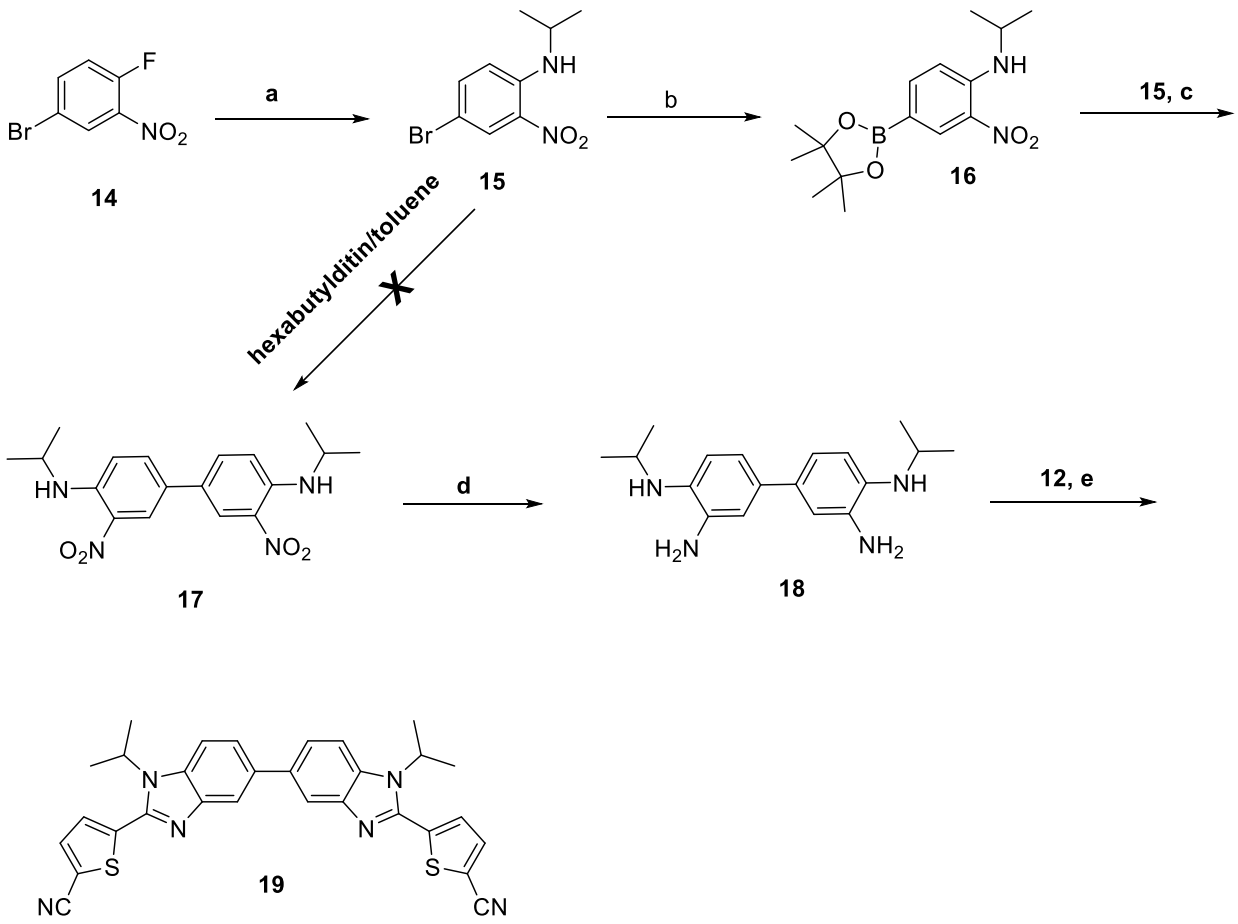
Scheme 1. Reagents and conditions: a) $Pd(PPh_3)_4$, Dioxane,H_2O, MeOH, K_2CO_3, 110 ^oC, 24 h; b) $PdCl_2(PPh_3)_2$, 1,4-Dioxane, Potassium acetate, 110 ^oC, 24 h.

Scheme 2 outlines the synthesis of the bisnitriles compounds **11 a-d** and **13 a, b**. Nucleophilic displacement of the starting difluoro nitro derivative **1** with different amines in ethanol afforded the amino substituted dinitro intermediates **9 a-c** in good yield. We tried the reduction of the dinitro compounds **9a-c** using both catalytic hydrogenation and tin chloride in ethanol, but the reactions were never complete presumably due to the insolubility of the starting dinitro compounds, and the impure product could not be chromatographed due to high polarity. Finally, we used sodium borohydride and Pd(C) in methanol/dichloromethane as a solvent to obtain the intermediate tetraamines **10 a-c** in good yield which were used directly in the next step without further purification. These amines were coupled with different aldehydes and sodium metabisulfite in DMSO to furnish the bisnitrile derivatives of benzobisimidazole **11 a-d** and **13 a, b** in a good yield [23,24].



Scheme 2. Reagents and conditions: a) amines/EtOH, rt, 24 h; b) $NaBH_4$, Pd(C), CH_2Cl_2,MeOH, rt., 4 h; c) $Na_2S_2O_5$/ DMSO, 130 ^oC, 30 mins.

The synthesis of the dibenzimidazole dinitrile **19** is described in Scheme 3. We started with a nucleophilic displacement of the fluoro derivative **14** by isopropylamine in ethanol to afford the amine derivative **15**. The boronic ester intermediate **16** was prepared by reaction of the starting bromo compound **15** with bis(pinacolato)diboron using bis(triphenylphosphine)palladium dichloride and potassium acetate in 1,4-dioxane. The former boronic ester underwent Suzuki coupling with the bromo compound **15** to produce the bis nitro intermediate **17**. With the aim of saving one step, we tried to make the biphenyl nitro derivative **17** by homocoupling of the bromo derivative **15** using hexabutylditin in toluene, but we never got a clean product. This nitro compound **17** was successfully reduced using sodium borohydride and Pd(C) in methanol/dichloromethane as a solvent to obtain the intermediate tetraamine **18** in good yield. The bibenzimidazole bisnitrile **19** was prepared by coupling of the intermediate tetramine and 5-formyl thiophene-2-carbonitrile using sodium metabisulfite in DMSO.



Scheme 3. Reagents and conditions: a) Isopropylamine/EtOH, rt, 24 h; b) Bis(pinacolato)diboron, $PdCl_2(PPh_3)_2$, K acetate, 1,4-Dioxane, 110 ^oC, 12 h; c) $Pd(PPh_3)_4$, K_2CO_3/H_2O, dioxane, reflux, 110 ^oC, 12 h; d) $NaBH_4$, Pd(C), CH_2Cl_2,MeOH, rt, 4 h.; e) $Na_2S_2O_5$/ DMSO, 130 ^oC, 30 mins.

Experimental.

All commercial reagents were used without purification. Melting points were determined on a Mel-Temp 3.0 melting point apparatus and are uncorrected. TLC analysis was carried out on silica gel 60 F254 precoated aluminum sheets using a UV light for detection. ^{1}HNMR spectra were recorded on a Bruker 400 MHz spectrometer using the indicated solvents, ^{13}CNMR spectra were recorded on a Bruker 200 MHz spectrometer using the indicated solvents. Mass spectra were obtained from the Georgia State University Mass Spectrometry Laboratory, Atlanta, GA.

4-(5-Formylthiophen-2-yl)benzonitrile (3).

K_2CO_3 (3.35 g, 25 mmol) in water (4 ml) and 4-cyanophenyl boronic acid (2.54 g, 17 mmol) in methanol (4 ml) was added to a stirred solution of the bromo compound (2.86 g, 15 mmol) in 1,4-dioxane (15 mL) and the mixture was deaerated under nitrogen for 10 min.

Tetrakis(triphenylphosphine) palladium (0.727 g, 0.6 mmol) was added, and the reaction mixture was vigorously stirred at 110 °C for 24 h and left to cool down. The formed solid was filtered, washed with 1,4-dioxane then water, and dried. White solid, yield (81%, 2.58 g), mp 215-217 ^{o}C; ^{1}HNMR (DMSO-d_6, 400MHz) δ 9.95 (s, 1H, CHO), 8.06 (d, 1H, *J*= 4.00 Hz, Ar), 7.98 (d, 2H, *J*=8.80 Hz, Ar), 7.91 (d, 1H, *J* = 8.80 Hz, Ar), 7.88 (d, 1H, *J*= 4.00 Hz, Ar).

(3-Chloro-4-cyanophenyl) boronic ester (6)

CH_3COOK (4.10 g, 42 mmol), bis(binacolato)diboron (5.31 g, 20 mmol) and 4-bromo-2-cholorobenzonitrile (3.00 g, 14 mmol) were stirred in a solution of 1,4-dioxane(25 mL), the mixture was deaerated under nitrogen for 10 minutes. 1,1-bis(diphenylphosphino)ferrocene-palladium(ii)dichloridedichloromethane (0.56 g, 0.7 mmol) was added and the reaction mixture was vigorously stirred at 110 °C for 24 h and left to cool. The solvent was evaporated under reduced pressure, the obtained solid was purified using column chromatography on silica gel, and hexanes/ethyl acetate as an eluent. Colorless solid, yield (89%, 3.27 g), mp 98-99 ^{o}C; ^{1}HNMR ($CDCl_3$, 400MHz) δ: 7.91 (s, 1H, Ar), 7.72-7.80 (m, 1H, Ar), 7.63-7.68 (m, 1H, Ar), 1.35 (s, 12H, $4CH_3$).

2-Chloro-4-(5-formylthiophen-2-yl) benzonitrile (7)

This compound was made by reaction between 5-bromothiophene-2-carbaldehyde and (3-chloro-4-cyanophenyl) boronic ester by applying the Suzuki coupling conditions mentioned above. White solid, yield (85 %). mp 151-152 ^{o}C; ^{1}HNMR (DMSO-d_6, 400MHz) δ 9.96 (s, 1H, CHO), 8.23 (d, 1H, *J*=1.60 Hz, Ar), 8.11 (d, 1H, *J*= 4.00 Hz, Ar), 8.06 (d, 1H, *J*=8.40 Hz, Ar), 8.01 (d,

1H, *J*=4.00 Hz, Ar), 7.95 (dd, 1H, *J* = 1.20, 8.00 Hz, Ar); ESI-HRMS: m/z calculated for $C_{12}H_7ClNOS$: 247.9931, found: 247.9896 (M^+).

Synthesis of *N*^{1}, *N*^{3}-dialkyl-4,6-dinitrobenzene-1,3-diamine (9a-c).

Amines (80 mmol) were added to 1,5-difluoro-2,4-dinitrobenzene (4.08 g, 20 mmol) suspension in ethanol (30 ml) and stirred at room temperature for 24 h. The precipitated yellow solid was filtered and washed with cooled ethanol and dried.

***N*^{1}, *N*^{3}-Dimethyl-4,6-dinitrobenzene-1,3-diamine (9a).**

Yellow solid (3.9 g 86 %), mp >250 ^{o}C dec. ^{1}HNMR (DMSO-d_6): δ 8.96 (br s, 1 H, Ar), 8.49 (s, 2 H, 2NH), 5.69 (s, 1 H, Ar), 2.99 (s, 6 H, 2 CH_3); ESI-HRMS: m/z calculated for $C_8H_{10}N_4O_4$: 225.0624, found: 225.0627 (M^+ - 1).

***N*^{1}, *N*^{3}-Diisopropyl-4,6-dinitrobenzene-1,3-diamine (9b).**

Yellow solid (4.9 g 88 %), mp >250 ^{o}C dec. ^{1}HNMR (DMSO-d_6): δ 8.94 (s, 1 H, Ar), 8.07 (m, 2 H, 2NH), 5.86 (s, 1 H, Ar), 3.96 (m, 2 H, 2CH), 1.29 (d, *J* = 6 Hz, 12 H, 4 CH_3); ESI-HRMS: m/z calculated for $C_{12}H_{19}N_4O_4$: 283.1406, found: 283.1418 (M^+ + 1).

***N*^{1}, *N*^{3}-Diisobutyl-4,6-dinitrobenzene-1,3-diamine (9c).**

Yellow solid (5.2 g 84 %), mp >250 ^{o}C dec. ^{1}HNMR (DMSO-d_6): δ 8.89 (s, 1 H, Ar), 8.36 (m, 2 H, 2NH), 5.74 (s, 1 H, Ar), 3.96 (t, *J* = 6 Hz, 4 H, 2CH_2), 1.97 (m, 2 H, 2CH), 0.97 (d, *J* = 6.8 Hz, 12 H, 4CH_3); ESI-HRMS: m/z calculated for $C_{14}H_{22}N_4O_4$: 309.1563, found: 309.1567 (M^+ - 1).

Synthesis of the tetraamines (10a-c).

Pd (C) (0.2 g) was added to a suspension of the nitro compound **2a-c** (4 mmol) in a deaerated mixture of dichloromethane/methanol (3/1, 60 ml), sodium borohydride (0.45 gm, 12 mmol) was added, and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture

was filtered, and the filtrate was concentrated under reduced pressure, the formed residue was dissolved in acetone (50 ml) and filtered. The filtrate was evaporated under reduced pressure and dried under vacuum at room temperature and used directly in the next step without further characterization.

Synthesis of the bisnitriles (11a-d and 13 a,b).

Sodium metabisulphite (1.14 g, 6 mmol) was added to a solution of the tetraamines **10a-c** (3 mmol) and the appropriate aldehydes (6 mmol) in DMSO (10 mL) and the mixture was heated at 150 ^{o}C for 30 min. The reaction mixture was poured into water, filtered, and dried. Purification was by crystallization from DMF and then acetone.

4,4'-((1,7-Dimethyl-1,7-dihydrobenzo[1,2-d:4,5-d']diimidazole-2,6-diyl)bis(thiophene-5,2-diyl))dibenzonitrile (11a).

Greenish solid (1.12 g, 68 %), mp > 300 ^{o}C; ^{1}HNMR (DMSO-d_6): δ 7.99 (m, 4 H, Ar), 7.93 (m, 5 H, Ar), 7.91 (m, 5 H, Ar), 4.15 (s, 6H, 2CH_3); ESI-HRMS: m/z calculated for $C_{32}H_{21}N_6S_2$: 553.1264, found: 553.1272 (M^+ + 1).

4,4'-((1,7-Diisopropyl-1,7-dihydrobenzo[1,2-d:4,5-d']diimidazole-2,6-diyl)bis(thiophene-5,2-diyl))dibenzonitrile (11b).

Greenish solid (1.07 g, 59 %), mp > 300 ^{o}C; ^{1}HNMR (DMSO-d_6): δ 8.03 (m, 4 H, Ar), 7.97 (m, 6 H, Ar), 7.54 (d, *J* = 3.2 Hz, 2 H, Ar), 7.37 (d, *J* = 3.2 Hz, 2 H, Ar), 5.42 (t, *J* = 6.8 Hz, 2 H, 2NH), 1.78 (d, *J* = 6.8 Hz, 12 H, 4CH_3); ESI-HRMS: m/z calculated for $C_{36}H_{28}N_6S_2$: 609.1895, found: 609.1901 (M^+ + 1).

4,4'-((1,7-Diisobutyl-1,7-dihydrobenzo[1,2-d:4,5-d']diimidazole-2,6-diyl)bis(thiophene-5,2-diyl))dibenzonitrile (11c).

Yellow solid (1.16 g, 61 %), mp > 300 ^{o}C; ^{1}HNMR (DMSO-d_6): δ 7.97 (d, *J* = 8.4 Hz, 4 H, Ar), 7.91 (d, *J* = 8.4 Hz, 4 H, Ar), 7.88 (br s, 2 H, Ar), 7.84 (d, *J* = 4 Hz, 2 H, Ar), 7.79 (d, *J* = 4 Hz, 2 H, Ar), 4.47 (d, *J* = 6.8 Hz, 4 H, 2CH_2), 2.52 (m, 2 H, 2CH), 0.93 (d, *J* = 6.8 Hz, 12 H, 4CH_3); ^{13}CNMR (DMSO-d_6): δ 147.2, 146.4, 143.6, 141.3, 140.1, 137.8, 135.9, 135.1, 133.7, 129.0, 127.9, 127.4, 126.6, 110.7; ESI-HRMS: m/z calculated for $C_{38}H_{33}N_6S_2$: 637.2208, found: 637.2217 (M^+ + 1).

4,4'-((1,7-Diisopropyl-1,7-dihydrobenzo[1,2-d:4,5-d']diimidazole-2,6-diyl)bis(thiophene-5,2-diyl))bis(2-chlorobenzonitrile) (11d).

Yellow solid (1.11 g, 55 %), mp > 300 ^{o}C; ^{1}HNMR (DMSO-d_6): δ 8.20 (br s, 2 H, Ar), 8.02 (m, 5 H, Ar), 7.97 (br s, 1 H, Ar), 7.89 (d, *J* = 8.4 Hz, 2 H, Ar), 7.74 (d, *J* = 3.6 Hz, 2 H, Ar), 5.26 (t, *J* = 6.8 Hz, 2 H, 2CH), 1.78 (d, *J* = 6.4 Hz, 12 H, 4CH_3); ESI-HRMS: m/z calculated for $C_{36}H_{27}Cl_2N_6S_2$: 677.1110, found: 677.1123 (M^+ + 1).

5,5'-(1,7-Diisopropyl-1,7-dihydrobenzo[1,2-d:4,5-d']diimidazole-2,6-diyl)bis(thiophene-2-carbonitrile) (13a).

Yellow solid (0.98 g, 72 %), mp > 300 ^{o}C; ^{1}HNMR (DMSO-d_6): δ 8.12 (d, *J* = 4 Hz, 2 H, Ar), 8.00 (br s, 1 H, Ar), 7.93 (br s, 1 H, Ar), 7.73 (d, *J* = 4 Hz, 2 H, Ar), 5.17 (m, 2 H, 2CH), 1.74 (d, *J* = 6.8 Hz, 12 H, 4CH_3); ESI-HRMS: m/z calculated for $C_{24}H_{21}N_6S_2$: 457.1269, found: 457.1264 (M^+ + 1).

5,5'-(1,7-Diisobutyl-1,7-dihydrobenzo[1,2-d:4,5-d']diimidazole-2,6-diyl)bis(thiophene-2-carbonitrile) (13b).

Yellow solid (0.99 g, 68 %), mp > 300 ^{o}C; ^{1}HNMR (DMSO-d_6): δ 8.09 (d, *J* = 4 Hz, 2 H, Ar), 8.01 (br s, 1 H, Ar), 7.94 (br s, 1 H, Ar), 7.86 (d, *J* = 4 Hz, 2 H, Ar), 4.46 (d, *J* = 7.2 Hz, 4 H, 2CH_2), 2.13 (m, 2 H, 2CH), 0.88 (d, *J* = 6.4 Hz, 12 H, 4CH_3); ^{13}CNMR (DMSO-d_6): δ 146.1,

140.9, 140.7, 140.1, 136.3, 127.7, 114.5, 110.3, 108.0, 92.6 ;ESI-HRMS: m/z calculated for $C_{26}H_{25}N_6S_2$: 485.1582, found: 485.1594 (M^+ + 1).

4-Bromo-*N*-isopropyl-2-nitroaniline (15).

Isopropylmine (2.36 g, 40 mmol) was added to 4-bromo-1-fluoro-2-nitrobenzene (4.4 g, 20 mmol) in ethanol (20 ml) and stirred at room temperature for 24 h. The reaction mixture was evaporated under reduced pressure. The product was filtered, washed with cold ethanol, and dried. Orange solid (3.67 g, 72 %), mp 97-98 ^oC; ^{1}HNMR (DMSO-d_6): δ 8.15 (br s, 1 H, Ar), 7.88 (d, *J* = 7.2 Hz, 1 H, Ar), 7.64 (d, *J* = 9.2 Hz, 1 H), 7.08 (d, *J* = 9.2 Hz, 1 H, NH), 3.92 (m, 1 H, CH), 1.25 (d, *J* = 6 Hz, 6 H, $2CH_3$); ESI-HRMS: m/z calculated for $C_9H_{12}BrN_2O_2$: 259.077, found: 259.066 (M^+ + 1).

***N*-Isopropyl-2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (16).**

Potassium acetate (5.88 g, 60 mmol) and bis(pinacolato)diboron (7.59 gm, 30 mmol) were added to a stirred solution of the bromo compound **6** (5.18 gm, 20 mmol) in 1,4-dioxane (60 mL) and the mixture was deaerated under nitrogen for 20 min. Dichlorobis(triphenylphosphine)palladium (0.56 g, 0.8 mmol) was added and the reaction mixture was vigorously stirred at 100 °C for 12 h under nitrogen. The solvent was evaporated under reduced pressure and the formed residue was purified using column chromatography on silica gel, and hexanes/ethyl acetate as an eluent.

Yellow solid (4.2 g, 70 %), mp 142-143 ^oC. ^{1}HNMR (DMSO-d_6): δ 8.35 (s, 1 H, Ar), 8.04 (d, *J* = 7.2 Hz, 1 H, Ar), 7.69 (d, *J* = 8.4 Hz, 1 H, Ar), 7.06 (d, *J* = 8.4 Hz, 1 H, NH), 3.95 (d, *J* = 6.4 Hz, 1 H, CH), 1.28 (s, 12 H, $4CH_3$), 1.26 (s, 6 H, $2CH_3$).

***N*^{4},*N*$^{4'}$-Diisopropyl-3,3'-dinitro-[1,1'-biphenyl]-4,4'-diamine (17).**

K_2CO_3 (2.76 g, 20 mmol) in water (5 ml) and the boronic ester **7** (3.36 gm, 11 mmol) methanol (10 ml) were added to a stirred solution of the bromo compound **6** (2.59 gm, 10 mmol) in 1,4-

dioxane (30 mL) and the mixture was deaerated under nitrogen for 20 min. Tetrakis(triphenylphosphine) palladium (0.46 g, 0.4 mmol) was added and the reaction mixture was vigorously stirred at 100 °C for 12 h. The solvent was evaporated under reduced pressure, the solid was partitioned between ethyl acetate (200 mL) and 2 M aqueous Na_2CO_3 (25 mL) containing 5 mL of concentrated ammonia, to remove palladium residues, then washed with water, passed through celite to remove the catalyst, dried (sodium sulfate) and evaporated. The product was purified using column chromatography on silica gel, and hexanes/ethyl acetate as an eluent.

Yellow solid (2.61, 73 %), mp > 250 ^{o}C. dec. ^{1}HNMR (DMSO-d_6): δ 8.25 (br s, 2 H, Ar), 7.93 (d, *J* = 8.4 Hz, 2 H, Ar), 7.88 (m, 2 H, Ar), 7.18 (d, *J* = 8.4 Hz, 2 H, 2NH), 3.99 (m, 2 H, 2CH), 1.29 (d, *J* = 6 Hz, 12 H, 4CH_3); ESI-HRMS: m/z calculated for $C_{18}H_{23}N_4O_4$: 359.1719, found: 359.1713 (M^+ + 1).

***N*^{4},*N*$^{4'}$-diisopropyl-[1,1'-biphenyl]-3,3',4,4'-tetraamine (18).**

This compound was prepared using the sodium borohydride method mentioned above starting from the bis-nitro compound **17**, and was used in the next step without further characterization.

5,5'-(1,1'-diisopropyl-1H,1'H-[5,5'-bibenzo[d]imidazole]-2,2'-diyl)bis(thiophene-2-carbonitrile) (19).

This compound was prepared using sodium metabisulphite method mentioned above starting from the tetraamine **18** and 5-formylthiophene-2-carbonitrile in DMSO.

Yellow solid (69 %), mp > 300 ^{o}C. ^{1}HNMR (DMSO-d_6): δ 8.11 (d, *J* = 4 Hz, 2 H, Ar), 8.02 (br s, 2 H, Ar), 7.93 (d, *J* = 8.4 Hz, 2 H, Ar), 7.74 (d, *J* = 4 Hz, 2 H, Ar), 7.66 (d, *J* = 8.4 Hz, 2 H, Ar), 5.12 (d, *J* = 6.8 Hz, 2 H, 2CH), 1.69 (d, *J* = 6.8 Hz, 12 H, 4CH_3); ^{13}CNMR (DMSO-d_6): δ 145.5,

144.3, 140.3, 140.0, 136.0, 133.8, 128.9, 123.5, 118.2, 114.4, 114.1, 110.7;ESI-HRMS: m/z calculated for $C_{30}H_{25}N_6S_2$: 533.1582, found: 533.1606 (M^+ + 1).

Conclusion.

Two new series of *N*-alkyl-Benzobisimidazole and *N*-alkyl-bibenzimidazole-based bisnitrile intermediates were prepared in a facile way for the first time. In a different investigation these bisnitriles intermediates will be converted to dicationic diamidines that are designed to bind selectively and strongly to mixed base-pair sequences in the DNA minor groove. These compounds could be the starting point for development of antileukemic drugs.

References.

[1] I. Zimmermann, S. Aghazada, M. K. Nazeeruddin. *Angew. Chem. Int. Ed.* **2019**, *58*, 1072-1076.

[2] A. J. Boydston, K. A. Williams, C. W. Bielawski. *J. Amer. Chem. Soc.* **2005**, *127*, 12496-12497.

[3] B. Karimi, P. F. Akhavan. *Chem. Commun*. **2011,** *47*, 7686-7688.

[4] Z. Guo, N. R. Song, J. H. Moon, M. Kim, E. J. Jun, J. Choi, J. Y. Lee, C.W. Bielawski, J. L. Sessler, J. Yoon. *J. Amer. Chem. Soc*. **2012**, *134*, 17846-17849.

[5] W. G. Schulz, E. B. Skibo. *J. Med. Chem*. **2000**, *43*, 629-638.

[6] V. Fagan, S. Bonham, M. P. Carty, F. Aldabbagh. *Org. Biomol. Chem*. **2010**, *8*, 3149-3156.

[7] A. A. Farahat, A. Kumar, M. Say, A. M. Barghash, F. E. Goda, H. M. Eisa, T. Wenzler, R. Brun, Y. Liu, L. Mickelson,W. D.Wilson, D. W. Boykin. *Bioorg. Med. Chem.* **2010**, *18*, 557-566.

[8] D. Branowska, A. A. Farahat, T. Wenzler, R. Brun, Y. Liu, W. D. Wilson, D. W. Boykin. *Bioorg. Med. Chem.*, **2010**, *18*, 3551-3558.

[9] C. S. Reid, A. A. Farahat, X. Zhu, T. Pandharkar, D. W. Boykin, K. A. Werbovetz. *Bioorg. Med. Chem Lett.* **2012**, *22*, 6806-6810.

[10] A. A. Farahat, C. B.Vaughn, E. M. Mineva, A. K., T. Wenzler, R. Brun, Y. Liu, W. D. Wilson, D. W. Boykin. *Bioorg. Med. Chem Lett.*, **2016**. 26, 5907-5910.

[11] A. A. Farahat, E. Paliakov, A. Kumar, A. M. Barghash, F. E. Goda, H. M. Eisa, T. Wenzler, R. Brun, Y. Liu, W. D. Wilson, D. W. Boykin. *Bioorg. Med. Chem*. **2011**, *19*, 2156-2167.

[12] A.A. Farahat, A. Kumar, M. Say, T. Wenzler, R. Brun, A. Paul, W. D. Wilson, D. W. Boykin. *Eur. J. Med. Chem.*, **2017**. *128*, 70-78.

[13] N. Erlitzki, A.A. Farahat, A. Kumar, D. W. Boykin, M. K. G. Poon. *Biophys. Chem.*, **2019**, *245*, 6-16.

[14] M. Lambert, S. Jambon, S. Depauw, M. H. David-Cordonnier, *Molecules* **2018**, *23*, 1479-1529.

[15] J. E. Darnell. *Nat. Rev. Cancer* **2002**, *2*, 740-749.

[16] M. Munde, S. Wang, A. Kumar, C. E. Stephens, A. A. Farahat, D. W. Boykin, W. D. Wilson, G. M. K. Poon. *Nucleic Acids Res.* **2014**, *42*, 1379-1390.

[17] I. Antony-Debré, J. Leite, A. Paul, H. M. Kim, A. Kumar, A. A Farahat, B. Bartholdy, S-R. Narayanagari, K. Mitchell, L. A. Carvajal, J. Chen, I. Mantzaris, A. Verma, B. Will1, D. W Boykin, W. D. Wilson, G. M. K. Poon, U. Steidl. *J. Clin. Invest.* **2017**, *127*, 4297-4313.

[18] P. Guo, A.A. Farahat, A. Paul, N. K. Harika, D. W. Boykin, W. D. Wilson. *J. Amer. Chem. Soc.*, **2018**, *140*, 14761-796.

[19] P. Guo, A. A. Farahat, A. Paul, A. Kumar, D. W. Boykin, W. D. Wilson. *Biochemistry* **2020**, *59*, 1756 - 1768.

[20] A. A. Farahat, P. Guo, H. Shoeib, A. Paul, D. W. Boykin, W. D. Wilson. *Chem. Eur. J.* **2020**, *26*, 4539 - 4551.

[21] A. A. Farahat, D.W. Boykin. *Heterocycles*. **2012**, *85*, 2437-2448.

[22] A. A. Farahat, D. W. Boykin. *J. Het. Chem.* **2013**, *50*, 585-589.

[23] S. Laughlin, S. Wang, A. A. Farahat, A. Kumar, D. W. Boykin, W. D. Wilson. *Chem. A Eur. J.* **2015**, *21*, 5528-5539.

[24] P. Guo, A. Paul, A. Kumar, A. A. Farahat, D. Kumar, S. Wang, D.W. Boykin, W. D. Wilson. *Chem. A Eur. J.*, **2016**, *22*, 15404-15412.