Tetrahedron 68 (2012) 4381–4389

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Aromatic garlands, as new foldamers, to mimic protein secondary structure

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ARTICLE INFO

Article history:
Received 6 October 2011
Received in revised form 10 February 2012
Accepted 14 February 2012
Available online 3 March 2012

Keywords:
Foldamer
Suzuki–Miyaura cross-coupling
Alpha-helix mimetic
Pyridine
Thiophene

ABSTRACT

Proteins modulate the majority of all biological functions and are composed of highly organized secondary structural elements such as helices, turns, and sheets. Many of these functions are affected by a small number of key structural element, protein–protein interactions. Their mimicry by peptide and non-peptide scaffolds has become a major focus of contemporary research. This paper examines oligomeric system as new foldamers, which either reproduce the local topography of the helix, or project appropriately functionality in a similar manner to residues of an alpha-helix.

1. Introduction

Protein–protein interactions domains play an important role in many biological pathways and have been the focus of intense investigation from structural molecular biology to cell biology for the majority of the last two decades. More recently, they are emerging as important targets for pharmaceutical intervention.

Alpha-helix represents the most abundant secondary structural motif in nature, with a significant proportion of all protein structures comprising this motif. Unsurprisingly, alpha-helices represent fundamental recognition elements in many protein–protein interactions.

Therefore, alpha-helix offers potential as a template for the elaboration of 'rule-based' small molecule inhibitors, in particular those based on 'foldamers': synthetic non-natural oligomers that adopt well-defined conformations reminiscent of an alpha-helix.[1]

Mimicking an alpha-helix can be achieved in three ways: (1) a type I mimetic, which reproduces the local topography of the helix, where, for example, covalent constraints are used to stabilize a conformation closed to alpha-helices; (2) a type II mimetic, which is a functional mimetic that does not need to mimic the structure of the original helix. It is typically small natural molecules; (3) a type III mimetic, which represents a topographical mimetic where positions key functional motifs in an identical spatial orientation to match those presented by the original alpha-helix.[2]

Numerous non-peptide small molecules mimicking alpha-helices have been published in literature (type III) (Fig. 1).

Early contributions from Hamilton and Jacoby showed that a terphenyl scaffold was capable of projecting functionality in a similar manner to the *i*, *i*+3 (or *i*+4), and *i*+7 residues of an alpha-helix (Fig. 1, terphenyl and terpyridyl compounds **a**).[3] Then, efforts have been exerted to decrease overall compound hydrophobicity as well as reduce the synthetic complexity of teraryl-based alpha-helix mimetics. This has been accomplished either by increasing the heteroaromatic nature of the core aryl units (Fig. 1, terpyridyl scaffold **b** and **e** to **l**) or by replacing some of the covalent character of the scaffold with a hydrogen-bonding aromatic ring isostere (Fig. 1, enaminone c and benzoylurea d scaffolds).

The structure of a 5–6–5 imidazole–phenyl-thiazole scaffold (Fig. 1e)[4] bearing additional heteroaromatic functionality has recently been reported. Rebek and co-workers have also published a series of pyridazine-based scaffolds (Fig. 1f–j) with a variety of aromatic and heteroaromatic peripheral groups.[5] Additionally, two piperazine-based scaffolds (Fig. 1k,[6] l[7]) have been reported: both display functional groups in a manner to mimic three or four alpha-helical side-chain positions. Otherwise, it has shown that hydrogen-bonding functional groups such as an enaminone (Fig. 1d)[8] or benzoylurea (Fig. 1c)[9] can replace

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doi:10.1016/j.tet.2012.02.035

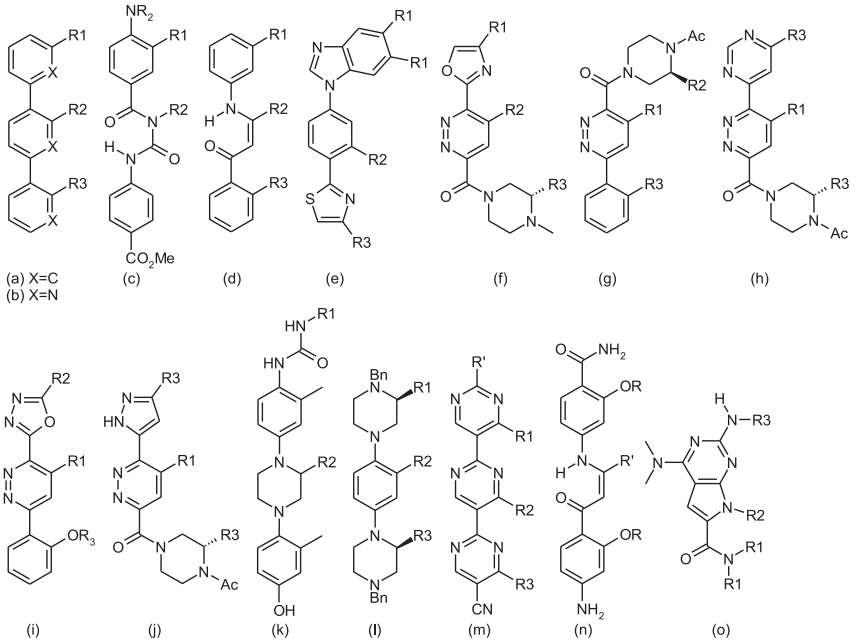


Fig. 1. Numerous non-peptide small molecules.

a central six-membered ring, reducing hydrophobicity and synthetic complexity of these types of scaffolds. Recently, McLaughlin and co-workers presented a facile iterative synthesis of 2,5-terpyrimidinylenes (Fig. 1m)[10] that are structurally analogous to alpha-helix mimics. In 2011, Hamilton and co-workers have constructed a new series of *i*, *i*+3 (or *i*+4), *i*+7 alpha-helix mimics based on the enaminone scaffold (Fig. 1n),[11] which represent a step forward in the pursuit of idealized monofacial alpha-helix mimetics. At the same time, Lee et al. report the design of a novel pyrrolopyrimidine-based scaffold and developed a facile solid-phase synthetic route to produce a large library of such compounds (Fig. 1o).[12]

Among all of these compounds, we are especially interested in Jacoby and Hamilton oligophenyl foldamers. At the same time, Che and Hamilton studied terpyridyl scaffolds and predicted a better percentage of helicity for terpyridyl than for terphenyl compounds (Fig. 2).[3b,13]

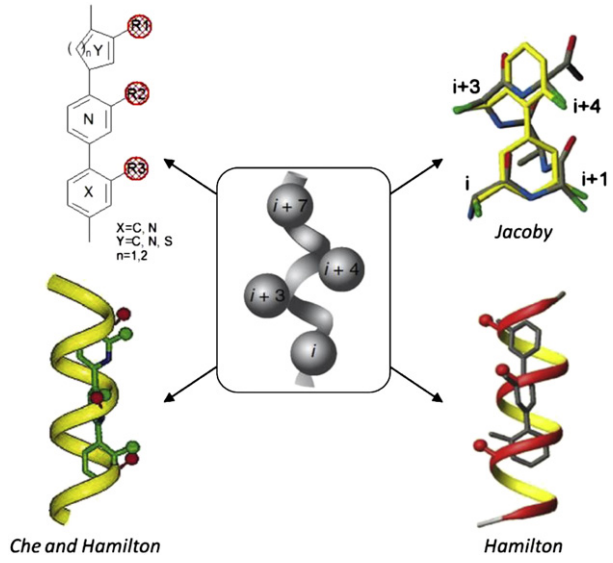


Fig. 2. Jacoby, Che, and Hamilton approaches.

Our proposed synthesis of the oligomeric pyridyl system as peptidomimetics involves three approaches of Jacoby, Hamilton, and Che and uses the Garlanding concept,[14] which allows building a linear chain from one ring by the implementation of cross-coupling reactions between boronic species and dihalogenated compounds. This is a regioselective, flexible, and highly reproducible approach to introduce various (het)aromatic rings especially since our laboratory is specialized in the preparation of boronic species and in the study of their ability to be good coupling partners.[15]

We will highlight the subtle role that the conformation of oligo(het)arylpyridines can play in adopting helical or elongated conformations. In parallel, we have just published a study about the ability of oligopyridyl scaffolds to mimic the alpha-helical twist. The theoretical as well as experimental studies (X-ray diffraction and NMR) on conformations of oligopyridines in the function of substituent and nitrogen pyridine positions were carried out.[16] Here, we describe the synthesis of oligopyridyl-, oligophenylpyridyl-, and oligothienylpyridyl-garlands and present preliminary results suggesting that these compounds could mimic alpha-helix.

2. Results and discussion

2.1. Oligopyridyl foldamers

Our first model considers the pioneering work of Che and Hamilton about terpyridyl compounds. The preparation of such compounds was described as long and difficult, using sequential Bohlmann–Rahtz heteroannulation reactions.[17] To overcome these difficulties, we have developed an efficient synthesis of oligopyridyl compounds by the implementation of cross-coupling metallocatalyzed Suzuki–Miyaura type reactions based on Garlanding concept.[18]

We have previously described that the regioselective control of the formation of the pyridine–pyridine linkage requires an efficient and flexible strategy leading to a selective coupling with the desired halogen when the pyridine bears two or more identical or different halogens.[19]

Even if the alpha position of the pyridine ring is more sensitive to a cross-coupling reaction than the beta one, the inevitable

formation of by-products is due to the poor selectivity of the reaction especially when the two halogens are identical. Faced with these problems, we reinvestigated the cross-coupling reaction according to the nature of the halogen and its position on the pyridine ring. Among halogens, it is known that iodine has a better reactivity than bromine or chlorine or fluorine. That is why we tried to increase the selectivity by using iodopyridine instead of bromopyridine ones.

Using these observations, we recently published the synthesis of the 5,6′-dibromo-3,5′-dimethyl-[2,3′]bipyridine **3a**[18] from 6-bromo-5-methylpyridin-3-yl boronic acid **1** and 5-bromo-2-iodo-3-methylpyridine **2** with 77% yield. We applied a first Br–I exchange with excellent yield to give iodo compound **3b**. Then, a second Suzuki–Miyaura cross-coupling reaction to couple with boronic acid **1** leads to the 5,6″-dibromo-3,5′,5″-trimethyl-[2,3′,6′,3″]terpyridine **4a** (75%). Then successive Br–I exchanges allow to gain in regioselectivity for subsequent reactions to achieve the preparation of new quaterpyridines **6a** and **6b** and sexipyridines **8a** and **8b** with satisfactory yields (Scheme 1).

In a similar way, we obtained these quaterpyridines **6c** and **6d** from bipyridines **3c** and **3a** (Scheme 2).

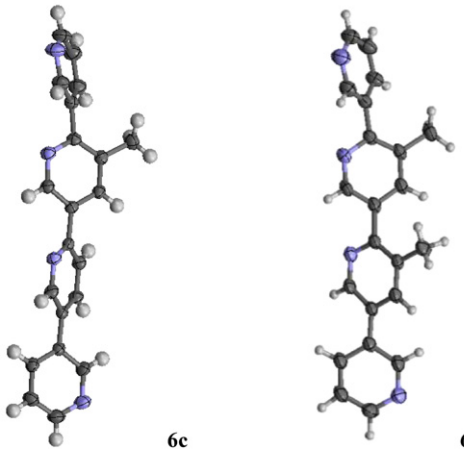
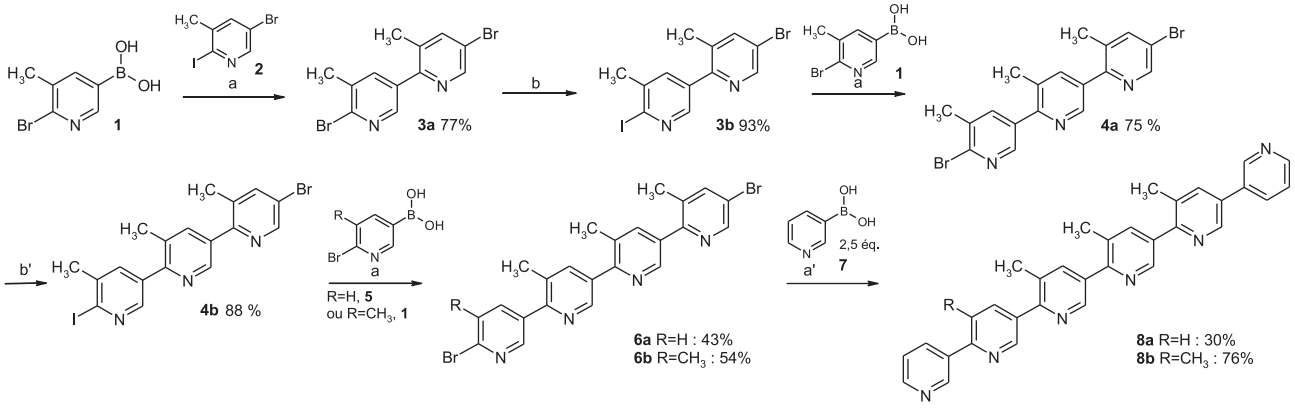
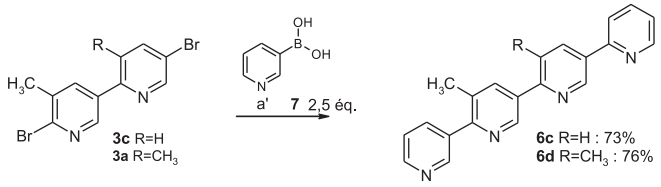


Fig. 3. ORTEP view of the crystal structures of **6c** (left) and **6d** (right).[16]



Scheme 1. Preparation of compounds **3**–**8**. Reagents and conditions: (a) Na_2CO_3 2.5 equiv, $Pd(PPh_3)_4$ 5%, 1,4-dioxane, reflux, 20 h; (a′) Na_2CO_3 5 equiv, $Pd(PPh_3)_4$ 10%, 1,4-dioxane, reflux, 20 h; (b) AcCl 2×1.5 equiv, NaI 2×2.5 equiv, CH_3CN, reflux, 2×4 h; (b′) AcCl 2×2.5 equiv, NaI 2×3.5 equiv, CH_3CN, reflux, 2×4 h.



Scheme 2. Preparation of compounds **6c** and **6d**. Reagents and conditions: (a′) Na_2CO_3 5 equiv, $Pd(PPh_3)_4$ 10%, 1,4-dioxane, reflux, 20 h.

Suitable crystals for X-ray diffraction studies were obtained by slow evaporation of a mixture of dichloromethane/ether (9:1). The solved structures confirmed the absence of eventual rearrangements in the cross-coupling reaction and the ORTEP diagrams of the **6c** and **6d** crystal structures are shown in Fig. 3.

A superposition of the X-ray structure of compounds **6c** and **6d** on an ideal alanine alpha-helix shows that oligopyridyl scaffolds can be aligned along the axis of the helix and the positions of methyl substituents coincide with the positions of Cβ atom of the alanine side chains (Fig. 4) as it is expected for a type III mimetic.

Furthermore, for compound **6d**, the two methyl substituents are positioned in close proximity of the side chains of *i* and *i*+3 residues. Thus, compound **6d** will be able to mimic *i* and *i*+3 side chains with its substituent groups.[13a]

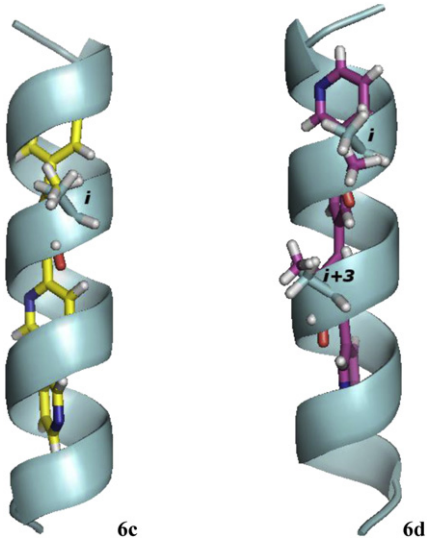


Fig. 4. The superposition of the X-ray structure of compound **6c** (left) and compound **6d** (right) on an alpha-helix.

2.2. Oligophenylpyridyl foldamers

Our second model alternates pyridine and phenyl rings to determine the influence of the phenyl ring instead of the pyridyl one on the position of substituents with respect to the positions *i*, *i*+3 (or *i*+4), *i*+7 of an alpha-helix. To date, one example of phenylpyridyl scaffold has been synthesized by Marshall and co-workers[13a] using iterative Stille cross-coupling reactions with disadvantages such as numerous protection–deprotection steps and tin toxicity. We suggest again using our Garlanding concept knowledge to obtain efficiently these compounds.

So, the preparation of 5′-bromo-3′,5-dimethyl-6-(2-methyl-4-pyridin-3-ylphenyl)-3,2′-bipyridine **13** can be achieved from pyridin-3-yl boronic acid **1** and 2-bromo-5-iodotoluene **9**.[20]

We obtained 3-(4-bromo-3-methylphenyl)pyridine **10** with excellent yield (85%). From compound **10**, a lithium–bromine exchange was carried out in ether at −78 °C with *n*-BuLi followed by a transmetallation reaction with B(O*i*-Pr)$_3$ and a hydrolysis to give boronic acid **11** (75%). The implementation of a Suzuki–Miyaura cross-coupling reaction between boronic acid **11** and iodobromobipyridine **3b** allowed to obtain 5′-bromo-3′,5-dimethyl-6-(2-methyl-4-pyridin-3-ylphenyl)-3,2′-bipyridine **13** with a very good yield (74%) (Scheme 3).

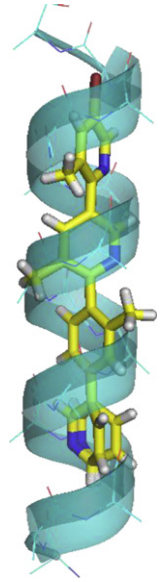
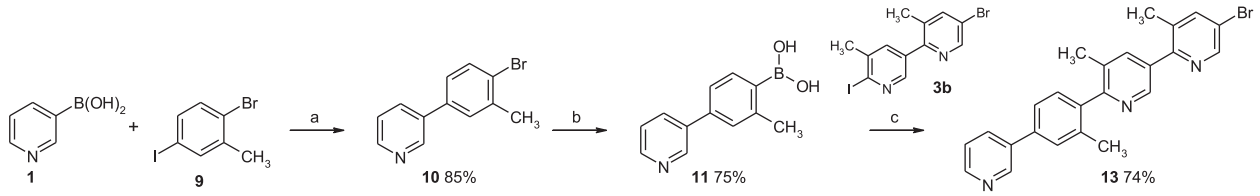


Fig. 6. The superposition of the X-ray structure of compound **13** on an alpha-helix.



Scheme 3. Preparation of 5′-bromo-3′,5-dimethyl-6-(2-methyl-4-pyridin-3-ylphenyl)-3,2′-bipyridine **13**. Reagents and conditions: (a) Na_2CO_3 (aq) 2.5 equiv, $Pd(PPh_3)_4$ 5%, DME, reflux, 24 h; (b) (1) *n*-BuLi 1.25 equiv, THF_{anhyd}, −78 °C, 1 h; (2) B(O*i*-Pr)$_3$ 1.25 equiv, THF_{anhyd}, −78 °C, 45 min; (3) hydrolysis; (c) K_3PO_4 (aq) 2.5 equiv, $Pd(PPh_3)_4$ 5%, DME, reflux, 20 h.

Suitable crystal for X-ray diffraction studies of **13** were obtained by slow evaporation of a mixture of dichloromethane/cyclohexane (1:5) and as above the solved structure is in agreement with expected one. The ORTEP diagram of the compound **13** crystal structure is shown in Fig. 5, a disorder is observed on the fourth ring (on the left).

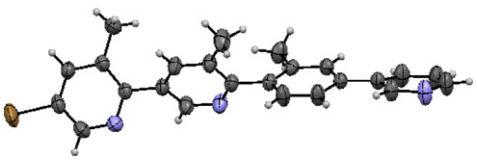


Fig. 5. ORTEP diagram of major conformation of **13**.

The superposition of solved X-ray structures with an alpha-helix shows that methyl groups occupy successively the place of *i*, *i*+4 side chains and the last methyl group is situated midway between residues *i*+3 and *i*+6 (Fig. 6). Note also that all the methyl substituents are really on the same side of the helix.

The crystal data show that compound **13** is also well able to distribute the attached functional groups at closed positions of side chains of an alpha-helix.

Compounds described above, i.e., pyridyl- and phenylpyridyl-scaffolds, represent a topographical mimetic, which positions key functional motifs in an identical spatial orientation to match those presented by the original alpha-helix. Here, we clearly identify the presence of type III foldamer compounds that would be able to disrupt the interacting in which a helix engages only one face.

2.3. Oligothienylpyridyl foldamers

In the light of these results and in order to modify the hydrophobicity and helicity of such oligomeric systems we decided to introduce thienyl units in our third model.

Very recently, we described the synthesis of new five-unit thienylpyridyl compounds, obtained from their three-unit congeners (Fig. 7). We have studied the reactivity of boronic acids and halogenated pyridines and/or thiophenes toward the Suzuki–Miyaura cross-coupling reaction in order to obtain bis-thienylpyridines. Secondly, we have functionalized these compounds by a reaction of bromination and the resultant bis-bromothienylpyridines have been engaged in a iterative Pd-catalyzed coupling based on a pseudo-Garlanding approach with a range of pyridyl boronic acids to produce a new library of thienylpyridyl oligomers.[21]

For example, we first studied the reaction between 3,5-dibromopyridine **14** and thiophenyl boronic acids **15a** and **15b** to produce directly the three-unit thienylpyridyl compounds **16a** and **16b** (Scheme 4, respectively, 92% and 79%).

Secondly, the bromination reaction of 3,5-di(thiophen-2-yl) pyridine **16a** with 3 equiv of *N*-bromosuccinimide (NBS) gives the dibrominated compound **17a** with excellent yield (92%) (Scheme 5).

When the same reaction was conducted starting from compound **16b** by using 3 equiv of NBS, the result was very different: dibrominated **17b′** (19% of conversion), tribrominated **17b″** (36% of conversion), and tetrabrominated **17b‴** (48% of

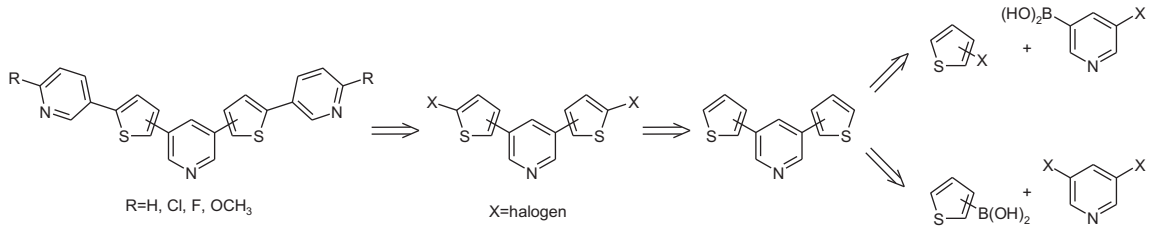
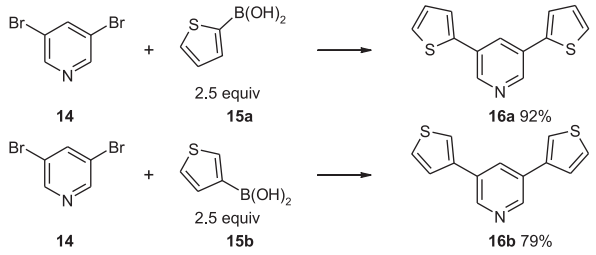
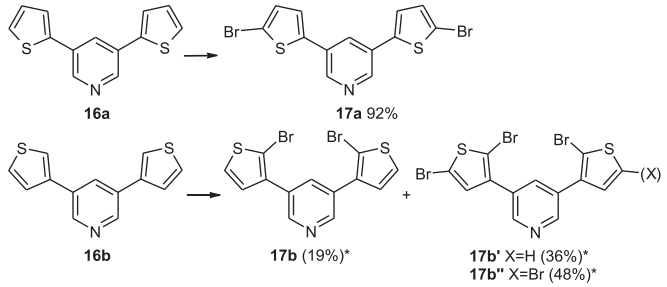


Fig. 7. Synthesis of five-unit thienylpyridyl compounds.



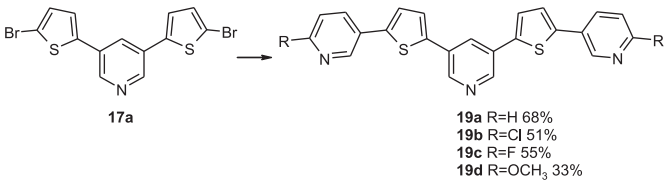
Scheme 4. Synthesis of 3,5-di(thiophen-2-yl)pyridine **16a** and 3,5-di(thiophen-3-yl) pyridine **16b**. Reagents and conditions: Na_2CO_3 2.5 equiv, $Pd(PPh_3)_4$ 5%, DME/EtOH, reflux, 2 h.



Scheme 5. Bromination of compounds **6a** and **6b**. Reagents and conditions: NBS (3 equiv), CH_2Cl_2/AcOH 1:1, rt, 3 h (**ratio of conversion %*).

conversion) compounds were obtained due to the mechanism of the electrophilic substitution which involves the formation of the carbocation stabilized by the pyridyl ring (Scheme 5).

Finally, brominated compounds were engaged in cross-coupling reactions to give new five-unit thienylpyridyl compounds **19a** and **19d** (for example, see Scheme 6).



Scheme 6. Reactivity of the compound **17a** with pyridylboronic acids **18a**–**d**. Pyridylboronic acids **18a**–**d** (3.5 equiv), 3,5-di(thiophen-2-yl)pyridine **17a** (1 equiv), Na_2CO_3 (aq) (4 equiv), $Pd(PPh_3)_4$ 10%, DME/EtOH, reflux, 24 h.

Then, we studied the behavior of these compounds as mimics of an alpha-helix and the influence of the introduction of thiophene in garlands.

Suitable crystal for X-ray diffraction studies were obtained for compound **16b** by slow evaporation of a mixture of dichloromethane/cyclohexane (1:1) (Fig. 8). To date, we do not obtain good crystals for longer chains.

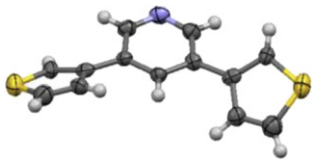


Fig. 8. ORTEP diagram of crystal majority conformation (76%) of compound **16b**.

The superposition of the X-ray structure of **16b** with an alpha-helix shows that this garland aligns well with a turn of alpha-helix. Each unit fits to a position of one residue in alpha-helix. For this type of scaffold, three units can cover one helix turn (3–4 residues) (see Fig. 9). 3,5-(Dithiophen-3-yl)pyridine reproduces the local topography (backbone mimetic) of an alpha-helix, which is expected for a type I foldamer.

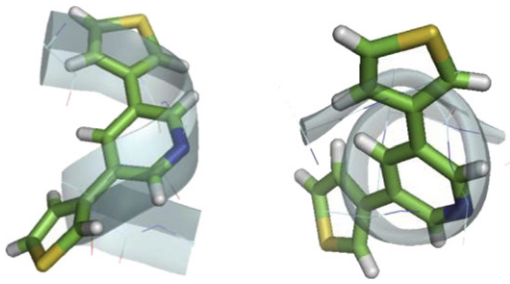


Fig. 9. A representation of the alignment of the 3,5-(dithiophen-3-yl)pyridine with an alpha-helix, based on the **16b** crystal structure.

Unfortunately, we did not have structural data of a five-unit thienylpyridyl compound. However, preliminary molecular modeling studies suggest that this structure will be in an elongated conformation and so mimics the topographical alpha-helix mimetic as expected in type III foldamer (Fig. 10).

3. Conclusion and future work

An equally important area for the design of surface mimetics is that of the side chain orientation beyond the Cα–Cβ bonds. Generally, rotations about the bonds of side chains are close to one of the three conformations (*trans*, *gauche*$^+$ and *gauche*$^-$) in which the attached atoms are staggered, with the conformation that gives the greatest separation of the bulkiest groups being favored. Those preferred side chain conformations are often referred as side chain rotamers. The variation in the conformer distribution of rotamers when the Cα–Cβ bond changes from an sp^3–sp^3 hybridization (in helix peptide) to an sp^2–sp^3 hybridization (in our oligopyridyl model) is a phenomenon to evaluate.

Our preliminary calculations[16] on bipyridines substituted in *ortho* position of the junction bond by the longer chain (i.e., leucine, isoleucine, and valine) and with the nitrogen atom in *meta* position

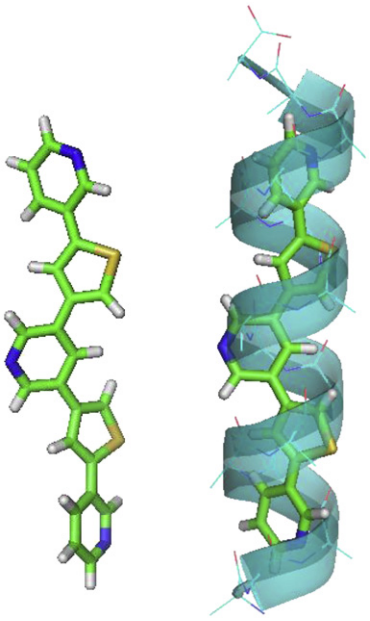


Fig. 10. A predicted structure of a five-unit thienylpyridyl compound (left) and its overlay with an alpha-helix (right).

(for substituted pyridine) and in *ortho* position (for non substituted one) showed that their potential energy profile is close to the methyl substituted (i.e., alanine) and one for all three other substituents (isobutyl for leucine, *sec*-butyl for isoleucine, and isopropyl for valine). As the methyl substituents of our oligopyridines overlapped with the helix side chains, we can hope that rotamer distributions for longer side chains on oligopyridyl scaffold will be closed also to those of alpha-helix one.

Otherwise, we have successfully synthesized compounds whose substituents attain positions *i*, *i*+3 (or *i*+4), *i*+7 of an alpha-helix. Today, we are working on the introduction of substituents, which resemble more likely to protein residues: the Garlanding approach is an effective methodology because it is based on potent reactions and can be applied from reactants bearing various substituents.

These data will furnish valuable information in the context of the exploration of perturbations of protein–protein interactions and consequently with the related biological properties. Further results will be reported in due time.

Collectively, these and related studies suggest that a large universe of new foldamers with distinctive structural and functional properties awaits discovery.

4. Experimental section

4.1. General

Commercial reagents were used as received without additional purification. Melting points (mp) were determined on a Köfler heating bench.

IR spectra were recorded on a Perkin Elmer BX FT-IR spectrophotometer. The band positions are given in reciprocal centimeters (cm^{-1}).

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 spectrometer. The chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referenced to tetramethylsilane (δ=0 ppm) and coupling constants in hertz.

Mass spectra were recorded on a JEOL JMS GC Mate spectrometer at ionizing potential of 70 eV (EI) and with PFK as internal standard for high-resolution procedure, or were performed using a spectrometer LC–MS Waters alliance 2695 (ESI^{+}).

Chromatography was carried out on a column using flash silica gel 60 Merck (0.063–0.200 mm) as the stationary phase. The eluting solvent, indicated for each purification, was determined by thin layer chromatography (TLC) performed on 0.2 mm pre coated plates of silica gel 60F-264 (Merck) and spots were visualized using an ultraviolet-light lamp.

Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen). The data for C, H, and N were within ±0.4 of the theoretical values for all final compounds.

4.2. 5-Bromo-6″-iodo-3,5′,5″-trimethyl-[2,3′;6′,3″]terpyridine 4b

A mixture of 885 mg (2.0 mmol) 5,6″-dibromo-3,5′,5″-trimethyl-[2,3′]terpyridine **4a**, sodium iodide 1.1 g (7.1 mmol, 3.5 equiv), and acetyl chloride 361 μL (5.1 mmol, 2.5 equiv) in acetonitrile (50 mL) was refluxed for 24 h. It was carefully quenched with water and treated with saturated aqueous solution of $NaHCO_3$ until pH=8. Product was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. The residue was subjected to above reaction condition again and worked up as above. Organic extract was washed with saturated aq solution of $NaHSO_3$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 9:1) to afford 860 mg of 5-bromo-6″-iodo-3,5′,5″-trimethyl-[2,3′;6′,3″]terpyridine **4b** as a white solid (88%). Mp: 130 °C. IR (KBr disc) 2916, 1578, 1454, 1384, 1256, 1147, 1111, 1076, 1035, 887, 772, 650, 523 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.69 (d, ^{4}J=1.9 Hz, 1H), 8.62 (d, ^{4}J=1.9 Hz, 1H), 8.40 (d, ^{4}J=1.9 Hz, 1H), 7.82 (d, ^{4}J=1.9 Hz, 1H), 7.80 (d, ^{4}J=1.9 Hz, 1H), 7.71 (d, ^{4}J=1.9 Hz, 1H), 2.47 (s, 3H), 2.46 (s, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 154.0, 153.5, 148.5, 147.6, 147.3, 141.1, 139.3, 139.0, 137.3, 135.3, 134.5, 133.1, 131.0, 124.9, 119.8, 26.2, 20.0, 19.9. HRMS (EI) *m*/*z* calcd: 478.94939, found: 478.94749. Anal. Calcd for $C_{18}H_{15}BrIN_3$: C, 45.03; H, 3.15; N, 8.75. Found: C, 45.32; H, 2.98; N, 8.54.

4.3. 5,6‴-Dibromo-3,5′,5″-trimethyl-[2,3′;6′,3″;6″,3‴]quaterpyridine 6a

To a glass vial containing a magnetic stirring bar was added 6-bromopyridin-3-yl boronic acid **6** 408 mg (2.0 mmol, 1.2 equiv) in 1,4-dioxane (40 mL) and the vial was purged with nitrogen. To the vial was added 5-bromo-6″-iodo-3,5′,5″-trimethyl-[2,3′;6′,3″]terpyridine **4b** 810 mg (2.2 mmol). To the vial was added a solution of tetrakis(triphenylphosphine) palladium(0) 97 mg (0.1 mmol, 0.05 equiv) in 1,4-dioxane (2.0 mL) and sodium carbonate (aq) 447 mg (4.2 mmol, 2.5 equiv), and the vial was once again purged with nitrogen and the mixture was refluxed for 24 h. The solution was cooled to room temperature and filtered through a pad of Celite (washing with dichloromethane) into a flask containing anhydrous magnesium sulfate. The solution was dried for 10 min and filtered through filter paper and the solvent was removed under reduced pressure to afford the crude product, which was purified on silica gel column chromatography (cyclohexane/ethyl acetate: 7:3) to afford 370 mg of 5,6‴-dibromo-3,5′,5″-trimethyl-[2,3′;6′,3″;6″,3‴]quaterpyridine **6a** as a white solid (43%). Mp: 186 °C. IR (KBr disc) 3049, 2950, 1576, 1445, 1412, 1379, 1091, 992, 931, 885, 774, 649 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.79 (d, ^{4}J=1.9 Hz, 1H), 8.73 (d, ^{4}J=1.9 Hz, 1H), 8.64 (d, ^{4}J=1.9 Hz, 2H), 7.91 (d, ^{4}J=1.9 Hz, 1H), 7.83 (m, 3H), 7.62 (d, ^{3}J=8.8 Hz, 1H), 2.53 (s, 3H), 2.48 (s, 3H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 154.5, 153.8, 153.6, 148.5, 147.6, 147.3, 141.8, 141.1, 139.5, 139.3, 135.3, 135.1, 134.4, 133.1, 131.2, 131.1, 127.7, 119.9, 20.1, 20.0, 19.9. HRMS (EI) *m*/*z* calcd: 507.99037, found:

507.98973. Anal. Calcd for $C_{23}H_{18}Br_2N_4$: C, 54.14; H, 3.81; N, 10.49. Found: C, 54.35; H, 3.81; N, 10.49.

4.4. 5,6‴-Dibromo-3,5′,5″,5‴-tetramethyl-[2,3′;6′,3″;6″,3‴] quaterpyridine 6b

To a glass vial containing a magnetic stirring bar was added 6-bromo-5-methylpyridin-3-yl boronic acid **1** 566 mg (2.6 mmol, 1.2 equiv) in 1,4-dioxane (50 mL) and the vial was purged with nitrogen. To the vial was added 5-bromo-6″-iodo-3,5′,5″-trimethyl-[2,3′;6′,3″]terpyridine **4b** 1.05 g (2.2 mmol). To the vial was added a solution of tetrakis(triphenylphosphine) palladium(0) 126 mg (0.1 mmol, 0.05 equiv) in 1,4-dioxane (2.0 mL) and sodium carbonate (aq) 580 mg (5.5 mmol, 2.5 equiv), and the vial was once again purged with nitrogen and the mixture was refluxed for 24 h. The solution was cooled to room temperature and filtered through a pad of Celite (washing with dichloromethane) into a flask containing anhydrous magnesium sulfate. The solution was dried for 10 min and filtered through filter paper and the solvent was removed under reduced pressure to afford the crude product, which was purified on silica gel column chromatography (cyclohexane/ethyl acetate: 7:3) to afford 623 mg of 5,6‴-dibromo-3,5′,5″,5‴-tetramethyl-[2,3′;6′,3″;6″,3‴]quaterpyridine **6b** as a white solid (54%). Mp: 186 °C. IR (KBr disc) 3423, 2956, 1585, 1448, 1412, 1380, 1086, 1048, 888, 773, 647 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.78 (d, ^4J=1.9 Hz, 1H), 8.72 (d, ^4J=1.9 Hz, 1H), 8.63 (d, ^4J=1.9 Hz, 1H), 8.44 (d, ^4J=1.9 Hz, 1H), 7.9 (d, ^4J=1.9 Hz, 1H), 7.84 (d, ^4J=1.9 Hz, 1H), 7.82 (d, ^4J=1.9 Hz, 2H), 2.52 (s, 3H), 2.48 (s, 3H), 2.47 (s, 3H), 2,46 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 154.6, 153.8, 153.6, 148.5, 147.4, 147.3, 147.2, 144.3, 141.1, 139.5, 139.4, 139.3, 135.3, 135.1, 135.0, 134.4, 133.2, 131.2, 131.1, 119.9, 22.0, 20.1, 20.0, 19.9. HRMS (EI) *m*/*z* calcd: 522.00538, found: 522.0072. Anal. Calcd for $C_{24}H_{20}Br_2N_4$: C, 54.99; H, 3.85; N, 10.69. Found: C, 55.13; H, 3.88; N, 10.75.

4.5. 3″,3‴,3⁗-Trimethyl-[3,2′;5′,2″;5″,2‴;5‴,2⁗;5⁗,3⁗⁗] sexipyridine 8a

To a glass vial containing a magnetic stirring bar was added pyridin-3-yl boronic acid **7** 102 mg (0.8 mmol, 2.5 equiv) in 1,4-dioxane (30 mL) and the vial was purged with nitrogen. To the vial was added, 6‴-dibromo-3,5′,5″-trimethyl-[2,3′;6′,3″;6″,3‴]quaterpyridine **6a** 170 mg (0.3 mmol). To the vial was added a solution of tetrakis(triphenylphosphine) palladium(0) 39 mg (0.03 mmol, 0.05 equiv) in 1,4-dioxane (2.0 mL) and sodium carbonate (aq) 177 mg (1.7 mmol, 5.0 equiv), and the vial was once again purged with nitrogen and the mixture was refluxed for 24 h. The solution was cooled to room temperature and filtered through a pad of Celite (washing with dichloromethane) into a flask containing anhydrous magnesium sulfate. The solution was dried for 10 min and filtered through filter paper and the solvent was removed under reduced pressure to afford the crude product, which was purified on silica gel column chromatography (cyclohexane/ethyl acetate: 7:3) to afford 40 mg of 3″,3‴,3⁗-trimethyl-[3,2′;5′,2″;5″,2‴;5‴,2⁗;5⁗,3⁗⁗]sexipyridine **8a** as a white solid (30%). Mp: 184 °C. IR (KBr disc) 3401, 2956, 2923, 1726, 1590, 1456, 1418, 1379, 1286, 1012, 776, 705 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.28 (d, ^4J=1.9 Hz, 1H), 9.00 (d, ^4J=1.9 Hz, 1H), 8.92 (d, ^4J=1.9 Hz, 1H), 8.84 (d, ^4J=1.9 Hz, 1H), 8.82 (d, ^4J=1.9 Hz, 2H), 8.70 (d, ^3J=4.9 Hz, 2H), 8.41 (dd, ^3J=7.8 Hz, ^4J=1.9 Hz, 1H), 8.11 (dd, ^3J=7.8 Hz, ^4J=1.9 Hz, 1H), 7.95 (m, 3H), 7.91 (d, ^3J=7.8 Hz, 1H), 7.87 (d, ^4J=1.9 Hz, 1H), 7.46 (d, ^3J=4.9 Hz, 1H), 7.44 (d, ^3J=4.9 Hz, 1H), 2.58 (s, 3H), 2.56 (s, 3H), 2.54 (s, 3H), 2,46 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 154.7, 154.6, 154.4, 154.1, 150.2, 150.0, 149.4, 148.3, 148.1, 147.5, 147.4, 145.7, 139.5, 139.4, 137.6, 137.2, 134.9, 135.0, 134.8, 134.4, 134.3, 133.0, 132.6, 131.6, 131.1, 131.0, 130.8, 123.8, 123.6, 120.0, 20.1, 20.0 (2C). HRMS (EI) *m*/*z* calcd: 506.22187, found: 506.22384. Anal. Calcd for $C_{33}H_{26}N_6$: C, 78.24; H, 5.17; N, 16.59. Found: C, 78.23; H, 5.79; N, 16.50.

4.6. 3′,3″,3‴,3⁗-Tetramethyl-[3,2′;5′,2″;5″,2‴;5‴,2⁗;5⁗,3⁗⁗] sexipyridine 8b

To a glass vial containing a magnetic stirring bar was added pyridin-3-yl boronic acid **7** 206 mg (1.7 mmol, 2.5 equiv) in 1,4-dioxane (30 mL) and the vial was purged with nitrogen. To the vial was added, 5,6‴-dibromo-3,5′,5″,5‴-tetramethyl-[2,3′;6′,3″;6″,3‴]quaterpyridine **6b** 370 mg (0.7 mmol). To the vial was added a solution of tetrakis(triphenylphosphine) palladium(0) 78 mg (0.07 mmol, 0.05 equiv) in 1,4-dioxane (2.0 mL) and sodium carbonate (aq) 534 mg (3.3 mmol, 5.0 equiv), and the vial was once again purged with nitrogen and the mixture was refluxed for 24 h. The solution was cooled to room temperature and filtered through a pad of Celite (washing with dichloromethane) into a flask containing anhydrous magnesium sulfate. The solution was dried for 10 min and filtered through filter paper and the solvent was removed under reduced pressure to afford the crude product, which was purified on silica gel column chromatography (CH_2Cl_2/MeOH: 98:2, 97:3; 96:4, 95:5 then 93/3) to afford 270 mg of 3′,3″,3‴,3⁗-tetramethyl-[3,2′;5′,2″;5″,2‴;5‴,2⁗;5⁗,3⁗⁗]sexipyridine **8b** as a white solid (76%). Mp: 223 °C. IR (KBr disc) 2949, 1725, 1589, 1392, 1260, 1009, 899, 807, 777, 710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.92 (d, ^4J=1.9 Hz, 1H), 8.89 (d, ^4J=1.9 Hz, 1H), 8.82 (d, ^4J=1.9 Hz, 4H), 8.69 (d, ^4J=1.9 Hz, 2H), 7.96 (dd, ^3J=7.8 Hz, ^4J=1.9 Hz, 1H), 7.94 (m, 4H), 7.86 (d, ^4J=1.9 Hz, 1H), 7.45 (m, 2H), 2.59 (s, 3H), 2.58 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 154.9, 154.7, 154.6, 154.5, 149.9, 149.4, 149.1, 148.1, 147.3, 147.4 (2C), 145.7, 139.2, 139.3 (2C), 137.2, 136.5, 135.9, 135.0, 134.8, 134.3, 133.0, 132.6, 131.5, 131.1, 131.0, 130.8, 128.8, 123.8, 123.1, 20.1, 20.0 (2C), 19.9. HRMS (EI) *m*/*z* calcd: 520.23752, found: 520.2351. Anal. Calcd for $C_{34}H_{28}N_6$: C, 78.44; H, 5.42; N, 16.14. Found: C, 78.92; H, 5.33; N, 16.58.

4.7. 3′-Methyl-[3,2′;5′,2″;5″,3‴]quaterpyridine 6c

Starting from pyridin-3-yl boronic acid **7** 421 mg (3.4 mmol, 1.25 equiv), 5,6′-dibromo-5′-methyl-[2,3′]bipyridine **3c** 450 mg (1.4 mmol), sodium carbonate 726 mg (6.9 mmol, 2.5 equiv), and tetrakis(triphenylphosphine)palladium(0) 159 mg (0.1 mmol, 0.05 equiv) and following the procedure described to obtain sexipyridines **8**, the product **6c** was obtained as a white solid (324 mg, 73%). Experimental data were found to be identical to that already described in the literature.[19a]

4.8. 3,3″-Dimethyl-[3,2′;5′,2″;5″,3‴]quaterpyridine 6d

Starting from pyridin-3-yl boronic acid **7** 898 mg (7.3 mmol, 1.25 equiv), 5,6′-dibromo-3,5′-dimethyl-[2,3′]bipyridine **3c** 1.0 g (2.9 mmol), sodium carbonate 1550 mg (14.6 mmol, 2.5 equiv), and tetrakis(triphenylphosphine)palladium(0) 338 mg (0.3 mmol, 0.05 equiv) and following the procedure described to obtain sexipyridines **8**, the product **6d** was obtained as a white solid (758 mg, 76%). Experimental data were found to be identical to that already described in the literature.[17a]

4.9. 5′-Bromo-3′,5-dimethyl-6-(2-methyl-4-pyridin-3-ylphenyl)-3,2′-bipyridine 13

To a stirred solution of 2-methyl-4-(pyridin-3-yl)phenylboronic acid **4b** 683 mg (3.20 mmol, 1.25 equiv) in dimethoxyethane (30 mL) under nitrogen were added 5′-bromo-3′,5-dimethyl-6-iodo-3,2′-bipyridine **3b** 1.0 g (2.56 mmol, 1 equiv) and tetrakis-(triphenylphosphine)palladium(0) 148 mg (0.13 mmol, 0.05 equiv). After 5 min of stirring, aq K_3PO_4 1.476 g (6.41 mmol, 2.5 equiv) in 5 mL of water was added. Then the mixture was heated to 80 °C until the starting material was consumed (TLC). After cooling down to room temperature, the

mixture was filtered on Celite and washed with CH_2Cl_2. The aqueous layer was extracted with EtOAc (2×50 mL). Combined organic layers were washed with saturated aq solution of NaCl (50 mL), and dried over $MgSO_4$. Solvent were removed in vacuo and the crude product was purified by column chromatography, with a gradient of solvent from 8:2 to 5:5 cyclohexane/EtOAc affording 5′-bromo-3′,5-dimethyl-6-(2-methyl-4-pyridin-3-ylphenyl)-3,2′-bipyridine **13** as a pale yellow solid (710 mg, 64%). Experimental data were found to be identical to that already described in the literature.[13a]

4.10. 3,5-Di(thiophen-2-yl)pyridine 16a

To a round bottom flask containing a magnetic stirring bar was added the 3,5-dibromopyridine **14** 370 mg (1.56 mmol), and the flask was purged with nitrogen. Then a solution of tetrakis(triphenylphosphine) palladium(0) 90 mg (0.078 mmol, 0.05 equiv) in dimethoxyethane (2.0 mL) and sodium carbonate 413 mg (aq) (3.90 mmol, 2.50 equiv) was added. The resultant solution was stirred at room temperature for 5 min when a slurry/solution of thiophen-2-yl boronic acid **15a** 500 mg (3.91 mmol, 2.50 equiv) in ethanol (2.00 mL) was added, the round bottom flask was purged with nitrogen and capped, and the mixture was heated to 90 °C and stirred until the consumption of the halide (2 h). The solution was cooled to room temperature and filtered through a pad of Celite (washing with dichloromethane) into a flask containing anhydrous magnesium sulfate. The solution was dried for 10 min and filtered through filter paper and the solvent was removed under reduced pressure to afford the crude product, which was purified on silica gel column chromatography (cyclohexane/ethyl acetate: 7:3) to afford 3,5-di(thiophen-3-yl) pyridine **16a** as a white solid (350 mg, 92%). Experimental data were found to be identical to that already described in the literature.[20]

4.11. 3,5-Di(thiophen-3-yl)pyridine 16b

Starting from 3,5-dibromopyridine **14** 500 mg (2.11 mmol), tetrakis(triphenylphosphine) palladium(0) 122 mg (0.105 mmol, 0.05 equiv) in dimethoxyethane (2.0 mL), sodium carbonate 559 mg (aq) (5.27 mmol, 2.50 equiv), and thiophen-3-yl boronic acid **15b** 517 mg (5.27 mmol, 2.50 equiv) in ethanol (2.0 mL) and following the procedure described above, 3,5-di(thiophen-3-yl) pyridine **16b** was obtained as a white solid (400 mg, 79%). Experimental data were found to be identical to that already described in the literature.[20]

4.12. Synthesis of brominated compounds 17

To a solution of starting material **16** (1.00 equiv) in a 50:50 (v/v) mixture of CH_2Cl_2 and glacial acetic acid was added *N*-bromosuccinimide (3.00 equiv). The resultant solution was stirred at room temperature for 3 h. The solution was washed twice with NaOH 4% and the organic layers were collected and dried on anhydrous magnesium sulfate. After filtration through filter paper, the solvent was removed under reduced pressure to afford the crude product, which was purified on silica gel column chromatography (cyclohexane/ethyl acetate 5:5) to afford compounds **17** as stable solids: **17a** as a beige solid (0.53 g, 92%), **17b′** as a brown solid (ratio of conversion: 19%), **17b″** as a brown solid (ratio of conversion: 36%), and **17b‴** as a brown solid (ratio of conversion: 48%).

Experimental data were found to be identical to that already described in the literature.[20]

4.13. General procedure for Suzuki–Miyaura reaction to obtain five units 19

To a glass vial containing a magnetic stirring bar was added the 3,5-bis(5-bromothiophen-2-yl)pyridine **17a** (1.00 equiv), and the vial was purged with nitrogen. To the vial was added a solution of tetrakis(triphenylphosphine) palladium(0) (10 mol%) in dimethoxyethane (2.00 mL) and sodium carbonate (aq) (5 equiv), and the vial was once again purged with nitrogen. The resultant solution was stirred at room temperature for 5 min when a slurry/solution of pyridin-3-yl boronic acids **18a**–**d** (3.00 equiv) in ethanol (2.00 mL) was added, the vial was purged with nitrogen and capped, and the mixture was heated to 90 °C and stirred until the consumption of the halide (24 h). The solution was cooled to room temperature and filtered through a pad of Celite (washing with dichloromethane) into a flask containing anhydrous magnesium sulfate. The solution was dried for 10 min and filtered through filter paper and the solvent was removed under reduced pressure to afford the crude product, which was purified on silica gel column chromatography (cyclohexane/ethyl acetate) to afford compounds **19a**–**d**.

*4.13.1. 3-(5-(5-(5-(Pyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine **19a**.* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **17a** (1.00 g, 2.49 mmol) and pyridin-3-yl boronic acid **18a** (1.07 g, 8.71 mmol) and following the general procedure the product **19a** was obtained as a yellow solid (0.67 g, 68%). Experimental data were found to be identical to that already described in the literature.[20]

*4.13.2. 2-Chloro-5-(5-(5-(5-(6-chloropyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine **19b**.* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **17a** (0.60 g, 1.49 mmol) and 6-chloropyridin-3-yl boronic acid **18b** (0.82 g, 5.21 mmol) and following the general procedure the product **19b** was obtained as a light brown solid (0.35 g, 51%). Experimental data were found to be identical to that already described in the literature.[20]

*4.13.3. 2-Fluoro-5-(5-(5-(5-(6-fluoropyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine **19c**.* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **17a** (0.50 g, 1.25 mmol) and 6-fluoropyridin-3-yl boronic acid **18c** (0.62 g, 4.37 mmol) and following the general procedure the product **19c** was obtained as a yellow solid (0.30 g, 55%). Mp: 198–200 °C. Experimental data were found to be identical to that already described in the literature.[20]

*4.13.4. 2-Methoxy-5-(5-(5-(5-(6-methoxypyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine **19d**.* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **17a** (0.46 g, 1.15 mmol) and 6-methoxypyridin-3-yl boronic acid **18d** (0.61 g, 4.01 mmol) and following the general procedure the product **19d** was obtained as a yellow solid (0.19 g, 33%). Experimental data were found to be identical to that already described in the literature.[20]

Acknowledgements

The authors gratefully acknowledge for the financial support from the 'Région Basse-Normandie' and the 'Ministero dell'Istruzione, dell'Università e della Ricerca Italiana'.

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