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Design and synthesis of thienylpyridyl garlands as non-peptidic alpha helix mimetics and potential protein–protein interactions disruptors

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ABSTRACT

This paper describes an efficient route leading to new thienylpyridyl garlands as non-peptidic alpha helix mimetics and potential protein–protein interactions disruptors. Firstly, we have studied the reactivity of boronic acids and halogenated pyridines and/or thiophenes towards 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 found to undergo 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.

1. Introduction

Protein–protein interactions (PPIs) are attractive targets because they control numerous cellular processes, such as proliferation, differentiation or apoptosis. Consequently their misregulation can result in numerous disease states, such as HIV, cancer, diabetes and neurodegenerative diseases.[1] Considerable effort has been directed towards targeting the PPIs implicated in these diseases.[2] Recognition between proteins is often facilitated by secondary structure elements, such as alpha helices, beta sheets and beta strands, which comprise the majority of protein secondary structures found at PP interfaces. Accordingly, these surfaces are crucial targets for small molecule mimicry and their use is an area of major current interest at the interface of chemical biology and medicinal chemistry.

Alpha helices comprise approximately 40% of all protein secondary structures, and as such are often found at PP interfaces.[3]

In particular, in oncology, among these PPI we are interested by Bcl-2 family proteins. Anti-apoptotic members (Bcl-2, Bcl-X_L, Mcl-1…) prevent apoptosis by inhibiting the function of pro-apoptotic members, such as Bax and Bak by binding to their BH3 domain, represented by an alpha helix.[4] In solid human tumors the anti-apoptotic members are over expressed, thus, their inhibition represents a novel and promising strategy for new anticancer drugs. Several approaches have been developed to target Bcl-2 and numerous strategies of non-peptidic small molecules, structurally and functionally alpha helix mimetics have been presented in the literature.[5] Hamilton and co-workers have synthesized terphenyl scaffolds and have shown these compounds were able to project functionalities in a similar manner than *i*, *i*+3 (or *i*+4) and *i*+7 residues of an alpha helix,[6] and for these compounds they calculated a percentage of helicity of 12%. Then, efforts have been exerted to design similar teraryl molecules in order to decrease the hydrophobicity and to increase the helicity.[1,7] In later work, Hamilton[8] has predicted that terpyridyl scaffolds, less hydrophobic, would adopt a percentage of helicity of about 39%. However, the synthesis of such compounds based on Bohlmann–Rahtz reaction, highlights low yields and numerous reaction steps,[9] and to date few compounds have been prepared.

It is the reason why we recently applied our experience in the synthesis of pyridyl boronic acids[10] and their reactivity[11] in palladocatalyzed cross-coupling reactions to produce easily numerous linear oligopyridines, using a strategy that we named Garlanding.[12] This methodology permitted us to produce a library of variously substituted ter, quater, quinque and sexipyridines possessing very promising biological properties.[13]

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Furthermore, in the case of the peculiar interaction of Bcl-X_L and the BH3 domain the length and the size of these oligopyridines were guided in one hand by our molecular modeling studies on bi-, ter- and quater-pyridines (data not yet published) and in the other hand by the work of Hamilton.[14]

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. The most general procedures used to synthesize arylthiophenes are conventional electrophilic substitution reactions,[15] CH-activation[16] and palladium catalyzed Stille and Suzuki cross-coupling reactions. Since its discovery,[17] the Suzuki–Miyaura reaction has become one of the most powerful and synthetically valuable processes for the construction of carbon–carbon bond.[18] The Suzuki route is potentially more versatile for the synthesis of arylthiophenes than the Stille reaction because the boronic derivatives are easier to handle and nontoxic byproducts are formed. For our synthesis we have chosen iterative Suzuki–Miyaura cross-coupling reactions involving boronic species and appropriately halogenated partners. However, such coupling reactions proceed smoothly when halothiophenes are reacted with aryl boronic acids while the use of thiophenyl boronic acids is plagued by several limitations because of their facile decomposition in polar protic reaction medium via protodeboronation prior to aryl–aryl coupling.[19]

Here we describe the synthesis of five unit thienylpyridyl compounds **9**, obtained from three unit thienylpyridyl compounds **6**, which represent the key element of our study. The first part of our work concerned three similar pathways to obtain them by using boronic acids and halogenated pyridines and/or thiophenes. Although the use of thiophenyl boronic acids is described as difficult (protodeboronation), we successfully overcame these limitations.

The second part of the present work concerned the study of the reactivity of compounds **6** towards bromination to obtain compounds **7** and their subsequent coupling reaction to produce five unit compounds **9** through a pseudo-Garlanding approach based on iterative Suzuki–Miyaura cross-coupling reaction (Scheme 1).

2. Results and discussion

To synthesize compounds **6** we have envisaged three similar pathways based on Suzuki–Miyaura cross-coupling reactions (Scheme 1):

- *Pathway* A (two steps): we studied the reactivity of thiophenyl boronic acids **2** with halogenated pyridines **1** to produce thienylpyridyl compounds **3** (TPy).
- *Pathway* B (twp steps): we studied the reactivity of pyridyl boronic acids **4** with halothiophenes **5** to produce the same thienylpyridyl compounds **3** (TPy).

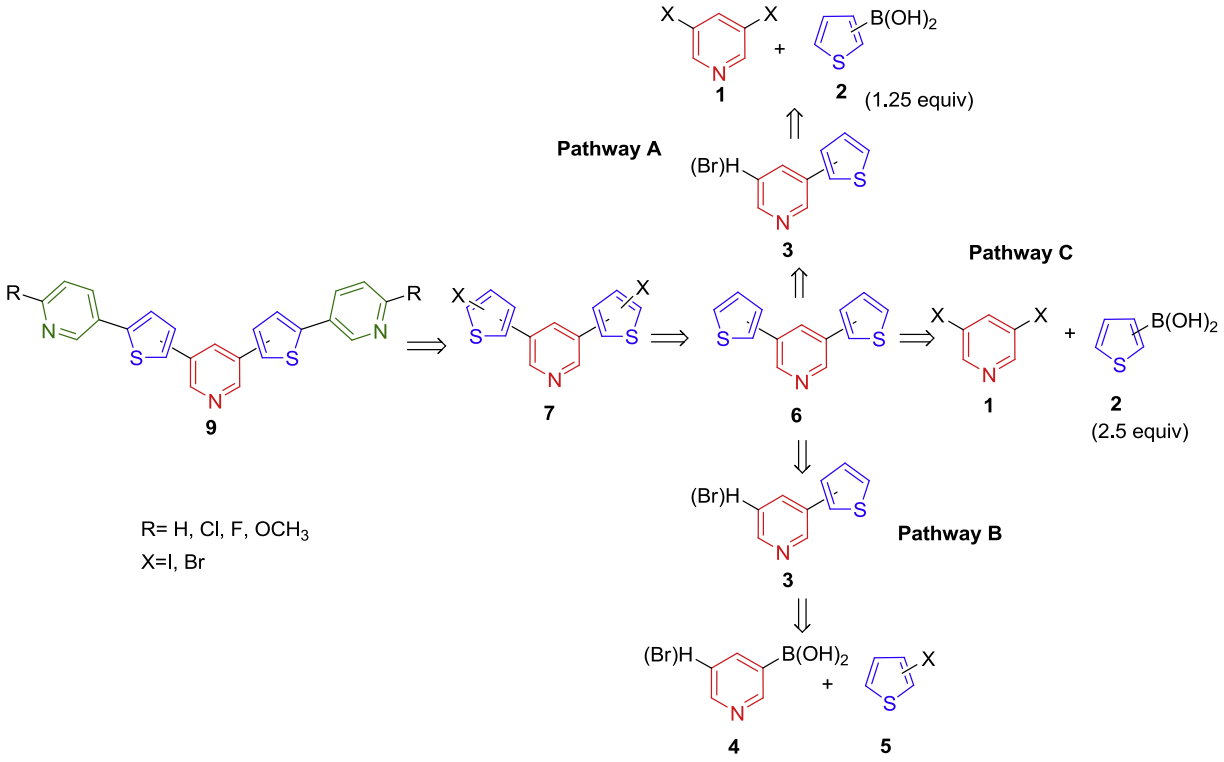
These two approaches were followed by another cross-coupling reaction to prepare the three unit thienylpyridyl compounds **6** (TPyT) from the thienylpyridines **3** (TPy).

- *Pathway* C (one step): we studied a one-pot reaction between dihalogenated pyridine **1** and thiophenyl boronic acids **2** to produce directly the three unit thienylpyridyl compounds **6** (TPyT).

The advantage of pathways A and B is that they leave an open coupling position, thus authorizing molecular diversity in contrast to pathway C, which has the advantage of obtaining three unit thienylpyridyl compounds with excellent yields.

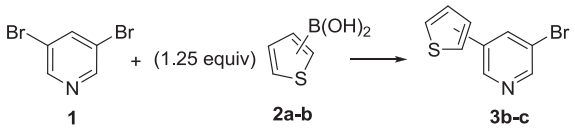
2.1. Pathway A

Coupling between the 3,5-dibromopyridine **1** and 1.25 equiv of 2-thiophenyl boronic acid **2a** or 3-thiophenyl boronic acid **2b** gave



Scheme 1. General strategy to prepare thienylpyridyl compounds through a pseudo-Garlanding approach.

3-bromo-5-(thiophen-2-yl)pyridine (TPy) **3b**[20] or 3-bromo-5-(thiophen-3-yl)pyridine **3c**[20] in moderate yields (Scheme 2).



Scheme 2. Synthesis of TPy **3** through pathways A. Reagents and conditions: 3,5-dibromopyridine **1** (1 equiv), thiophenyl boronic acid **2a**,**b** (1.25 equiv), Na_2CO_3 aq (2.5 equiv), $Pd(PPh_3)_4$ 5%, DME/EtOH, reflux, 2 h.

Initially we investigated the Suzuki–Miyaura cross-coupling reaction in 1,4-dioxane under reflux for 24 h. No conversion in the desired product was detected presumably because of side reactions, such as protodeboronation, prior to aryl–aryl coupling, which was already described in literature.[19] These failures prompted us to reinvestigate the experimental conditions of this cross-coupling reaction. After several attempts we found that the reaction must be conducted in 1,2-dimethoxyethane (DME) and that the thiophenyl boronic acid must be dissolved in small amounts of ethanol and added dropwise to the reaction mixture.

With these conditions the expected cross-coupling reaction occurred and the desired TPy **3b** (16%) and (TPy) **3c** (32%, in literature: 53%[20]) were obtained in modest yields (Table 1).

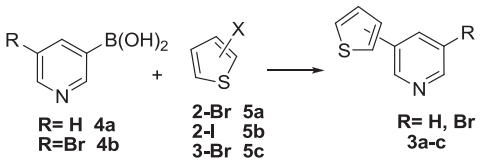
But, with these new experimental conditions, thiophenyl boronic acids were so good partners, that we could observe the formation of three unit compounds TPyT. These undesired reactions due to the high reactivity of thiophenyl boronic acids **2a** and **2b** with the second bromine atom of the 3,5-dibromopyridine **1** led to the formation of 3,5-di(thiophen-2-yl)pyridine **6a** (TPyT) (47%) and 3,5-di(thiophen-3-yl)pyridine **6b** (TPyT) (35%), lowering the yields of the desired thienylpyridines **3b** (16%) and **3c** (32%) and making their purification more difficult.

Table 1
Cross-coupling reactions through pathways A and B to obtain TPy **3a**–**c**

Pathway	Halide	Boronic acid	Product	Yield (%)
A	**1**	**2a**	**3b**	16
A	**1**	**2b**	**3c**	32/53[20]
B	**5a**	**4a**	**3a**	62
B	**5b**	**4a**	**3a**	78
B	**5a**	**4b**	**3b**	40
B	**5b**	**4b**	**3b**	92
B	**5c**	**4b**	**3c**	40

2.2. Pathway B

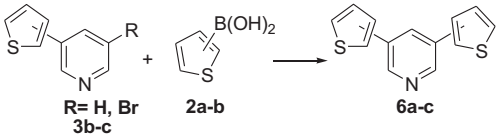
To avoid the side formation of TPyT found in pathway A, we decided to explore the reactivity of halothiophenes **5a**–**c** towards Suzuki–Miyaura cross-coupling reaction[15] with pyridin-3-yl boronic acid **4a**[11] and 5-bromo-pyridin-3-yl boronic acid **4b**[11] (Scheme 3).



Scheme 3. Synthesis of TPy **3** through pathways B. Reagents and conditions: pyridin-3-yl boronic acid **4a**,**b** (2 equiv), thiophene halide **5a**–**c** (1 equiv), Na_2CO_3 aq (2.5 equiv), $Pd(PPh_3)_4$ 5%, 1,4-dioxane, reflux, 24 h.

In this way we obtained 3-(thiophen-2-yl)pyridine **3a** (in 78% yield by using 2-iodothiophene and in 62% yield by using 3-bromothiophene), 3-bromo-5-(thiophen-2-yl)pyridine **3b** (in 40% yield by using 2-bromothiophene and in 92% yield by using the 2-iodothiophene) and 3-bromo-5-(thiophen-3-yl)pyridine **3c** (in 40% yield by using 3-bromothiophene) without traces of subproducts (Table 1).

Then, compounds **3b** and **3c** were engaged in a second coupling reaction with 1.25 equiv of 2-thiophenyl boronic acid **2a** or 3-thiophenyl boronic acid **2b** to obtain the desired symmetric 3,5-di(thiophen-2-yl)pyridine **6a** (16%) and 3,5-di(thiophen-3-yl)pyridine **6b** (35%). But this pathway allowed also to synthesize the dissymmetric 3-(thiophen-2-yl)-5-(thiophen-3-yl)pyridine **6c** (71%) when **3b** was coupled with **2b** (Scheme 4 and Table 2).



Scheme 4. Synthesis of TPyT **6** from TPy **3**. Reagents and conditions: thiophenyl boronic acids **2a** or **2b** (1.25 equiv), TPy **3b**–**c** (1 equiv), Na_2CO_3 aq (2.5 equiv), $Pd(PPh_3)_4$ 5%, DME/EtOH, reflux, 2 h.

Concerning compounds **6a** and **6b**, these later results are really disappointing compared with results obtained in pathway A where these compounds were formed as byproducts during the synthesis of compounds **3b** and **3c** with higher yields. We have not found explanation about the lack of reactivity of compounds **3b** and **3c** towards the pathway B.

In front of these poor results we decided to take advantage of the reactivity of thiophenyl boronic acids found in pathway A and we envisaged the pathway C, quite similar with 2.5 equiv of thiophenyl boronic acids.

2.3. Pathway C

The 3,5-dibromopyridine **1** was reacted with an excess (2.5 equiv) of 2-thiophenyl boronic acid **2a** or 3-thiophenyl boronic acid **2b** to obtain in a one-step reaction and short reaction time

Table 2
Cross-coupling reaction to obtain TPyT **6a–c**

Pathway	Halide	Boronic acid	Product	Yield (%)
A or B	**3b**	**2a**	**6a**	16
A or B	**3b**	**2b**	**6c**	71
A or B	**3c**	**2b**	**6b**	35
C	**1**	**2a**	**6a**	92
C	**1**	**2b**	**6b**	79

(2–3 h) TPyT **6a** and **6b** with excellent yields (**6a**: 79% and **6b**: 92%) (Scheme 5 and Table 2).

Scheme 5. Synthesis of TPyT **6** through pathway C. Reagents and conditions: thiophene boronic acid **2a** or **2b** (2.5 equiv), 3,5-dibromopyridine **1** (1 equiv), Na_2CO_3 aq (2.5 equiv), $Pd(PPh_3)_4$ 5%, DME/EtOH, reflux, 2 h.

In the second part of our work, with these TPyT **6** in hand, we were interested in the preparation of the five unit compounds **9** (PyTPyTPy) (see Scheme 1). The first step was the bromination of compounds **6** (Scheme 6).

dibrominated compound **7a** was formed as the sole product of the reaction in excellent yields (92%) (Scheme 6).

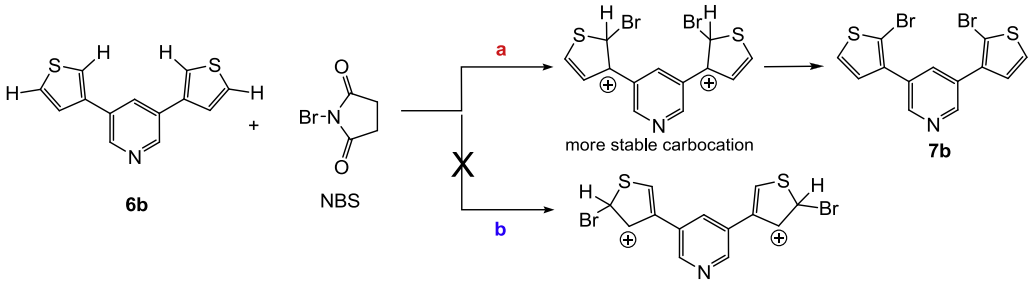
In contrast, when the same reaction was conducted starting from compound **6b** by using 3 equiv of NBS, the result was very different. The desired dibrominated compound **7b** was not obtained and the only dibrominated isomer was the undesired **7b′** (19% ratio of conversion).

Its structure was confirmed by ^{1}H NMR and the selectivity of this unexpected reaction could be explained by the mechanism of the electrophilic substitution with *N*-bromosuccinimide, which could involved the formation of a carbocation stabilized by the pyridyl ring, as shown in Scheme 7.

The bromination reaction of compound **6b** gave also the tribromo compound **7b″** (36% of conversion) and the tetrabromo compound **7b‴** (48% of conversion), which have been separated by

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

The alpha CH centers flanking the sulfur atom of thiophene moiety are susceptible to electrophilic reactions, so when TPyT **6a** was treated with 3 equiv of *N*-bromosuccinimide (NBS) in a 50:50 (v/v) mixture of dichloromethane and glacial acetic acid, the chromatography. We have tried to decrease the quantity of NBS but in these cases the reaction mixtures were more complex with the presence of both the different brominated compounds and the starting material **6b**.



Scheme 7. Mechanism of bromination reaction with *N*-bromosuccinimide.

Moreover, because the TPyT **6b** is not planar, as confirmed by X-ray crystallography (Fig. 1), the alpha-position of thiophene rings are easily accessible for the bromination and this is the reason why this dibromination did not suffer of the steric hindrance.

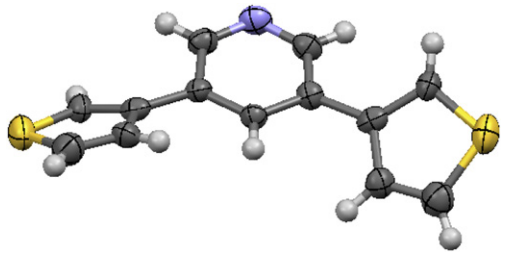


Fig. 1. ORTEP diagram of crystal majority conformation (76%) of compound **6b**.

Finally, when the TPyT **6c** was brominated following the same experimental procedure, we observed the formation of a mixture of dibromo and tribromo compounds **7c** and **7c′**. Their formation was highlighted through LC–MS analyses but their separation by chromatography column proved troublesome.

In the third part, as our aim was to apply a pseudo-Garlanding approach for the construction of new linear thienylpyridyl scaffolds (PyTPyTPy) **9**, which could mimic alpha helices, only the 3,5-di(thiophen-2-yl)pyridine **7a** was engaged in a second Suzuki–Miyaura reaction to couple with different pyridin-3-yl boronic acids **8a**–**d**.

Initially the reaction between the compound **7a** and the pyridin-3-yl boronic acid **8a** was carried out by using 2.5 equiv of the second one but the coupling reaction was not total and only the four unit **10a** was formed (55%) (Scheme 8).

In order to obtain the five unit compounds PyTPyTPy, we have increased the equivalents of boronic acid to 3.5 equiv: in this case we observed the formation of the desired 3-(5-(5-(5-(pyridin-3-yl) thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine **9a** in 68% yield and we found only traces of the four unit compound **10a** (5%) separated from the first one by chromatographic column.

Then, this synthetic way was made profitable to obtain PyTPyT **10b**–**d** by using 6-substituted pyridin-3-yl boronic acids **8b**–**d**.[10,21] All desired products have been isolated after chromatography as stable solids with acceptable yields (2-chloro-5-(5-(5-(5-(6-chloropyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl) pyridine **9b**: 51%; 2-fluoro-5-(5-(5-(5-(6-fluoropyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine **9c**: 55%; 2-methoxy-5-(5-(5-(5-(6-methoxypyridin-3-yl)thiophen-2-yl) pyridin-3-yl)thiophen-2-yl)pyridine **9d**: 33%) (see Table 3 and Scheme 9).

In all cases we observed the formation of quater TPyTPy in different amounts (5-(5-(5-(5-bromothiophen-2-yl)pyridin-3-yl)thiophen-2-yl)-2-chloropyridine **10b**: 38%; 5-(5-(5-(5-bromothiophen-2-yl)pyridine-3-yl)thiophen-2-yl)-2-fuoropyridine **10c**: 40%; 5-(5-(5-(5-bromothiophen-2-yl)pyridine-3-yl)thiophen-2-yl)-2-methoxypyridine **10d**: 42%). The use of more than 3.5 equiv of boronic acids did not change these results and electronic effects of chlorine, fluorine atoms and methoxy group placed on the pyridine ring could decrease the reactivity of boronic acids in the coupling reaction.

The preliminary molecular modeling studies, based on X-ray diffraction data, showed that in a garland of three unit thienylpyridyl compound **6b** (TPyT) where thienyl moieties are attached in position 3 and 5 of the pyridine, each unit can fit to a position of one residue in alpha helix (see Fig. 2). For this type of scaffold, three units can cover one helix turn (3–4 residues).

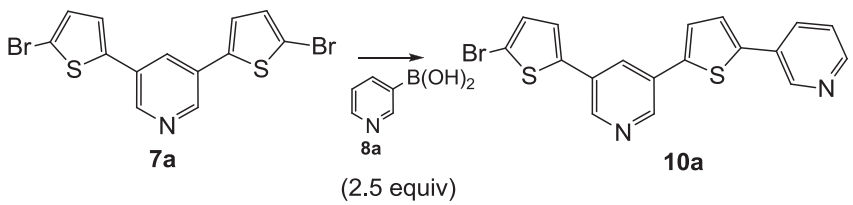
On the other hand, the molecular mechanic simulation on a garland of four and five units showed that the minimum energy conformation corresponds to an extended conformation.

The successive pyridine and thiophene units in modelised garland are not coplanars: planes of cycles are twisted one with respect to other of about 45° (Fig. 3). This preferential orientation of planes of about 45° was confirmed by the mechanic quantum calculation of potential energy scan for pyridine/thiophene units (Gaussian 98[22]).

The superposition of modelised five unit garland (PyTPyTPy) with an alpha helix suggests that this conformation aligned well along the helix axis (see Fig. 3). Thus the substituents on this scaffold will be distributed on the different positions of an alpha helix in function of position where they will be attached.

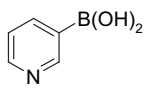
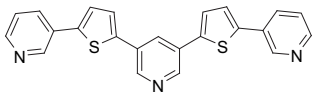
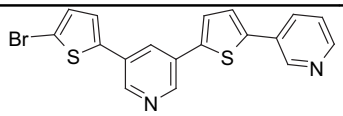
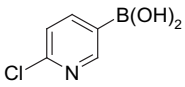
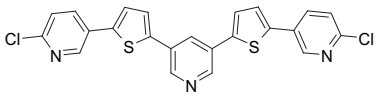
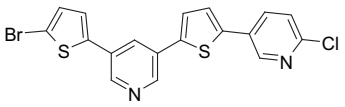
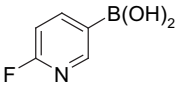
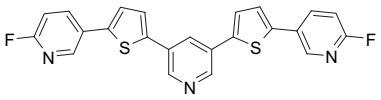
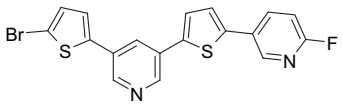
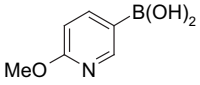
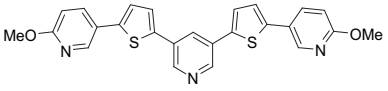
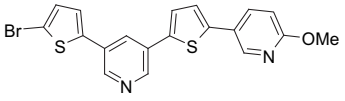
3. Conclusion and future work

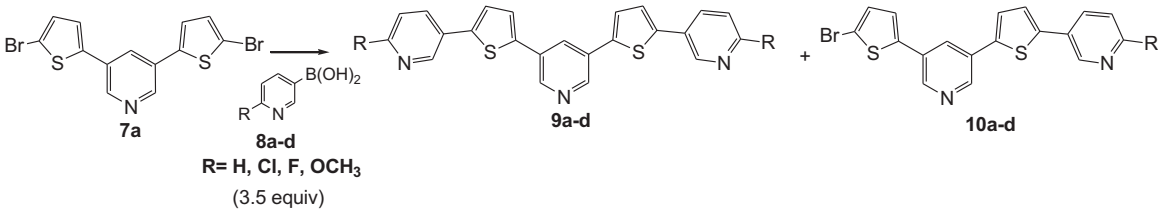
We successfully developed the regiocontrolled synthesis of five unit pyridylthienyl scaffolds by applying an efficient pseudo-



Scheme 8. Reactivity of the compound **7a** with pyridyl boronic acid **8a**. Reagents and conditions: pyridine boronic acid **8a** (2.5 equiv), 3,5-di(thiophen-2-yl)pyridine **7a** (1 equiv), Na_2CO_3 aq (2.5 equiv), $Pd(PPh_3)_4$ 10%, DME/EtOH, reflux, 24 h.

Table 3
Cross-coupling reaction between substituted pyridin-3-yl boronic acid **8a–d** and the 3,5-di(thiophen-2-yl)pyridine **7a**

Boronic acid		PyTPyTPy		Yield (%)	TPyTPy		Yield (%)
8a		**9a**		68	**10a**		5
8b		**9b**		51	**10b**		38
8c		**9c**		55	**10c**		40
8d		**9d**		33	**10d**		42



Scheme 9. Synthesis of compound PyTPyTPy **9a–d** and PyTPyT **10a–d**. Reagents and conditions: pyridyl boronic acids **8a–d** (3.5 equiv), 3,5-di(thiophen-2-yl)pyridine **7a** (1 equiv), Na_2CO_3 aq (4 equiv), $Pd(PPh_3)_4$ 10%, DME/EtOH, reflux, 24 h.

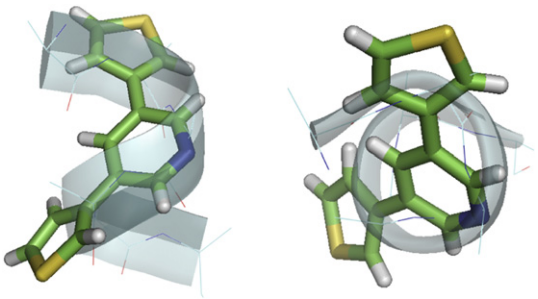


Fig. 2. A representation of the alignment of the 3,5-(dithiophen-3-yl)pyridine with an alpha helix, based on the **6b** crystal structure.

Garlanding approach. Crystallographic and NMR analyses are currently undergone in our laboratory in order to establish their helicity in solid and liquid state. Moreover, the fact that terpyridines were studied as DNA binding agents[23] and taking into account that a careful screening of the literature describes very few cytotoxic effects of oligopyridyl derivatives, all compounds described in this paper were preliminary screened for a potential cytotoxic activity by an in vitro assay of growth inhibition against KB cells. In general, the obtained results suggest that the compounds did not produce a relevant change in cell viability in KB cells (none of them shows a cytotoxic activity on KB cells at 10^{-5} M). This data will furnish valuable information in the context of the exploration of biological properties of perturbations of protein–protein interactions. Further results will be reported in due time.

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}).

^1H 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 purifications, 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.

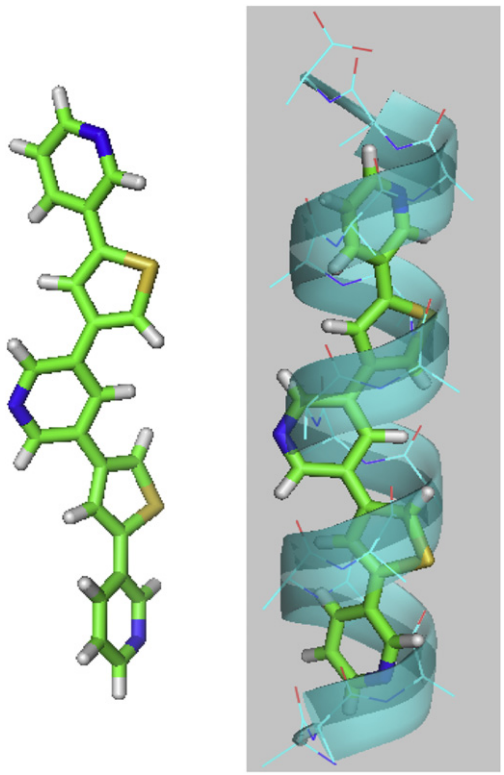


Fig. 3. A predicted structure of a five unit thienylpyridyl compound (left) and its overlay with an alpha helix (right).

4.2. General procedure for Suzuki–Miyaura cross-coupling reaction to obtain TPy compounds 3b–c through pathway A

To a round bottom flask containing a magnetic stirring bar was added the 3,5-dibromopyridine **1** (1.00 equiv), and the flask was purged with nitrogen. Then a solution of tetrakis(-triphenylphosphine) palladium(0) (5% mol) in dimethoxyethane (2.00 mL) and sodium carbonate (aq) (2.50 equiv) was added. The resultant solution was stirred at room temperature for 5 min when a slurry/solution of thiophenyl boronic acid **2a** or **2b** (1.25 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 (washed with dichloromethane) into a flask containing anhydrous magnesium sulfate. The solution was dried for 10 min, filtered 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 compounds **3b**,**c**.

*4.2.1. 3-Bromo-5-(thiophen-2-yl)pyridine (**3b**).* Starting from 3,5-dibromopyridine **1** (1.00 g, 4.22 mmol) and 2-thiophenyl boronic acid **2a** (0.68 g, 5.28 mmol) and following the general procedure, the product **3b** was obtained as a yellow solid (0.16 g, 16%). Mp<50 °C. IR (KBr disc): 3040, 2925 (stretching C–H aromatic), 1577, 1543, 1445, 1422, 1409 (stretching C–C, C–N, C–S), 1100, 1016, 973, 877, 757, 697 (bending C–H) cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.78 (d, 1H, H_2, J=1.9 Hz), 8.57 (d, 1H, H_6, J=1.9 Hz), 8.01 (dd, 1H, H_4, J=1.9, 3.9 Hz), 7.41 (d, 1H, $H_{5'}$, J=2.9 Hz), 7.38 (d, 1H, $H_{3'}$, J=2.9 Hz), 7.15–7.13 (dd, 1H, $H_{4'}$, J=2.9, 4.9 Hz). ^{13}C NMR ($CDCl_3$) δ 149.05 (C_6), 144.83 (C_2), 138.41 ($C_{2'}$), 135.12 ($C_{4'}$), 131.77 (C_5), 128.60 ($C_{3'}$), 127.05 ($C_{5'}$), 124.99 (C_4), 120.84 (C_3). MS (EI): 240 $[M^+]^*$, 242 $[M^++2]^*$. Anal. Calcd for C_9H_6BrNS: C, 45.02; H, 2.52; N, 5.83. Found: C, 44.96; H, 2.49; N, 5.78.

*4.2.2. 3-Bromo-5-(thiophen-3-yl)pyridine (**3c**).* Starting from 3,5-dibromopyridine **1** (0.50 g, 2.11 mmol) and 3-thiophenyl boronic acid **2b** (0.34 g, 2.64 mmol) and following the general procedure, the product **3c** was obtained as a yellow oil (0.16 g, 32%). Experimental data were found to be identical to that already described in the literature.[19]

4.3. General procedure for Suzuki–Miyaura cross-coupling reaction to obtain TPy compounds 3a–c through pathway B

A mixture of pyridin-3-yl boronic acid **4a**,**b** (2.00 equiv), halothiophene **5a**–**c** (1.00 equiv), tetrakis(triphenylphosphine) palladium(0) (5% mol) and aq Na_2CO_3 (2.50 equiv) in 1,4-dioxane was heated at 80 °C for 1 h then under reflux until the complete consumption of aryl halide (as monitored by TLC) (23 h). The reaction mixture was concentrated and extracted with ethyl acetate. Organic layer was dried over $MgSO_4$ and concentrated. The residue was purified on silica gel column chromatography (cyclohexane/ethyl acetate: 7/3) to afford compounds **3a**–**c**.

*4.3.1. 3-(Thiophen-2-yl)pyridine (**3a**).* Starting from pyridin-3-yl boronic acid **4a** (0.60 g, 4.88 mmol) and 2-iodothiophene **5b** (0.51 g, 2.44 mmol) and following the general procedure, the product **3a** was obtained as a brown oil (0.31 g, 78%). When 2-bromothiophene **5a** was used instead of 2-iodothiophene **5b** yield was of 62%. Experimental data were found to be identical to that already described in the literature.[19]

*4.3.2. 3-Bromo-5-(thiophen-2-yl)pyridine (**3b**).* Starting from 5-bromo-pyridin-3-yl boronic acid **4b** (1.00 g, 4.95 mmol) and 2-iodothiophene **5b** (0.52 g, 2.48 mmol) and following the general procedure, the product **3b** was obtained as a yellow oil (0.55 g, 92%). When 2-bromothiophene **5a** was used instead of 2-iodothiophene **5b** yield was of 40%. Same experimental data as described above.

*4.3.3. 3-Bromo-5-(thiophen-3-yl)pyridine (**3c**).* Starting from 5-bromo-pyridin-3-yl boronic acid **4b** (2.28 g, 11.30 mmol) and 3-bromothiophene **5c** (1.00 g, 5.65 mmol) and following the general procedure, the product **3c** was obtained as a yellow oil (0.47 g, 33%). Experimental data were found to be identical to that already described in the literature.[19]

4.4. General procedure for Suzuki–Miyaura cross-coupling reaction to obtain TPyT compounds 6a–c (as continuation of pathways A and B)

To a round bottom flask containing a magnetic stirring bar was added the TPy **3b**–**c** (1.00 equiv), and the flask was purged with nitrogen. Then a solution of tetrakis(triphenylphosphine) palladium(0) (5% mol) in dimethoxyethane (2.00 mL) and sodium carbonate (aq) (2.50 equiv) was added. The resultant solution was stirred at room temperature for 5 min when a slurry/solution of thiophenyl boronic acid **2a**,**b** (1.25 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 compounds **6a**–**c**.

*4.4.1. 3,5-Di(thiophen-2-yl)pyridine (**6a**).* Starting from the 3-bromo-5-(thiophen-2-yl)pyridine **3b** (0.50 g, 2.08 mmol) and 2-thiophenyl boronic acid **2a** (0.33 g, 2.60 mmol) and following the general procedure, the product **6a** was obtained as a white solid (0.08 g, 16%). Mp: 144–146 °C. IR (KBr disc): 3086, 3066, 2924, 1589, 1440, 1410, 1343, 881, 850, 829, 723, 701 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.78 (d, 2H, H_2 and H_6, J=2.9 Hz), 8.02 (dd, 1H, H_4, J=1.9, 3.9 Hz), 7.43 (d, 2H, $H_{3'}$ and $H_{3''}$, J=4.9 Hz), 7.40 (d, 2H, $H_{5'}$ and $H_{5''}$, J=4.9 Hz), 7.16–7.14 (dd, 2H, $H_{4'}$ and $H_{4''}$, J=3.9, 4.9 Hz). ^{13}C NMR ($CDCl_3$) δ 145.65 (C_2 and C_6), 139.97 ($C_{2'}$ and $C_{2''}$), 130.49 (C_3 and C_5), 129.96 (C_4), 128.34 ($C_{4'}$ and $C_{4''}$), 126.32 ($C_{3'}$ and $C_{3''}$), 124.62 ($C_{5'}$ and $C_{5''}$). MS (EI): 244 $[M^+]^*$. Anal. Calcd for $C_{13}H_9NS_2$: C, 64.16; H, 3.73; N, 5.76. Found: C, 64.05; H, 3.70; N, 5.76.

*4.4.2. 3,5-Di(thiophen-3-yl)pyridine (**6b**).* Starting from the 3-bromo-5-(thiophen-2-yl)pyridine **3c** (0.50 g, 2.08 mmol) and 3-thiophenyl boronic acid **2b** (0.33 g, 2.60 mmol) and following the general procedure, the product **6b** was obtained as a white solid (0.18 g, 35%). Mp: 144–146 °C. IR (KBr disc): 3089, 1478, 1440, 1323, 1215, 1087, 896, 830, 782, 639 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.79 (d, 2H, H_2 and H_6, J=1.9 Hz), 8.02 (dd or t, 1H, H_4, J=1.9, 3.9 Hz), 7.58 (d, 2H, $H_{2'}$ and $H_{2''}$, J=2.9Hz), 7.49–7.47 (dd, 2H, $H_{4'}$ and $H_{4''}$, J=2.9, 4.9 Hz), 7.45–7.43 (d, 2H, $H_{5'}$ and $H_{5''}$, J=4.9 Hz). ^{13}C NMR ($CDCl_3$) δ 146.16 (C_2 and C_6), 138.63 ($C_{4'}$ and $C_{4''}$), 131.52 ($C_{2'}$ and $C_{2''}$), 131.14 (C_4), 127.04 ($C_{5'}$ and $C_{5''}$), 125.97 ($C_{3'}$ and $C_{3''}$), 121.66 (C_3 and C_5). MS (EI): 244 $[M^+]^*$. Anal. Calcd for $C_{13}H_9NS_2$: C, 64.16; H, 3.73; N, 5.76. Found: C, 64.09; H, 3.68; N, 5.70.

*4.4.3. 3-(Thiophen-2-yl)-5-(thiophen-3-yl)pyridine (**6c**).* Starting from the 3-bromo-5-(thiophen-2-yl)pyridine **3b** (0.50 g, 2.08 mmol) and 3-thiophenyl boronic acid **2b** (0.33 g, 2.60 mmol) and following the general procedure, the product **6c** was obtained as a brown solid (0.36 g, 71%). Mp: 144–146 °C. IR (KBr disc): 3088, 1589, 1433,895, 785, 690, 655 cm^{-1}. ^1H NMR ($CDCl_3$) 8.79 (d, 1H, H_2, J=1.9 Hz), 8.76 (d, 1H, H_6, J=1.9 Hz), 8.01 (dd, 1H, H_4, J=1.9, 3.9 Hz), 7.58 (s, 1H, $H_{2''}$), 7.47 (d, 1H, $H_{5'}$, J=3.9 Hz), 7.44 (1H, $H_{5''}$, J=4.9 Hz), 7.42 (d, 1H, $H_{3'}$, J=3.9 Hz), 7.39 (d, 1H, $H_{4''}$, J=4.9 Hz), 7.16–7.14 (dd, 1H, $H_{4'}$, J=3.9, 4.87 Hz). ^{13}C NMR ($CDCl_3$) δ 146.38 (C_2), 145.42 (C_6), 140.22 ($C_{3''}$), 138.40 ($C_{2'}$), 131.58 (C_5), 130.57 (C_4), 130.38 (C_3), 129.10 ($C_{4''}$), 128.32 ($C_{5''}$), 126.18 ($C_{4'}$), 125.97 ($C_{3'}$), 124.43 ($C_{5'}$), 121.85 ($C_{2''}$). MS (EI): 244 $[M^+]^*$. Anal. Calcd for $C_{13}H_9NS_2$ C, 64.16; H, 3.73; N, 5.76. Found: C, 64.08; H, 3.67; N, 5.74.

4.5. General procedure for Suzuki–Miyaura cross-coupling reaction to obtain TPyT 6a,b through pathway C

To a round bottom flask containing a magnetic stirring bar was added the 3,5-dibromopyridine **1** (1.00 equiv), and the flask was purged with nitrogen. Then a solution of tetrakis(-triphenylphosphine) palladium(0) (5% mol) in dimethoxyethane (2.00 mL) and sodium carbonate (aq) (2.50 equiv) was added. The resultant solution was stirred at room temperature for 5 min when a slurry/solution of thiophenyl boronic acid **2a** or **2b** (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 compounds **6a** and **6b**.

*4.5.1. 3,5-Di(thiophen-2-yl)pyridine (**6a**).* Starting from the 3,5-dibromopyridine **1** (0.37 g, 1.56 mmol) and 2-thiophenyl boronic acid **2a** (0.50 g, 3.91 mmol) and following the general procedure, the product **6a** was obtained as a white solid (0.35 g, 92%). Same experimental data described above.

*4.5.2. 3,5-Di(thiophen-3-yl)pyridine (**6b**).* Starting from the 3,5-dibromopyridine **1** (0.50 g, 2.11 mmol) and 3-thiophenyl boronic acid **2b** (0.68 g, 5.27 mmol) and following the general procedure, the product **6b** was obtained as a white solid (0.40 g, 79%). Same experimental data as described above.

4.6. Synthesis of brominated compounds 7a and 7b

To a solution of starting material **6a** or **6b** (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 **7a** or **7b** as stable solids.

*4.6.1. 3,5-Bis(5-bromothiophen-2-yl)pyridine (**7a**).* Starting from TPyT **6a** (0.50 g, 2.06 mmol) and NBS (1.10 g, 6.18 mmol) and following the general procedure, the product **7a** was obtained as a beige solid (0.53 g, 92%). Mp: 110–112 °C. IR (KBr disc): 3077, 3015, 2923, 1586, 1441, 1419, 1157, 1019, 966, 801, 705 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.70 (d, 2H, H_2 and H_6, J=1.9 Hz), 7.83 (dd, 1H, H_4, J=1.9, 3.9 Hz), 7.16 (d, 2H, $H_{4'}$ and $H_{4''}$, J=3.9 Hz), 7.10 (d, 2H, $H_{3'}$ and $H_{3''}$, J=3.9 Hz). ^{13}C NMR ($CDCl_3$) δ 145.49 (C_2 and C_6), 141.03 ($C_{2'}$ and $C_{2''}$), 131.17 ($C_{4'}$ and $C_{4''}$), 129.80 (C_3 and C_5), 129.16 (C_4), 124.97 ($C_{3'}$ and $C_{3''}$), 113.34 ($C_{5'}$ and $C_{5''}$). MS (EI): 402 $[M^+]^*$, 404 $[M^++2]^*$, 406 $[M^++4]^*$. Anal. Calcd for $C_{13}H_7Br_2NS_2$: C, 38.92; H, 1.76; N, 3.49. Found: C, 38.90; H, 1.68; N, 3.34.

*4.6.2. 3,5-Bis(2-bromothiophen-3-yl)pyridine (**7b′**).* Starting from TPyT **6b** (0.10 g, 0.41 mmol) and NBS (0.22 g, 1.23 mmol) and following the general procedure, the product **7b′** was obtained as a brown solid (ratio of conversion: 19%). Mp: 129–130 °C. IR (KBr disc): 2956, 2924, 2853, 1441, 1261, 1022, 799, 728 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.71 (d, 2H, H_2 and H_6, J=1.9 Hz), 8.11 (dd, 1H, H_4, J=1.9, 3.9 Hz), 7.37 (d, 2H, $H_{5'}$ and $H_{5''}$, J=5.8 Hz), 7.07 (d, 2H, $H_{4'}$ and $H_{4''}$, J=5.8 Hz). ^{13}C NMR ($CDCl_3$) δ 148.18 (C_2 and C_6), 137.40 ($C_{3'}$ and $C_{3''}$), 135.65 (C_4), 130.60 (C_3 and C_5), 128.61 ($C_{5'}$ and $C_{5''}$), 126.77 ($C_{4'}$ and $C_{4''}$), 110.25 ($C_{2'}$ and $C_{2''}$). MS (EI): 402 $[M^+]^*$, 404 $[M^++2]^*$, 406 $[M^++4]^*$. Anal. Calcd for $C_{13}H_7Br_2NS_2$: C, 38.92; H, 1.76; N, 3.49. Found: C, 38.87; H, 1.69; N, 3.39.

*4.6.3. 5-(2,5-Dibromothiophen-3-yl)-3-(2-bromothiophen-3-yl)pyridine (**7b″**).* Starting from TPyT **6b** (0.10 g, 0.41 mmol) and NBS (0.219 g, 1.23 mmol) and following the general procedure, the product **7b″** was obtained as a brown solid (ratio of conversion: 36%). Mp: 90–91 °C. IR (KBr disc): 2962, 2922, 2852, 1435, 1261, 1097, 1022, 798, 710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.72 (d, 1H, H_2, J=1.9 Hz), 8.68 (d, 1H, H_6, J=1.9 Hz), 8.02 (dd, 1H, H_4, J=1.9, 3.9 Hz), 7.33 (d, 1H, $H_{5'}$, J=4.9 Hz), 7.03 (d, 1H, $H_{4'}$, J=4.9 Hz), 7.01 (s, 1H, $H_{4''}$). ^{13}C NMR ($CDCl_3$) δ 147.89 (C_2), 147.75 ($C_{3'}$), 147.31 (C_6), 145.33 ($C_{3''}$), 136.06 (C_3 and C_5), 131.03 (C_4), 128.48 ($C_{5''}$), 126.99 ($C_{4''}$), 125.03 ($C_{4'}$), 112.56 ($C_{5'}$), 110.61 ($C_{2'}$), 109.67 ($C_{2''}$). MS (EI): 477.80 $[M^+]^*$, 479.80 $[M^++2]^*$, 481.80 $[M^++4]^*$, 483.80 $[M^++6]^*$. Anal. Calcd for $C_{13}H_6Br_3NS_2$: C, 32.53; H, 1.26; N, 2.92. Found: C, 32.32, H, 1.18, N, 2.87.

*4.6.4. 3,5-Bis(2,5-dibromothiophen-3-yl)pyridine (**7b‴**).* Starting from TPyT **6b** (0.10 g, 0.41 mmol) and NBS (0.22 g, 1.23 mmol) and

following the general procedure, the product **7b‴** was obtained as a brown solid (ratio of conversion: 48%). Mp: 117–119 °C. IR (KBr disc): 2923, 2853, 1439, 1261, 1095, 807 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.75 (d, 2H, H_2 and H_6, J=1.9 Hz), 8.01 (dd, 1H, H_4, J=1.9, 3.9 Hz), 7.08 (s, 2H, $H_{4'}$ and $H_{4''}$). ^{13}C NMR ($CDCl_3$) δ 148.15 (C_2 and C_6), 146.38 ($C_{3'}$ and $C_{3''}$), 138.18 (C_3 and C_5), 135.65 (C_4), 131.01 ($C_{4'}$ and $C_{4''}$), 112.50 ($C_{5'}$ and $C_{5''}$), 109.76 ($C_{2'}$ and $C_{2''}$). MS (EI): 555.66 $[M^+]^*$, 557.67 $[M^+{+}2]^*$, 559.67 $[M^+{+}4]^*$, 561.66 $[M^+{+}6]^*$, 563.66 $[M^+{+}8]^*$. Anal. Calcd for $C_{13}H_5Br_4NS_2$: C, 27.94; H, 0.90; N, 2.51. Found: C, 27.87; H, 0.79; N, 2.50.

4.7. General procedure for Suzuki–Miyaura reaction to obtain five units PyTPyTPy 9a–d and four unit TPyTPy 10a–d

To a glass vial containing a magnetic stirring bar was added the 3,5-bis(5-bromothiophen-2-yl)pyridine **7a** (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 **8a–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 **9a–d** and their five unit derivatives **10a–d**.

*4.7.1. 3-(5-(5-(5-(Pyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine (**9a**).* Starting from 3,5-bis(5-bromothiophen-2-yl) pyridine **7a** (1.00 g, 2.49 mmol) and pyridin-3-yl boronic acid **8a** (1.07 g, 8.71 mmol) and following the general procedure the product **9a** was obtained as a yellow solid (0.67 g, 68%). Mp: 190–192 °C. IR (KBr disc): 2974, 2936, 2738, 2676, 2491, 1579, 1475, 1433, 1383, 1170, 1035, 789, 697 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.94 (d, 2H, $H_{2''}$ and $H_{6''}$, J=1.9 Hz), 8.83 (d, 2H, H_2 and $H_{2'''}$, J=1.9 Hz), 8.57 (dd, 2H, H_6 and $H_{6'''}$, J=1.9, 4.9 Hz), 8.07–8.06 (dd, 1H, $H_{4''}$, J=1.9, 2.9 Hz), 7.94–7.91 (dt, 2H, H_4 and $H_{4'''}$, J=1.9, 7.8 Hz), 7.47 (d, 2H, $H_{4'}$ and $H_{4''}$, J=3.9 Hz), 7.43 (d, 2H, $H_{3'}$ and $H_{3''}$, J=3.9 Hz), 7.38–7.35 (dd, 2H, H_5 and $H_{5'''}$, J=4.9, 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 148.89 ($C_{2''}$ and $C_{2'''}$), 146.79 ($C_{6''}$ and $C_{6'''}$), 145.63 ($C_{2''}$ and $C_{6''}$), 141.27 ($C_{5'}$ and $C_{2''}$), 140.16 ($C_{2'}$ and $C_{5''}$), 132.86 (C_4 and $C_{4'''}$), 130.13 ($C_{3''}$ and $C_{5''}$), 129.85 (C_3 and $C_{3'''}$), 129.40 ($C_{4''}$), 125.81 ($C_{3'}$ and $C_{4''}$), 125.40 ($C_{4'}$ and $C_{4''}$), 123.76 (C_5 and $C_{5'''}$). MS (EI): 398 $[M^+]^*$. Anal. Calcd for $C_{23}H_{15}N_3S_2$: C, 69.49; H, 3.80; N, 10.57. Found: C, 69.44; H, 3.74; N, 10.45.

*4.7.2. 2-Chloro-5-(5-(5-(5-(6-chloropyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine (**9b**).* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **7a** (0.60 g, 1.49 mmol) and 6-chloropyridin-3-yl boronic acid **8b** (0.82 g, 5.21 mmol) and following the general procedure the product **9b** was obtained as a light brown solid (0.35 g, 51%). Mp: 188–190 °C. IR (KBr disc) 2922, 1637, 1582, 1448, 1108, 798 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.83 (d, 2H, $H_{2''}$ and $H_{6''}$, J=1.9 Hz), 8.69 (d, 2H, H_6 and $H_{2'''}$, J=1.9 Hz), 8.04–8.03 (dd, 1H, $H_{4''}$, J=1.9, 3.9 Hz), 7.89–7.87 (dd, 2H, H_4 and $H_{4'''}$, J=2.9, 7.8 Hz), 7.46 (d, 2H, $H_{4'}$ and $H_{3''}$, J=3.9 Hz), 7.41 (d, 2H, H_3 and $H_{5'''}$, J=2.9 Hz), 7.39 (d, 2H, $H_{3'}$ and $H_{4''}$, J=3.9 Hz). ^{13}C NMR ($CDCl_3$) δ 150.47 (C_2 and $C_{6'''}$), 146.39 ($C_{2''}$ and $C_{6''}$), 145.76 (C_6 and $C_{2'''}$), 140.56 ($C_{2'}$ and $C_{5''}$), 139.81 ($C_{5'}$ and $C_{2''}$), 135.51 (C_4 and $C_{4'''}$), 129.99 ($C_{4''}$), 129.44 ($C_{3''}$ and $C_{5''}$), 128.87 (C_5 and $C_{3'''}$), 125.91 ($C_{4'}$ and $C_{3''}$), 125.81 ($C_{3'}$ and $C_{4''}$), 124.48 (C_3 and $C_{5'''}$). MS (EI): 466 $[M^+]^*$. Anal. Calcd for $C_{23}H_{13}Cl_2N_3S_2$: C, 59.23; H, 2.81; N, 9.01. Found: C, 59.17; H, 2.76; N, 9.00.

*4.7.3. 2-Fluoro-5-(5-(5-(5-(6-fluoropyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine (**9c**).* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **7a** (0.50 g, 1.25 mmol) and 6-fluoropyridin-3-yl boronic acid **8c** (0.62 g, 4.37 mmol) and following the general procedure the product **9c** was obtained as a yellow solid (0.30 g, 55%). Mp: 198–200 °C .IR (KBr disc): 2922, 1580, 1491, 1453, 1241, 805 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.83 (d, 2H, $H_{2''}$ and $H_{6''}$, J=1.9 Hz), 8.52 (d, 2H, H_6 and $H_{2'''}$, J=1.9 Hz), 8.05–8.04 (dd, 1H, $H_{4''}$, J=1.9, 2.9 Hz), 8.03–8.00 (dd, 2H, H_3 and $H_{5'''}$, J=2.9, 7.8 Hz), 7.46 (d, 2H, $H_{4'}$ and $H_{3''}$, J=3.9 Hz), 7.36 (d, 2H, $H_{3'}$ and $H_{4''}$, J=3.9 Hz), 7.03–7.00 (dd, 2H, H_4 and $H_{4'''}$, J=2.9, 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 145.68 ($C_{2''}$ and $C_{6''}$), 144.62 (C_2 and $C_{6'''}$), 144.47 (C_6 and $C_{2'''}$), 140.15 ($C_{2'}$ and $C_{5''}$), 139.92 ($C_{5'}$ and $C_{2''}$), 138.39 (C_4 and $C_{4'''}$), 130.04 ($C_{3''}$ and $C_{5''}$), 129.38 (C_5 and $C_{3'''}$), 128.14 ($C_{4''}$), 125.80 ($C_{4'}$ and $C_{3''}$), 125.44 ($C_{3'}$ and $C_{4''}$), 110.08 (C_3 and $C_{5'''}$). MS (EI): 434 $[M^+]^*$. Anal. Calcd for $C_{23}H_{13}F_2N_3S_2$: C, 63.73; H, 3.02; N, 9.69. Found: C, 63.68; H, 2.96; N, 9.65.

*4.7.4. 2-Methoxy-5-(5-(5-(5-(6-methoxypyridin-3-yl)thiophen-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine (**9d**).* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **7a** (0.46 g, 1.15 mmol) and 6-methoxypyridin-3-yl boronic acid **8d** (0.61 g, 4.01 mmol) and following the general procedure the product **9d** was obtained as a yellow solid (0.19 g, 33%). Mp: 204–206 °C. IR (KBr disc) 2923, 1602, 1500, 1461, 1436, 1287, 1020, 803, 691 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.79 (d, 2H, $H_{2''}$ and $H_{6''}$, J=1.9 Hz), 8.48 (d, 2H, H_6 and $H_{2'''}$, J=1.9 Hz), 8.03–8.02 (dd, 1H, $H_{4''}$, J=1.9, 3.9 Hz), 7.84–7.81 (dd, 2H, H_3 and $H_{5'''}$, J=1.9, 7.8 Hz), 7.73–7.69 (m, 2H, H_4 and $H_{4'''}$), 7.42 (d, 2H, $H_{3'}$ and $H_{4''}$, J=3.9 Hz), 6.82 (d, 2H, $H_{4'}$ and $H_{3''}$, J=3.9 Hz), 3.99 (s, 6H, $2OCH_3$). ^{13}C NMR ($CDCl_3$) δ 163.82 (C_2 and $C_{6'''}$), 145.24 ($C_{2''}$ and $C_{6''}$), 143.91 (C_6 and $C_{2'''}$), 141.77 ($C_{2'}$ and $C_{5''}$), 138.81 ($C_{5'}$ and $C_{2''}$), 136.26 (C_4 and $C_{4'''}$), 134.89 ($C_{4''}$), 130.50 ($C_{3''}$ and $C_{5''}$), 125.60 ($C_{3'}$ and $C_{4''}$), 124.02 ($C_{4'}$ and $C_{3''}$), 123.51 (C_5 and $C_{3'''}$), 111.14 (C_3 and $C_{5'''}$), 53.70 ($2OCH_3$). MS (EI): 457 $[M^+]^*$. Anal. Calcd for $C_{25}H_{19}N_3O_2S_2$: C, 65.62; H, 4.19; N, 9.18. Found: C, 65.57; H, 4.07; N, 9.10.

*4.7.5. 3-(5-(5-(5-Bromothiophene-2-yl)pyridin-3-yl)thiophen-2-yl)pyridine (**10a**).* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **7a** (1.00 g, 2.49 mmol) and pyridin-3-yl boronic acid **8a** (1.07 g, 8.71 mmol) and following the general procedure the subproduct **10a** was obtained as a yellow solid (0.04 g, 5%). Mp: 142–144 °C. IR (KBr disc): 2923, 2853, 1585, 1451, 1408, 1018, 867, 791, 699 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.93 (d, 1H, $H_{2''}$, J=1.9 Hz), 8.82 (d, 1H, $H_{6''}$, J=1.9 Hz), 8.71 (d, 1H, H_2, J=1.9 Hz), 8.57–8.55 (dd, 1H, H_6, J=1.9, 4.9 Hz), 7.94–7.93 (dd, 1H, H_5, J=1.9, 2.8 Hz), 7.92–7.89 (dt, 1H, H_4, J=1.9, 7.8 Hz), 7.44 (d, 1H, $H_{4'}$, J=3.9 Hz), 7.41 (d, 1H, $H_{3'}$, J=3.9 Hz), 7.37–7.34 (dd, 1H, $H_{4''}$, J=4.9 Hz), 7.19 (d, 1H, $H_{4'''}$, J=3.9 Hz), 7.12 (d, 1H, $H_{3'''}$, J=3.9 Hz). ^{13}C NMR ($CDCl_3$) δ 148.92 (C_2), 146.81 (C_6), 145.69 ($C_{2''}$), 145.49 ($C_{6''}$), 141.33 ($C_{2'''}$), 141.18 ($C_{5'}$), 140.08 ($C_{2'}$), 132.83 (C_4), 131.20 ($C_{4''}$), 130.19 (C_3), 129.84 ($C_{5''}$ and $C_{3''}$), 129.32 ($C_{4'''}$), 125.81 ($C_{3'''}$), 125.38 ($C_{4'}$), 124.99 ($C_{3'}$), 123.74 (C_5), 113.32 ($C_{5'''}$). MS (EI): 399$[M^+]^*$, 401 $[M^+{+}2]^*$. Anal. Calcd for $C_{18}H_{11}BrN_2S_2$: C, 54.14; H, 2.78; N, 7.02. Found: C, 54.09; H, 2.74; N, 6.87.

*4.7.6. 5-(5-(5-(5-Bromothiophen-2-yl)pyridin-3-yl)thiophen-2-yl)-2-chloropyridine (**10b**).* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **7a** (0.60 g, 1.49 mmol) and 6-chloropyridin-3-yl boronic acid **8b** (0.82 g, 5.21 mmol) and following the general procedure the subproduct **10b** was obtained as a light brown solid (0.20 g, 38%). Mp: 118–120 °C. IR (KBr disc): 2855, 1573, 1462, 1279, 1227, 1105, 827, 796 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.79 (d, 1H, H_6,

J=1.9 Hz), 8.70 (d, 1H, $H_{2''}$, J=1.9 Hz), 8.68 (d, 1H, $H_{6''}$, J=2.9 Hz), 7.96–7.95 (dd, 1H, $H_{4''}$, J=1.9, 4.9 Hz), 7.89–7.87 (dd, 1H, H_3, J=1.9, 7.8 Hz), 7.44(d, 1H, $H_{4'''}$, J=3.9 Hz), 7.40–7.39 (dd, 1H, H_4, J=1.9, 5.9 Hz), 7.20 (d, 2H, $H_{3'}$ and $H_{4'}$, J=3.9 Hz), 7.12 (d, 1H, $H_{3'''}$, J=3.9 Hz). ^{13}C NMR ($CDCl_3$) δ 150.43 (C_6), 147.69 (C_2), 146.29 ($C_{6''}$), 145.06 ($C_{2''}$), 141.43 ($C_{2'''}$), 140.72 ($C_{2'}$), 139.87 ($C_{5'}$), 137.24 (C_4), 134.62 ($C_{4''}$), 131.27 ($C_{4'''}$), 129.68 ($C_{3'''}$), 126.51 ($C_{5''}$), 125.05 ($C_{3''}$), 125.88 ($C_{4'}$), 125.21 (C_5), 124.75 ($C_{3'}$), 124.56 (C_3), 113.65 ($C_{5'''}$). MS (EI): 433[M^+]*, 435[M^++2]*. Anal. Calcd for $C_{18}H_{10}BrClN_2S_2$: C, 49.84; H, 2.32; N, 6.46. Found: C, 49.78; H, 2.27; N, 6.40.

*4.7.7. 5-(5-(5-(5-Bromothiophen-2-yl)pyridin-3-yl)thiophen-2-yl)-2-fluoropyridine (**10c**).* Starting from 3,5-bis(5-bromothiophen-2-yl) pyridine **7a** (0.50 g, 1.25 mmol) and 6-fluoropyridin-3-yl boronic acid **8c** (0.62 g, 4.37 mmol) and following the general procedure the subproduct **10c** was obtained as a yellow solid (0.17 g, 40%). Mp: 138–140 °C. IR (KBr disc): 2922, 1581, 1494, 1451, 1264, 801 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.79 (d, 1H, $H_{2''}$, J=1.9 Hz), 8.70 (d, 1H, $H_{6''}$, J=1.9 Hz), 8.50 (d, 1H, H_6, J=1.9 Hz), 8.03–7.98 (dd, 1H, H_3, J=1.9, 7.8 Hz), 7.93 (dd, 1H, $H_{4''}$, J=1.9, 3.9 Hz), 7.42 (d, 1H, $H_{3'''}$, J=3.9 Hz), 7.34 (d, 1H, $H_{4'''}$, J=3.9 Hz), 7.19 (d, 1H, $H_{4'}$, J=3.9 Hz), 7.11 (d, 1H, $H_{3'}$, J=3.9 Hz), 7.01–6.99 (dd, 1H, H_4, J=1.9, 8.7 Hz). ^{13}C NMR ($CDCl_3$) δ 162.12 (C_2), 145.42 ($C_{2''}$), 145.30 ($C_{6''}$), 144,58 (C_6), 144.42 (C_4), 140.98 ($C_{5''}$), 139.98 ($C_{3''}$), 138.41 ($C_{2'}$), 138.33 ($C_{5'}$), 131.22 ($C_{4''}$), 130.18 (C_5), 130.01 ($C_{2'''}$), 129.45 ($C_{4'''}$), 125.87 ($C_{3'''}$), 125.45 ($C_{4'}$), 125.08 ($C_{3'}$), 113.48 ($C_{5'''}$), 109.72 (C_3). MS (EI): 417[M^+]*, 419 [M^++2]*. Anal. Calcd for $C_{18}H_{10}BrFN_2S_2$: C, 51.81; H, 2.42; N, 6.71. Found: C, 51.67; H, 2.32; N, 6.58.

*4.7.8. 5-(5-(5-(5-Bromothiophen-2-yl)pyridin-3-yl)thiophen-2-yl)-2-methoxypyridine (**10d**).* Starting from 3,5-bis(5-bromothiophen-2-yl)pyridine **7a** (0.46 g, 1.15 mmol) and 6-methoxypyridin-3-yl boronic acid **8d** (0.61 g, 4.01 mmol) and following the general procedure the subproduct **10d** was obtained as a yellow solid (0.17 g, 42%). Mp: 94–96 °C. IR (KBr disc): 2949, 1605, 1502, 1464, 1287, 1263, 1022, 797 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.79 (d, 1H, $H_{2''}$, J=2.9 Hz), 8.68 (d, 1H, $H_{6''}$, J=1.9 Hz), 8.46 (d, 1H, H_6, J=1.9 Hz), 7.93–7.92 (dd, 1H, $H_{4''}$, J=1.9, 3.9 Hz), 7.83–7.80 (dd, 1H, H_4, J=1.9, 8.7 Hz), 7.79 (d, 1H, H_3, J=2.9 Hz), 7.39 (d, 1H, $H_{4'''}$, J=3.9 Hz), 7.11 (d, 1H, $H_{3'''}$, J=3.9 Hz), 6.81 (d, 1H, $H_{4'}$, J=8.7 Hz), 6.66 (d, 1H, $H_{3'}$, J=8.7 Hz), 3.98 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 164.08 (C_2), 145.16 ($C_{2''}$), 144.73 ($C_{6''}$), 143,88 (C_6), 141.98 ($C_{2'''}$), 141.05 ($C_{2'}$), 138.29 ($C_{5'}$), 131.22 (C_4), 130.61 ($C_{3''}$), 130.07 ($C_{5''}$), 129.48 ($C_{4''}$), 127.71 ($C_{4'''}$), 125.80 ($C_{3'''}$), 125.08 ($C_{4'}$), 124.10 ($C_{3'}$), 123.50 (C_5), 111.17 ($C_{5'''}$), 111.04 (C_3), 53.77 (OCH_3). MS (EI): 428[M^+]*, 430 [M^++2]*, 432[M^++4]*. Anal. Calcd for $C_{19}H_{13}BrN_2S_2O$: C, 53.15; H, 3.05; N, 6.52. Found: C, 53.06; H, 2.97; N, 6.47.

Supplementary data

Crystallographic data (excluding structure factors) for the structures of compounds **6b** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 816509. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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