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Using halo (het) arylboronic species to achieve synthesis of foldamers as protein–protein interaction disruptors*

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Abstract: Protein–protein interactions (PPIs) play a central role in all biological processes and have been the focus of intense investigations from structural molecular biology to cell biology for the majority of the last two decades and, more recently, are emerging as important targets for pharmaceuticals. A common motif found at the interface of PPIs is the α-helix, and apart from the peptidic structures, numerous nonpeptidic small molecules have been developed to mimic α-helices. The first-generation terphenyl scaffold is able to successfully mimic key helix residues and disrupt relevant interactions, including Bcl-xL-Bak interactions that are implicated in apoptosis mechanism. These scaffolds were designed and evaluated in silico. Analysis revealed that substituents on aromatic scaffolds can efficiently mimic side-chain surfaces. Unfortunately, the literature describes a long and difficult procedure to access these aromatic-based scaffolds. The search for new simpler methodology is the aim of the research of our medicinal chemistry team. On the basis of structural requirements, we developed a program concerning the synthesis of new oligo(het)aryl scaffolds produced by iterative couplings of boronic species (*garlanding*) in which substituents on rings project functionality in spatial orientations that mimic residues of an α-helix.

Keywords: α-helix mimetic; C–C bond formation; cross-coupling reactions; foldamers; medicinal chemistry; palladium; protein interactions; pyridine; thiophene.

PROTEIN–PROTEIN INTERACTIONS

Protein–protein interactions (PPIs) take place between two identical or dissimilar proteins at their domain interfaces that regulate the function of the protein complex [1]. Surfaces involved in these interactions are flat and often lacking in suitable pockets for small molecules to bind [2]. But it is now well established that for robust modulation of a PPI, a molecule is not required to cover the large protein–protein contact surface in full. In fact, a small molecule needs only to interact with a subset of a few amino acids, which is called a hot-spot, where most of the PPI binding energy is localized. Binding of a ligand to a hot-spot competes with the original protein partner of the PPI, resulting in disruption of function (Fig. 1).

PPI domains play an important role in many biological pathways. For example, Bcl-2 family proteins constitute a critical control point for the regulation of apoptosis. All these proteins are character-

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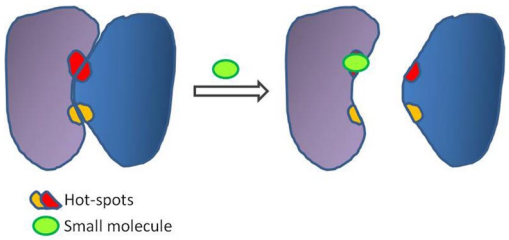


Fig. 1 Hot-spot approach to protein–protein inhibition.

ized by exhibiting at least one of the four highly conserved Bcl-2 homology domains (BH1-BH4). Some proteins promote apoptosis (hereafter referred to as pro-apoptotic) and others prevent it (anti-apoptotic). The direction or not to apoptosis in a cell is defined as the relative ratio between pro-apoptotic proteins (like Bax or Bak) and anti-apoptotic proteins (like Bcl-2 or Bcl-xL). The cell death activity is due, in main part, to the dimerization of anti-apoptotic with pro-apoptotic members of the Bcl-2 family.

In normal cell conditions, pro-apoptotic and anti-apoptotic proteins bind and neutralize them. After a death signal, homodimerization of pro-apoptotic proteins allows the release of cytochrome c, which leads to caspase pathway activation and cell death.

In response to prosurvival stimuli, anti-apoptotic proteins undergo a conformational change that leads to sequester pro-apoptotic proteins, compromising cell capability to undergo apoptosis.

What is the nature of interactions between pro-apoptotic and anti-apoptotic proteins? And how can we disrupt these interactions?

These interactions are based on a BH3 domain, common to all family members, also called the essential death domain. The NMR-derived structure of the Bcl-xL/Bak BH3 domain complex indicated that the Bak peptide is an amphiphilic α-helix that interacts with Bcl-xL by projecting its side chains of Val74, Leu78, and ILe81, on one face of the helical backbone, into a hydrophobic cleft of Bcl-xL (Fig. 2).

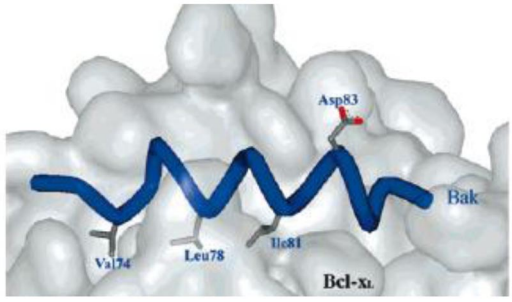


Fig. 2 Interface of the Bcl-xL/Bak BH3 domain complex [3].

The design of small-molecule mimics of the BH3 domain of the pro-apoptotic members of the Bcl-2 family can be considered as an appealing strategy for designing new anticancer agents. These small molecules have to adopt a staggered conformation and project appropriately positioned substituents in a manner similar to an α-helix.

Foldamers are synthetic non-natural oligomers that adopt well-defined conformations reminiscent of an α-helix to reproduce many of the structural features of α-helices and replicate the role of the α-helix in helix-mediated PPIs [4].

Mimicking an α-helix can be achieved in three ways: (1) a type I mimetic, which reproduces the local topography of the helix, where covalent constraints are used to stabilize a conformation closed to α-helices; (2) a type II mimetic, which is a functional mimetic that need not mimic the structure of the original helix (it is typically small natural molecules); (3) a type III mimetic (Fig. 3), which represents a topographical mimetic where positions of key functional motifs in an identical spatial orientation match those presented by the original α-helix [5].

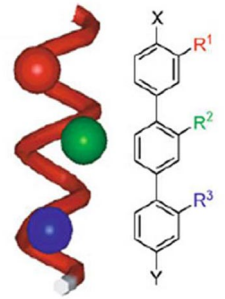


Fig. 3 Type III mimetic foldamer: α-helix illustrating *i*, *i* + 3, and *i* + 7 side chains and generic structure of the terphenyl scaffold.

Numerous nonpeptide small molecules mimicking α-helices have been published in the literature (type III) (Fig. 4).

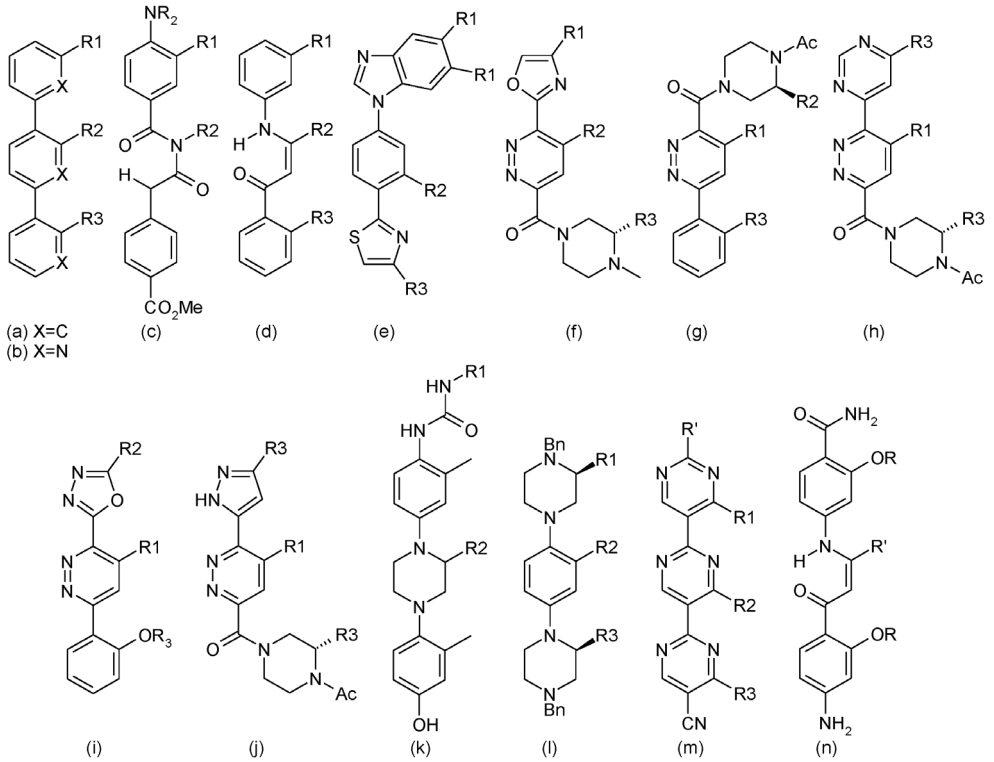


Fig. 4 Examples of nonpeptide small-molecule α-helix mimetic.

Early contributions from Hamilton and co-workers 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 α-helix (Fig. 4, compound **a**) [6].

Then, efforts have been exerted to decrease overall compound hydrophobicity as well as to reduce the synthetic complexity of teraryl-based α-helix mimetics. This has been accomplished either by increasing the heteroaromatic nature of the core aryl units (Fig. 4, compounds **b** and **e** to **l**) or by replacing some of the covalent character of the scaffold with a hydrogen-bonding aromatic ring isostere (Fig. 4, compounds **c**, **d**).

The structure of a 5-6-5 imidazole-phenyl-thiazole scaffold (**e**) [7] bearing additional heteroaromatic functionality has recently been reported. Rebek and co-workers have also published a series of pyridazine-based scaffolds (**f** to **j**) with a variety of aromatic and heteroaromatic peripheral groups [8]. Additionally, two piperazine-based scaffolds (**k** [9], **l** [10]) have been reported: both display functional groups in a manner to mimic three or four α-helical side-chain positions. Otherwise, it has shown that hydrogen-bonding functional groups such as an enaminone (**d**) [11] or benzoylurea (**c**) [12] can replace 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 (**m**) [13] that are structurally analogous to α-helix mimics. Hamilton et al. have constructed a new series of *i*, *i* + 3 (or *i* + 4), *i* + *7* α-helix mimics based on the enaminone scaffold (**n**) [14] which represent a step forward in the pursuit of idealized monofacial α-helix mimetics.

RESULTS AND DISCUSSION

Among all of these compounds, we are especially interested in Hamilton and co-workers' oligophenyl foldamer works [Figs. 5 (1) and (2)]. Hamilton studied terpyridyl scaffolds (3) and predicted a better percentage of helicity for terpyridyl than for terphenyl compounds (2) [15].

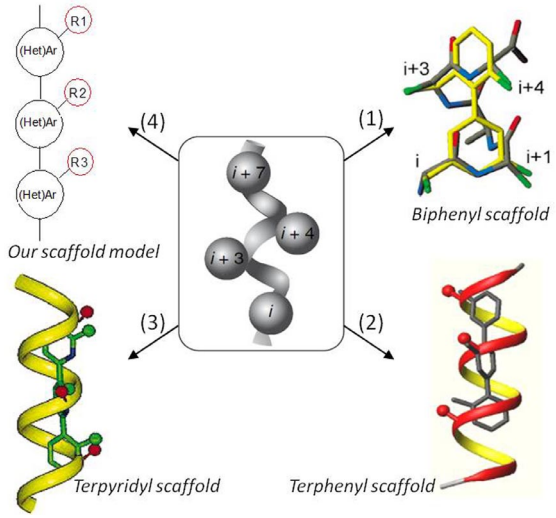


Fig. 5 Jacoby, Hamilton, and Che scaffold models as α-helix mimics.

Chemical methodology

Our proposed synthesis of the oligomeric pyridyl system [Fig. 5 (4)] as peptidomimetics involves three approaches of Jacoby, Hamilton, and Che and uses the "garlanding" concept [16], 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 specializes in the preparation of boronic species and in the study of their ability to be good coupling partners [17].

We will highlight the subtle role that the conformation of oligo(het)arylpyridines can play in adopting helical or elongated conformations. Here, we describe the synthesis of oligopyridyl-, oligophenylpyridyl-, and oligothienylpyridyl garlands and present preliminary results showing that these compounds could act as α-helix mimetics.

Garlanding concept

The chemical strategy named the "garlanding" concept (Fig. 6) highlights the importance both of the regioselective control in the coupling reaction and of the choice of the coupling partners. This approach allows us to build a linear chain from one ring by the implementation of iterative cross-coupling reactions between boronic species and dihalogenated compounds.

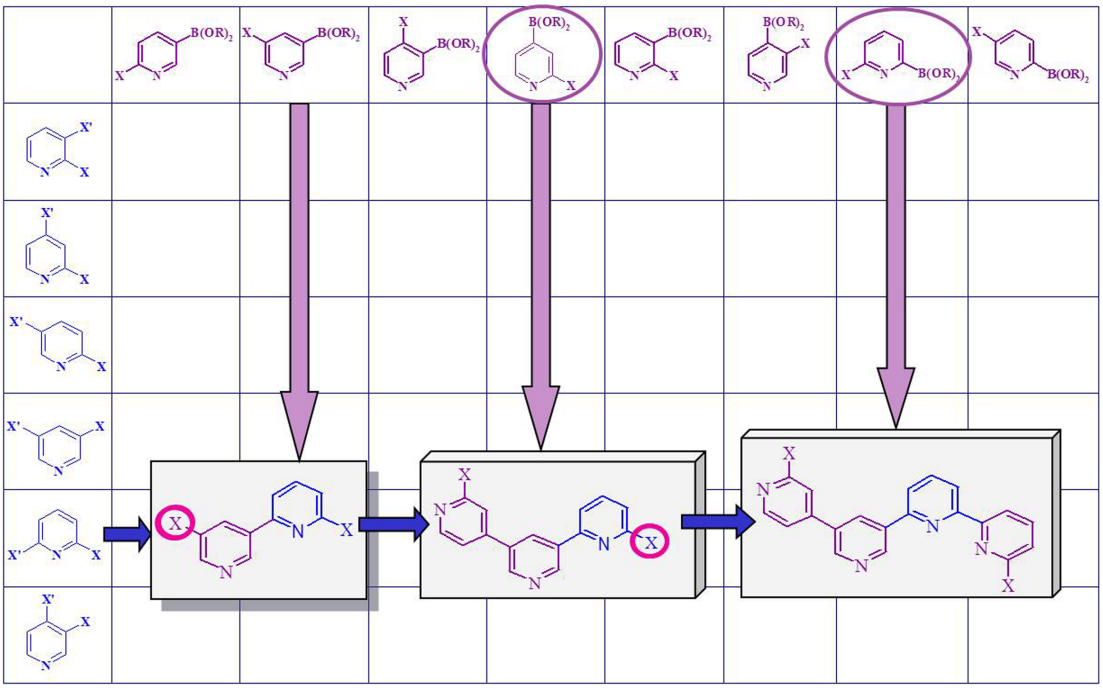


Fig. 6 Garlanding concept using bifunctional (het)arylboronic species and dihalopyridines.

Indeed, this methodology takes advantage of the nature as well as the position of the halogen atom on the ring. In addition, it uses bifunctional (het)arylboronic acids that represent a highly promising platform for this type of synthetic strategy.

In details (Fig. 6), from the 5-halopyridin-3-ylboronic acid in the presence of the 2,6-dihalopyridine, it is possible to produce the 6,5'-dihalo-[2,3']bipyridine. The residual halogen may again be involved in a second cross-coupling reaction with another boronic acid to give only the 6,2"-dihalo-[2,3';5',4"]terpyridine. In the same way, the residual halogen of this dihaloterpyridine may be engaged anew in a third cross-coupling reaction to give the 6,2"'-dihalo-[2,2';6',3";5",4"']quaterpyridine. And so on... So to implement this strategy, we need to synthesize the boronic species and control the regioselectivity of the cross-coupling reaction.

Boronic species synthesis

To produce several boronic species, two methodologies have been considered: halogen-metal exchange and *ortho*lithiation (Fig. 7) [17].

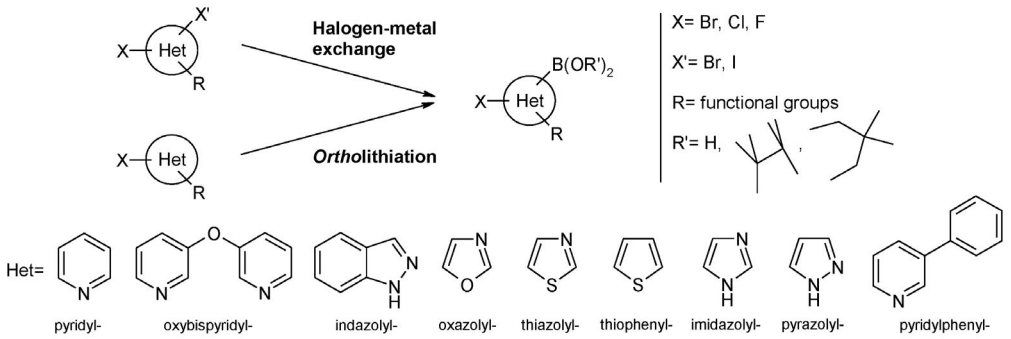
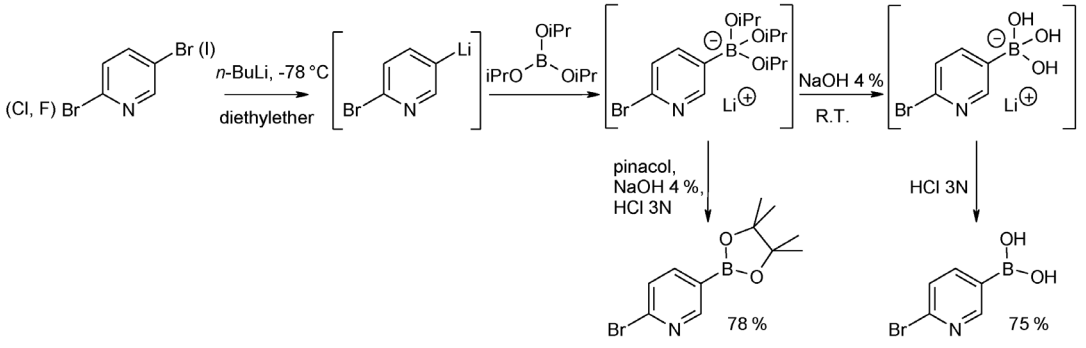


Fig. 7 Halogen-metal exchange and *ortho*lithiation approaches.

Halogen-metal exchange

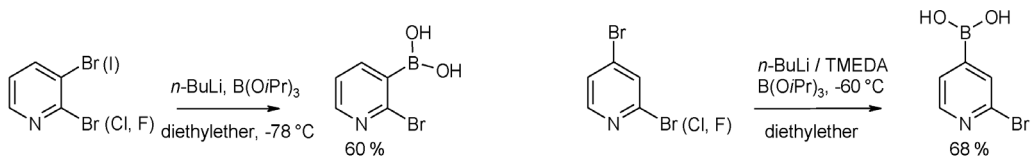
From commercially available 2,5-dibromopyridine, well known for the difference of reactivity between its two bromine atoms, a bromine–lithium exchange is carried out in ether at –78 °C with *n*-butyllithium followed by the reaction with triisopylborate to give 6-bromopyridin-3-ylboronic acid. Considering the amphoteric character of acid, we studied the direct formation of its pinacol ester, adapting the method of Coudret [18] who described the synthesis of 4-pyridylboronic pinacol ester in 74 % yield starting from 4-iodopyridine. These same conditions applied to 2,5-dibromopyridine, giving the corresponding pinacol ester in a one-pot procedure (78 % yield) (Scheme 1).



Scheme 1 6-Bromopyridin-3-ylboronic acid and pinacol ester.

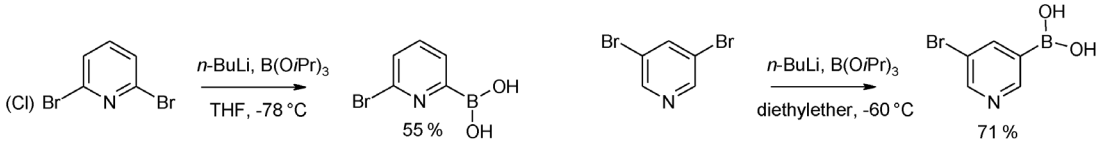
In order to generalize this method and considering that the nature of the halogen atoms should not considerably modify the reactivity of the system, we decided to prepare boronic species from the other 2,5-dihalopyridines (chloro-, iodo-, and fluoro- analogous).

In the same way, from 2,3- and 2,4-dihalopyridines, we successfully obtained corresponding boronic acids (or esters) (Scheme 2).



Scheme 2 2-Bromopyridin-3-yl- and 2-bromopyridin-4-yl boronic acids.

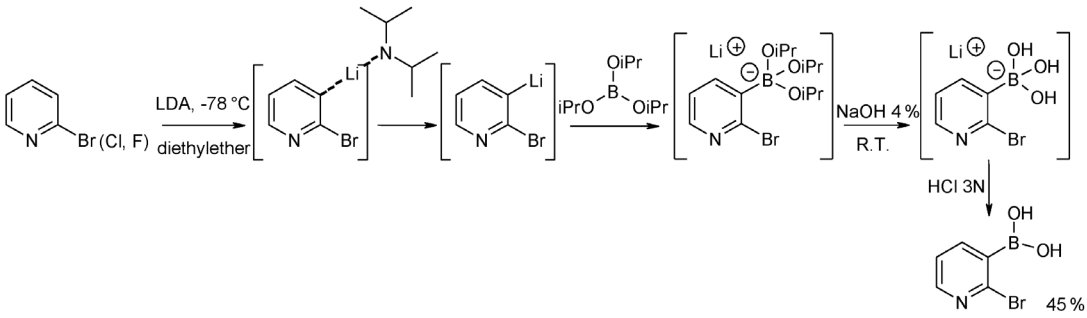
Even if the 2,6- and 3,5-dibromopyridines possess two potential sites for bromine lithium exchange, only monolithiation is observed by reverse addition of 2,6- or 3,5-dibromopyridines to *n*-butyllithium (Scheme 3).



Scheme 3 2-Bromopyridin-6-yl- and 3-bromopyridin-5-yl boronic acids.

*Ortho*lithiation

Direct *ortho*lithiation (Directed *ortho*Metalation, DoM) described using lithium diisopropylamide from 2-bromopyridine in ether at –60 °C, followed by quenching with triisopylborate, gives regioselectively the corresponding boronic acid (Scheme 4). Work at low temperature allows good control of the regioselectivity of the reaction.



Scheme 4 2-Bromopyridin-6-yl- and 3-bromopyridin-5-yl boronic acids.

A DoM on 4-chloropyridine is performed to obtain with great regioselectivity 4-chloropyridin-3-yl boronic acid (Scheme 5). In the case of 3-bromopyridine, DoM has been studied by Gribbe [19] (LDA, THF, –78 °C). In our case, we performed the metalation in ether at –95 °C by 1 equiv of LDA. These conditions resulted in the regioselective lithiation of the C-4 position due to the relative acidity of C-4 vs. C-2, affording the 3-bromo-4-lithiopyridine. Quenching this anion at low temperature with triisopylborate gave the expected 3-bromopyridin-4-yl boronic acid. The directed and regioselective deprotonation of 3-bromopyridine is much more difficult (than 3-chloropyridine or 3-fluoropyridine) because of the ability of bromine to undergo halogen metal exchange; it is the reason why the temperature is lowered to –95 °C.

In these two cases, performing the in situ transesterification with pinacol gives the corresponding ester.

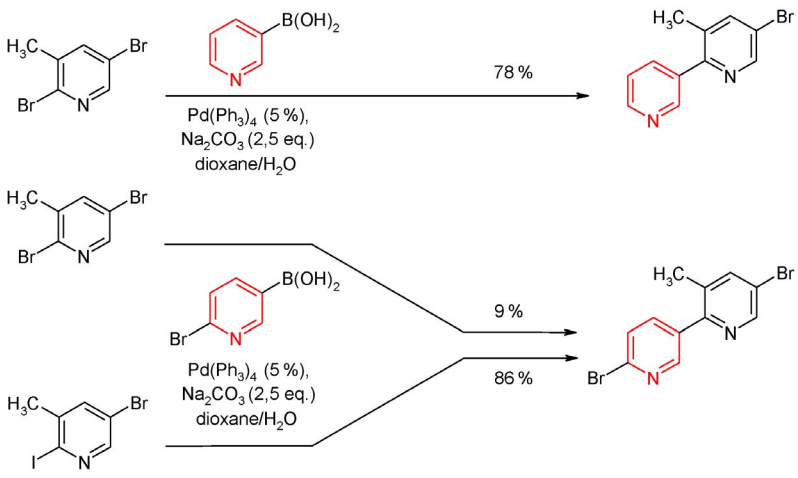
Scheme 5 4-Chloropyridin-3-yl- and 3-bromopyridin-4-yl boronic acids.

All these boronic species can be engaged in palladocatalyzed cross-coupling reactions like the Suzuki–Miyaura reaction to create C–C bonds [20] and thus respond to our objectives to enchain (het)aromatic rings to each other. Moreover, in our strategy, we must control the regioselectivity of cross-coupling reactions that could increase their yields.

Control of the regioselectivity

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 [21]. Even if the α-position of the pyridine ring is more sensitive to a cross-coupling reaction than the β-position, the inevitable formation of byproducts is due to the poor selectivity of the reaction especially when the two halogens are identical.

For example (Scheme 6), if the cross-coupling reaction of 2,5-dibromopicoline with 3-pyridylboronic acid is considered, the resulting bipyridine is obtained with good yields (78 %). If the same reaction is applied with 6-bromopyridin-3-ylboronic acid, the resulting dibromobipyridine is produced with low yields because of the presence of several byproducts. To overcome this lack of selectivity, 5-bromo-2-iodopicoline is used and the dibromobipyridine is achieved with excellent yields because of the high regioselectivity of the cross-coupling reaction.

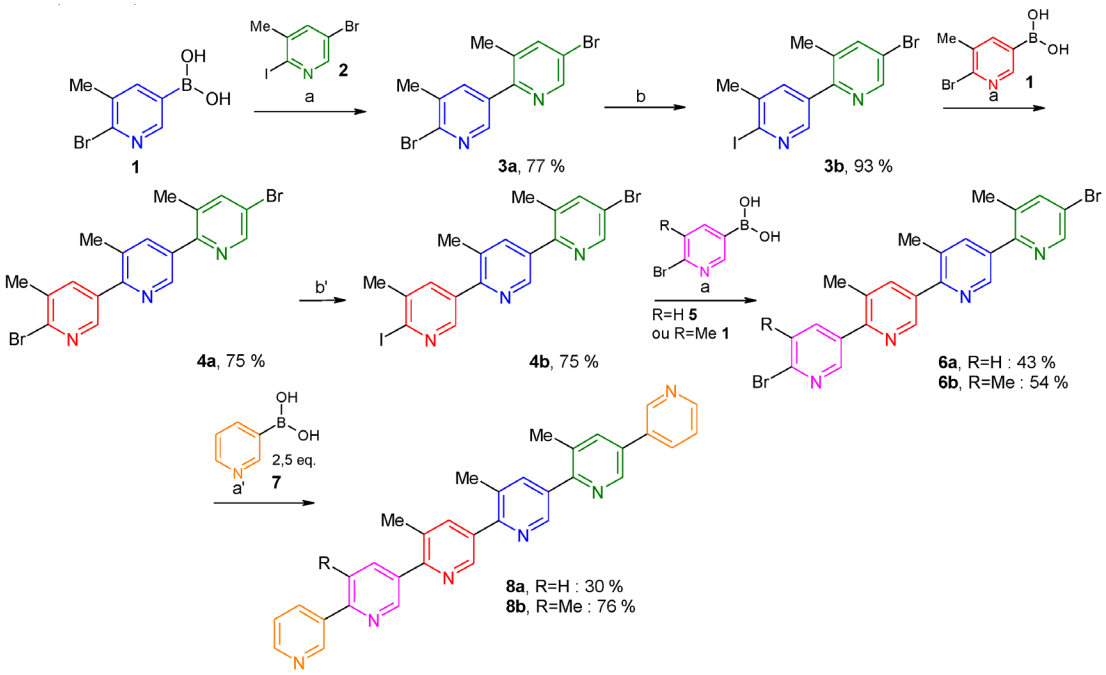


Scheme 6 Example of control of the regioselectivity.

Synthesis of oligopyridyl foldamers

Using these observations, we recently published the synthesis of the 5,6'-dibromo-3,5'-dimethyl-[2,3']bipyridine **3a** [21] from 6-bromo-5-methyl-pyridin-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 result in a gain in regioselectivity for subsequent reactions to achieve the preparation of new quaterpyridines **6a,b** and sexipyridines **8a,b** with satisfactory yields (Scheme 7).



Scheme 7 Preparation of compounds **3–8**. Reagents and conditions: a- Na_2CO_3 2.5 equiv, $Pd(PPh_3)_4$ 5 %, 1,4-dioxane, rfx 20 h; a'- Na_2CO_3 5 equiv, $Pd(PPh_3)_4$ 10 %, 1,4-dioxane, rfx 20 h; b- AcCl 2 × 1.5 equiv, NaI 2 × 2.5 equiv, CH_3CN, rfx, 2 × 4 h; b'- AcCl 2 × 2.5 equiv, NaI 2 × 3.5 equiv, CH_3CN, rfx, 2 × 4 h.

Synthesis of oligopyridylthienyl foldamers

Our second model alternates pyridines and thiophenes to determine the influence of the thiophene 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 α-helix.

Very recently, we described the synthesis of new five-unit thienylpyridyl compounds **9a–d**, obtained from their three-unit congeners **10** (Fig. 8). 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 **11**. Secondly, we have functionalized these compounds by a reaction of bromination and the resultant bis-bromothienylpyridines have been engaged in an 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 **9a–d** [22].

A similar work concerning oligophenylpyridyl foldamers is currently under investigations [23].

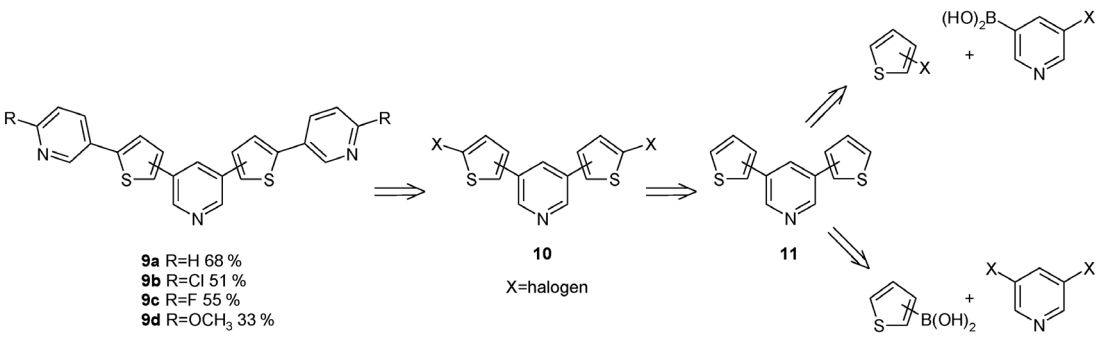


Fig. 8 Production of a new library of thienylpyridyl oligomers.

CONCLUSION: ENCOURAGING PRELIMINARY RESULTS

The assessment of preliminary studies is very encouraging considering the results of X-ray diffraction and NMR (nuclear Overhauser effect spectroscopy) analyses [24]. We observed an alignment of (het)arylpyridyl foldamers with an α-helix.

A superposition of the X-ray structure of methylquaterpyridines on an ideal alanine α-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. 9) as it is expected for a type III mimetic where positions of key functional motifs match those presented by the original α-helix.

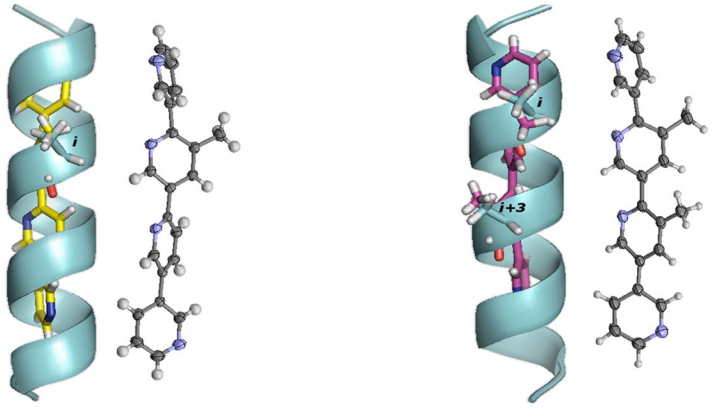


Fig. 9 The superposition of the X-ray structure of methylquaterpyridines on an α-helix.

The superposition of the X-ray structure of a three-unit thienylpyridyl compound with an α-helix shows that this garland aligns well with a turn of the α-helix. Each unit fits to a position of one residue in the α-helix. For this type of scaffold, three units can cover one helix turn (3–4 residues) (Fig. 10A). 3,5-(Dithiophen-3-yl)pyridine reproduces the local topography of an α-helix, which is expected for a type I foldamer. Unfortunately, we have not 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 α-helix mimetic as expected in type III foldamer (Fig. 10B) [22].

Results of biological evaluation are encouraging since these compounds have properties of PPI disruptors within the Bcl-2 protein family.

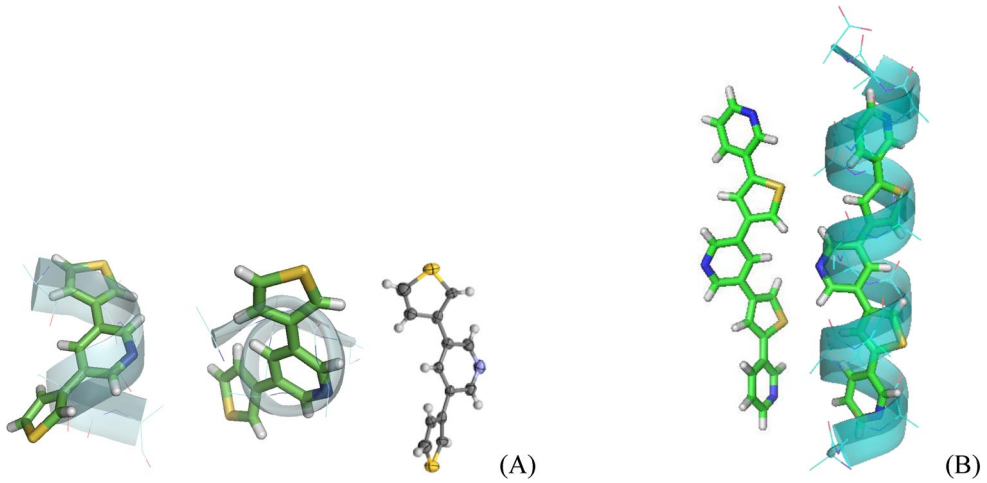


Fig. 10 (A) Representation of the alignment of the 3,5-(dithiophen-3-yl)pyridine with an α-helix, based on the crystal structure; (B) predicted structure of a five-unit thienylpyridyl compound and its overlay with an α-helix.

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REFERENCES

1. G. Zinzalla, D. E. Thurston. *Future Med. Chem.* **1**, 65 (2009).
2. T. Clackson, J. A. Wells. *Science* **267**, 383 (1995).
3. H. Yin, G. I. Lee, K. A. Sedey, O. Kutzki, H. S. Park, B. P. Orner, J. T. Ernst, H. G. Wang, S. M. Sebti, A. D. Hamilton. *J. Am. Chem. Soc.* **127**, 10191 (2005).
4. S. H. Gellman. *Acc. Chem. Res.* **31**, 173 (1998).
5. A. S. Ripka, D. H. Rich. *Curr. Opin. Chem. Biol.* **2**, 441 (1998).
6. B. P. Orner, J. T. Ernst, A. D. Hamilton. *J. Am. Chem. Soc.* **123**, 5382 (2001).
7. C. G. Cummings, N. T. Ross, W. P. Katt, A. D. Hamilton. *Org. Lett.* **11**, 25 (2009).
8. (a) S. M. Biros, L. Moisan, E. Mann, A. Carella, D. Zhai, J. C. Reed, J. Rebek. *Bioorg. Med. Chem. Lett.* **17**, 4641 (2007); (b) A. Volonterio, L. Moisan, J. Rebek. *Org. Lett.* **9**, 3733 (2007).
9. P. Maity, B. Konig. *Org. Lett.* **10**, 1473 (2008).
10. P. Restorp, J. Rebek. *Bioorg. Med. Chem. Lett.* **18**, 5909 (2008).
11. J. M. Rodriguez, A. D. Hamilton. *Tetrahedron Lett.* **47**, 7443 (2006).
12. J. M. Rodriguez, A. D. Hamilton. *Angew. Chem., Int. Ed.* **46**, 8614 (2007).
13. L. Anderson, M. Zhou, V. Sharma, J. M. McLaughlin, D. N. Santiago, F. R. Fronczek, W. C. Guida, M. L. McLaughlin. *J. Org. Chem.* **75**, 4288 (2010).
14. M. J. Adler, A. D. Hamilton. *J. Org. Chem.* **76**, 7040 (2011).

15. (a) G. T. Bourne, D. J. Kuster, G. R. Marshal. *Chem.—Eur. J.* **16**, 8439 (2010); (b) E. Jacoby. *Bioorg. Med. Chem. Lett.* **12**, 891 (2002); (c) J. T. Ernst, J. Becerril, H. S. Park, H. Yin, A. D. Hamilton. *Angew. Chem., Int. Ed.* **42**, 535 (2003); (d) J. T. Ernst, O. Kutzki, A. K. Debnath, S. Jiang, H. Lu, A. D. Hamilton. *Angew. Chem., Int. Ed.* **41**, 278 (2002); (e) O. Kutzki, H. S. Park, J. T. Ernst, B. P. Orner, H. Yin, A. D. Hamilton. *J. Am. Chem. Soc.* **124**, 11838 (2002); (f) Y. Che, B. R. Brooks, G. R Marshall. *J. Comp.-Aided Mol. Des.* **20**, 109 (2006); (g) Y. Che, G. R. Marshall. *Expert Opin. Ther. Targets* **12**, 1 (2008).
16. (a) A. Bouillon, A. S. Voisin, A. Robic, J. C. Lancelot, V. Collot, S. Rault. *J. Org. Chem.* **68**, 10178 (2003); (b) A. S. Voisin-Chiret, A. Bouillon, G. Burzicki, M. Célant, R. Legay, H. El-Kashef, S. Rault. *Tetrahedron* **65**, 607 (2009).
17. (a) A. Bouillon, J. C. Lancelot, V. Collot, P. R. Bovy, S. Rault. *Tetrahedron* **58**, 2885 (2002); (b) A. Bouillon, J. C. Lancelot, V. Collot, P. R. Bovy, S. Rault. *Tetrahedron* **58**, 3323 (2002); (c) A. Bouillon, J. C. Lancelot, V. Collot, P. R. Bovy, S. Rault. *Tetrahedron* **58**, 4369 (2002); (d) A. Bouillon, J. C. Lancelot, V. Collot, P. R. Bovy, S. Rault. *Tetrahedron* **59**, 10043 (2003); (e) T. Cailly, F. Fabis, A. Bouillon, S. Lemaître, J. Sopková-de Oliveira Santos, S. Rault. *Synlett* **1**, 53 (2006); (f) N. Primas, C. Mahatsekake, A. Bouillon, J. C. Lancelot, J. Sopková-de Oliveira Santos, J. F. Lohier, S. Rault. *Tetrahedron* **64**, 4596 (2008); (g) N. Primas, A. Bouillon, J. C. Lancelot, H. El-Kashef, S. Rault. *Tetrahedron* **65**, 5739 (2009); (h) N. Primas, A. Bouillon, J. C. Lancelot, S. Rault. *Tetrahedron* **65**, 6348 (2009); (i) N. Primas, A. Bouillon, S. Rault. *Tetrahedron* **66**, 8121 (2010); (j) A. Caruso, A. S. Voisin-Chiret, J. C. Lancelot, M. S. Sinicropi, A. Garofalo, S. Rault. *Heterocycles* **71**, 2203 (2007).
18. C. Coudret. *Synth. Commun.* **26**, 3543 (1996).
19. G. W. Gribble, M. G. Saulnier. *Tetrahedron Lett.* **21**, 4137 (1980).
20. (a) N. Miyaura, A. Suzuki. *Chem. Rev.* **7**, 2457 (1995); (b) A. Suzuki. *J. Organomet. Chem.* **576**, 147 (1999).
21. (a) G. Burzicki, A. S. Voisin-Chiret, J. Sopková-de Oliveira Santos, S. Rault. *Tetrahedron* **65**, 5413 (2009); (b) G. Burzicki, A. S. Voisin-Chiret, J. Sopková-de Oliveira Santos, S. Rault. *Synthesis* **16**, 2804 (2010).
22. M. De Giorgi, A. S. Voisin-Chiret, J. Sopková-de Oliveira Santos, F. Corbo, C. Franchini, S. Rault. *Tetrahedron* **67**, 6145 (2011).
23. (a) A. S. Voisin-Chiret, M. Muraglia, G. Burzicki, S. Perato, F. Corbo, J. Sopková-de Oliveira Santos, C. Franchini, S. Rault. *Tetrahedron* **66**, 8000 (2010); (b) S. Perato, A. S. Voisin-Chiret, J. Sopková-de Oliveira Santos, R. Legay, H. Oulyadi, R. Bureau, S. Rault. *Tetrahedron* **68**, 1910 (2012).
24. J. Sopková-de Oliveira Santos, A. S. Voisin-Chiret, G. Burzicki, L. Sebaoun, M. Sebban, J. F. Lohier, R. Legay, H. Oulyadi, R. Bureau, S. Rault. *J. Chem. Inf. Model.* **52**, 429 (2011).

