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Synthesis and helical self-organization of achiral polyheterocyclic pyridine–pyrimidine strands

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Summary — The synthesis of the polyheterocyclic pyridine–pyrimidine strands **1b**, **2b** and **3** is described. These molecules have been designed so that they take up a curled form resulting in an extended helical conformation (two turns for **3**) both in solution and in the solid state. As a consequence, special features are observed such as dynamic interconversion between the enantiomeric helical forms and pyridine excimer fluorescence. The spontaneous formation of the helical structure amounts to a molecular self-organization process directed by the structure of the polyheterocyclic strand and conformational information encoded in it.

polyheterocyclic strand / helicity / self-organization / pyridine excimer

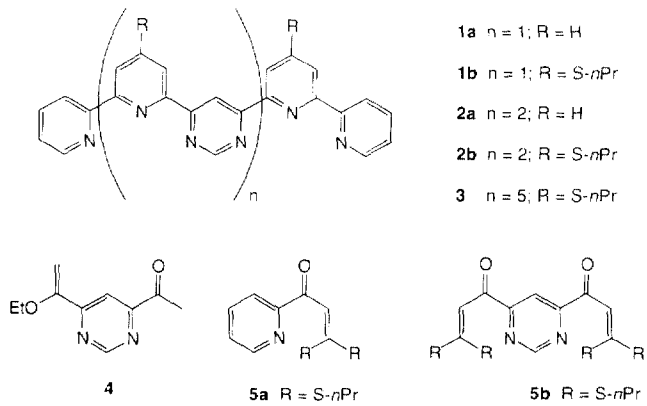
Résumé — Synthèse et autoorganisation en hélice de chaînes polyhétérocycliques pyridine–pyrimidine achirales. La synthèse des molécules polyhétérocycliques linéaires **1b**, **2b** et **3** formées par une séquence d'unités pyridine et pyrimidine a été réalisée. Ces molécules ont été conçues de sorte à ce qu'elles adoptent une forme enroulée résultant en une structure hélicoïdale (deux tours dans le cas de **3**) à la fois en solution et à l'état solide. En conséquence, des propriétés particulières sont observées, comme par exemple l'interconversion dynamique des formes hélicoïdales énantiomériques et une fluorescence d'excimère. La formation spontanée d'une structure hélicoïdale représente un processus d'autoorganisation moléculaire dirigé par la structure du brin polyhétérocyclique et l'information conformationnelle qu'il contient.

molécule polyhétérocyclique / hélicité / autoorganisation / excimère

Introduction

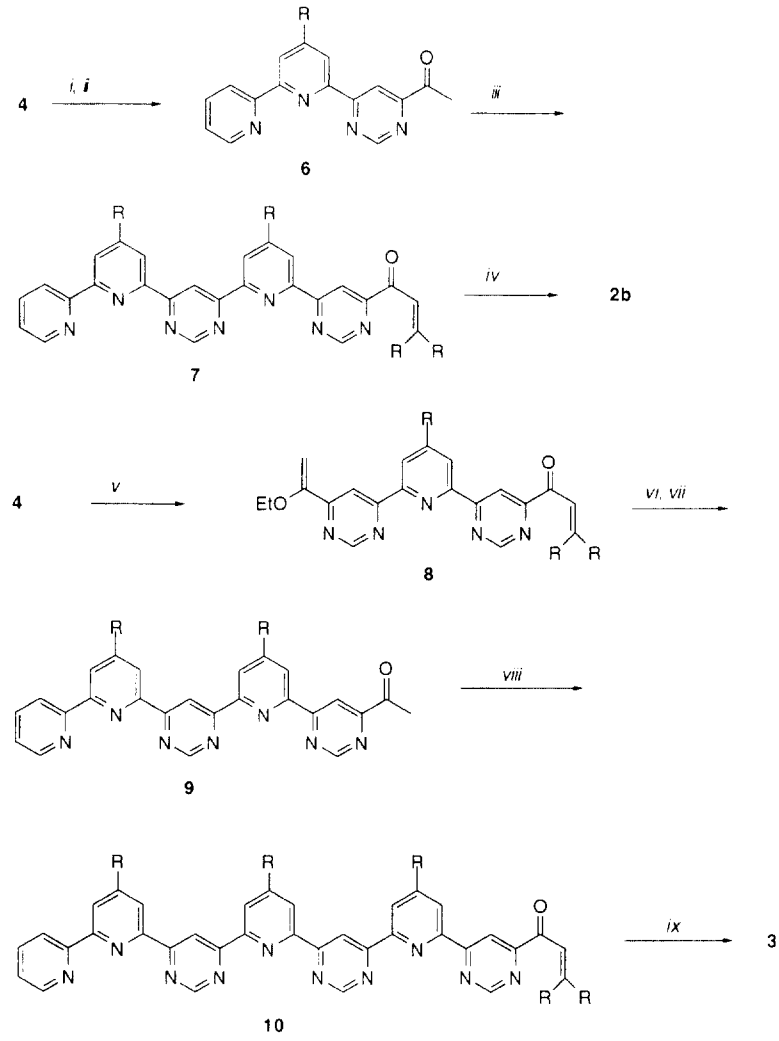
The intrinsic geometrical features of helical structures, as well as their ubiquity and importance in biological systems, has made the understanding of the factors governing their formation and structural characteristics particularly attractive and significant. Helicity in numerous organic molecules, hydrogen-bonded polymers, as well as proteins and nucleic acids, is a consequence of carbon asymmetry in the backbone components [1, 2]. In contrast, the generation of double and triple helical structures (helicates) through the self-assembly of achiral linear ligands with specific metal ions is based on the design of ligands encoding the necessary structural information [3]. The spontaneous formation of helical structures from achiral linear strands can be achieved through the interplay of intramolecular non-bonded interactions within a molecule[1].

We have designed a new structural motif based on the known preference of 2,2′-bipyridine for a *transoid* conformation that leads to the formation of helical structures from achiral linear molecules [5]. It relies on the combination of three basic features: (a) an alternating sequence of pyridine and pyrimidine units, (b) the linkage of these units at specific positions, (c) the *transoid* conformation adopted by the single bonds linking the units. The combination of these features in a series of molecules comprising alternating pyridine–pyrimidine heterocycles (compounds **1**, **2** and **3**) serves to demonstrate the generality of the concept. Com-



[1] In a recent paper, the preference for a *cisoid* orientation in *N*-methyl urea was shown to impart a helical structure to oligomeric strands of diphenylurea [4].

* Correspondence and reprints



Scheme 1. Reagents: (i) t-BuOK, **5a**, THF (RT), NH_4OAc (36%); (ii) HCl_{aq} (70%); (iii) *t*-BuOK, **5b**, THF (RT), NH_4OAc (47%); (iv) *t*-BuOK, 2-acetylpyridine, THF (RT), NH_4OAc (78%); (v) *t*-BuOK, **5b**, DMSO (RT), NH_4OAc (44%); (vi) *t*-BuOK, 2-acetylpyridine, THF (RT), NH_4OAc (53%); (vii) HCl_{aq} (70%); (viii) *t*-BuOK, **5b**, THF (RT), NH_4OAc (46%); (ix) *t*-BuOK, **9**, THF (reflux), NH_4OAc (47%).

pound **3**, composed of thirteen heterocycles, was recently reported to form a helical structure composed of two spiral turns both in the solid and in solution [6]. We now describe the synthesis and properties of these compounds. Their use in the construction of metallosupramolecular assemblies will be reported elsewhere.

Results

Synthesis of the polyheterocyclic strands **1b**, **2b** *and* **3**

The use of tin-mediated cross-coupling reactions (Stille coupling) was successfully applied to the synthesis of **1a** and **2a** [7], but extension of this methodology to the construction of longer helical segments is not straightforward. Furthermore, it was predicted that the presence of side chains would be desirable in larger molecules to enhance their solubility in organic solvents. For these reasons, alternative synthetic routes were explored, such as those resulting from the disconnection of a pyridine or pyrimidine heterocycle. The latter approach suffers from the fact that synthesis of pyrimidines from the corresponding β-diketone and urea results in the formation of 2-pyrimidinones that must then be reduced. In contrast, the synthesis of pyridines from ene-1,5-diones leads to the desired heterocycle without the need for additional transformation. Two well-established methodologies for the synthesis of substituted pyridines were developed independently by Potts [8] and Kröhnke [9]. Both make use of aryl- or alkylmethylketones as precursors and are particularly well-adapted to the preparation of 2,6-disubstituted pyridines. This approach has recently been applied to the synthesis of cyclosexipyridine [10].

These considerations led to the strategy outlined in scheme 1 for the synthesis of the polyheterocyclic strands **1b**, **2b** and **3**. The incorporation of substituents in the 4-position of the pyridine ring was expected to enhance solubility without interfering with helication, as these would lie on the exterior surface of the helix. The preparation of 4,6-diacetylpyrimidine from the corresponding dichloro derivative using 1-ethoxyvinyltributyltin has been described [11], and was adapted to a stepwise procedure in order to obtain the unsymmet-

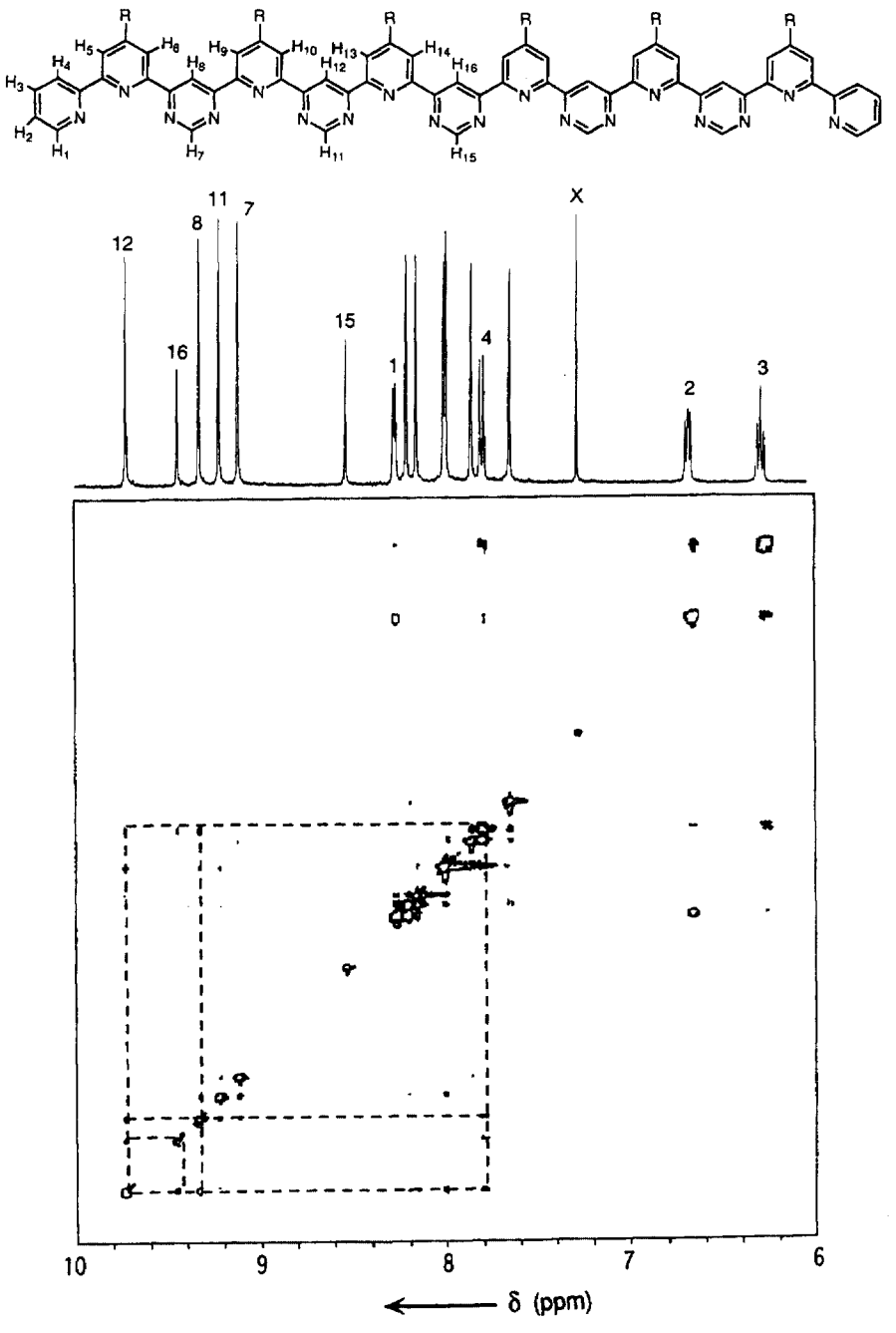


Fig 1. Aromatic portion of the ^{1}H NMR and ROESY spectrum of **3** in $CDCl_3$. Dashed lines indicate interactions between protons oriented towards the interior of the helix.

rically substituted pyrimidine **4**. Reaction of the latter with 3,3-bis(*n*-propylthio)-1-(2-pyridyl)prop-2-en-1-one **5a** followed by hydrolysis of the ethoxyvinyl group gives **6** in 25% yield. Monoaddition of **6** to **5b** forms **7** (47%), which can be used to obtain **2b** by reaction with 2-acetylpyridine (78%). Likewise, **1b** can be obtained in one step from **5b** and 2-acetylpyridine in 65% yield. Monoaddition of **4** to **5b** gives **8** (44%), a key component in the design of longer strands, combining a Michael acceptor group with a protected enolate in a triheterocyclic fragment. Its reaction with 2-acetylpyridine (53%) followed by deprotection in aqueous acid (70%) gives **9**. Reaction of two equivalents of **9** with **5b** in THF at room temperature invariably led to the monocoupled product **10** and recovery of one equivalent of **9**. The second coupling to give **3** was eventually achieved in 46% yield by condensation of **9** with **10** at higher temperatures (THF, reflux) in the presence of 18-crown-6. Despite the presence of thirteen heterocycles, **3** is highly soluble in chloroform, although only sparingly so in other common organic solvents. Other combinations of the intermediates presented in scheme 1 offer the potential of preparing a wide variety of oligo(pyridine–pyrimidine) strands.

Proton NMR spectrum of **3**

The aromatic portion of the ^{1}H NMR spectrum of **3** (fig 1) is considerably simplified by symmetry and by the substitution pattern of the rings. Except for the

protons in the terminal pyridines, each proton appears as a singlet exhibiting a weak long-distance coupling (ca 1–2 Hz). Identification of the protons pertaining to the central pyrimidine ring is straightforward as they are the only signals integrating to one proton. Protons belonging to the same ring were identified through a COSY experiment, whereas interannular connectivity was established by examining the ROESY spectrum of **3** shown in fig 1. Nevertheless, protons corresponding to the trisubstituted pyridines (H5 , H6, H9, H10, H13 and H14) could not be unambiguously assigned. By comparison to **1b**, the protons assigned to the terminal pyridine rings (H2 and H3) are considerably shifted upfield (H2: 7.37 vs 6.65 ppm; H3: 7.83 vs 6.25 ppm for **1b** and **3**, respectively) indicating significant shielding by nearby heterocycles. Strong NOE interactions are observed in the ROESY NMR spectrum between H4 and H8, H8 and H12, and H12 and H16. This is consistent with a helical conformation in which the pyrimidine C5 carbons are oriented towards the interior and the propylthio side chains towards the outside of the helix. The interior cavity is lined with alternating pyridine nitrogen and pyrimidine C–H sites. Such a structure places H2 and H3 above a central pyridine ring, which accounts for their significant upfield chemical shifts.

Dynamic structural interconversion of **3**

The formation of a chiral helical structure in **3** is expected to be a rapid process, leading to a dynamic equilibrium composed of equal proportions of each enantiomer in rapid exchange. The exchange process may be followed by NMR using the propylthio groups as probes, as the presence of a chiral center is expected to render the methylene protons diastereotopic (fig 2). In particular, the α-thiomethylene protons giving a signal at 3.1 ppm may be decoupled from the vicinal methylene group. At room temperature, this results in the observation of three singlets, one for each two chains related by symmetry, because the interconversion of enantiomers is fast on the NMR timescale. However, as the temperature is lowered the signals split into an AB quartet (fig 3). At 228 K, a maximum separation of $\Delta\nu = 23.3$ Hz and $J = 12.4$ Hz is observed. Further lowering of the temperature results in signal broadening, but no apparent increase of $\Delta\nu$. The coalescence was determined to occur at $T_c = 251$ K. Equation (1) gives the exchange rate, k_c, in an AB system composed of equally populated states at coalescence [12]:

$$k_c = \frac{\pi\sqrt{\Delta\nu^2 + 6J_{AB}^2}}{\sqrt{2}} \qquad (1)$$

where $\Delta\nu$ and J_{AB} are the chemical shift difference and the coupling constant in hertz in the low-temperature AB pattern. From the above data, a value of $k_c = 85\ s^{-1}$

Fig 2. Interconversion of enantiomeric helices results in the exchange of the diastereotopic protons H_a and H_b of the α-thiomethylene protons in **3**.

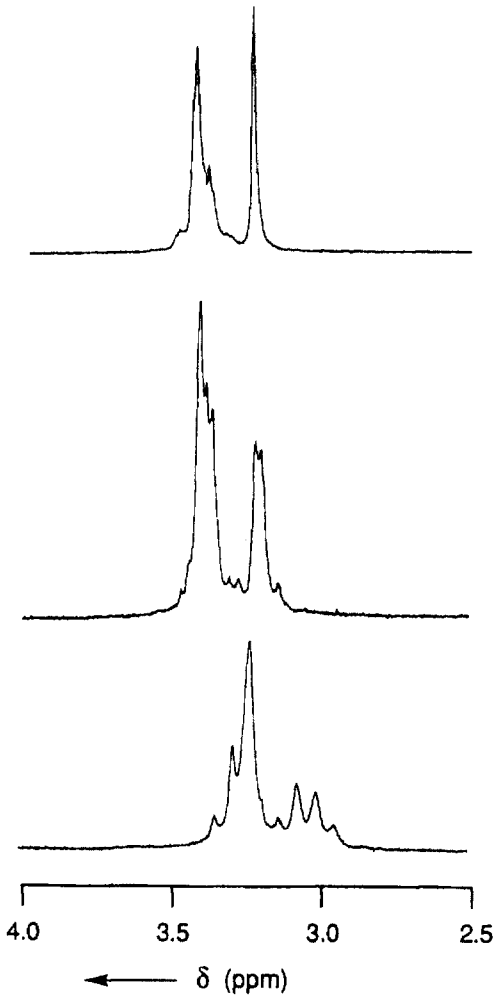


Fig 3. Alkyl portion of the ^{1}H NMR spectrum of **3** in $CDCl_3$ showing the signal of the α-thiomethylene protons decoupled from the vicinal CH_2. At 300 K (top trace) it is a singlet due to rapid interconversion of the helical enantiomers. At 251 K (middle trace) decoalescence occurs, resulting in the observation of an AB quartet at 228 K (bottom trace).

at 251 K is calculated, giving a free energy of activation at coalescence of $\Delta G_c^{\neq} = 12.3$ kcal/mol (51.6 kJ/mol).

Fluorescence spectra of **1b**, **2b** *and* **3**

The formation of a helical structure in **3** results in the intramolecular stacking of the aromatic groups in the strand. In addition to providing stabilization to the structure through π-stacking, this also results in the observation of electronic interactions occurring in the electronically excited state that can be observed by fluorescence spectroscopy. The fluorescence spectra of **1b**, **2b** and **3** in dichloromethane are shown in fig 4. Upon excitation of dilute solutions of **1b** or **2b**, pyridine-like fluorescence is observed at ca 400 nm.[2] However, excitation of **3** under similar conditions results in the observation of a broad, structureless band at 540 nm, and only weak residual pyridine fluorescence. The band at longer wavelengths could be due to emission from intramolecular pyridine excited state dimers (excimers) re-

[2] The pyrimidine heterocycles could also be involved.

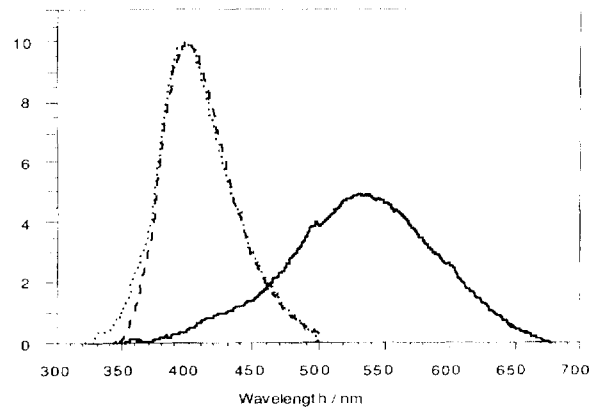


Fig 4. Fluorescence emission spectra of **1b** (dotted curve), **2b** (dashed curve), and **3** (solid curve) in dichloromethane upon excitation at 280 nm.

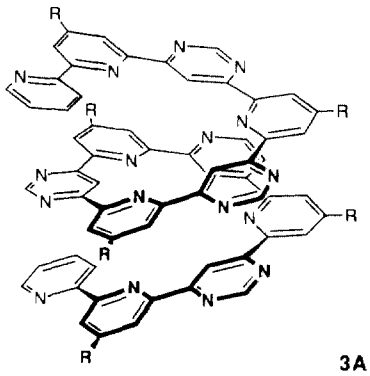
sulting from the self-organized stacking of the pyridine residues in the helix. The lack of excimer fluorescence in **2a** [5, 7] or **2b**, despite the overlap of the terminal pyridines, may be attributed to their greater mobility, since **2** forms only one helicoidal turn, or to an unfavorable orientation. In the solid, the terminal pyridines in **2a** are located 4.52 Å apart, and form an angle of 36° [5]. Fluorescence emission in polypyridine polymers has been reported to occur at 550 nm, and was assigned to excimer formation [13].

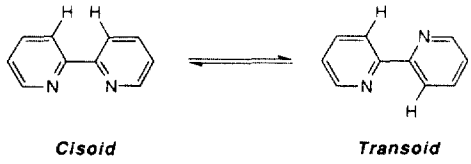
Solid state structure of **3**

The crystal structure of **3** has been reported earlier [6]. It is shown in fig 5, and unambiguously identifies the solid-state structure as helical. The unit cell is centrosymmetric, containing four molecules of **3** (two enantiomeric pairs) and eight molecules of acetonitrile. In the crystal, the molecules are stacked one on top of the other along a central axis, thus forming long channels, a feature of interest for ion channel design. Each molecule possesses a two-fold rotation axis passing through the central pyrimidine The pyridine–pyrimidine torsional angles are between 8.0° and 14.0°, whereas the two terminal pyridines are offset by only 3.5°. The structure possesses an interior void of 2.6 Å diameter and a helical pitch of 3.75 Å.

Discussion

The results described above indicate that the polyheterocyclic strand **3** undergoes self-organization into a helical structure schematically represented by **3A** both in solution and in the solid state. The formation of helical structures by compounds **2** and **3** rests on the application of the design principle outlined in the introduction. Stacking of the aromatic residues restricts the helical pitch (3.75 Å in the solid state) to values equal to the Van der Waals thickness of a benzene ring. The 1,3-substitution of the heterocycles in the strands defines the angles (60°) formed by the heterocyclic subunits which, combined with the size of the subunits, determines the diameter of the overall structure and the size of the interior void. Proper curvature results from the pattern of connection between the heterocycles and the preference for a *transoid* geometry about the single bonds in 2,2′-bipyridine and related species [5].





The latter may be attributed to electrostatic repulsion between the nitrogen dipoles and steric repulsion between the CH's in the *cisoid* conformation, as well as C–H···N hydrogen bonding in the *transoid* form. The planar *transoid* form has been calculated to be ca 25 kJ mol^{-1} more stable than the *cisoid* (non-planar) form [14]. In addition, other factors, in particular Van der Waals interactions between stacked heteroaromatic rings may provide additional stabilization of the helical superstructure. In this respect it is worth noting that *m*-deciphenyl was found to adopt a helical shape in the solid state [15]. In contrast to the more rigid helicenes [16], the ^1H NMR spectrum of **3** indicates that the enantiomeric helices rapidly interconvert at room temperature in solution. The conversion of one enantiomer into its opposite necessarily involves the unwinding of the helix by rotation about the single bonds connecting the pyridine and pyrimidine rings. This process invariably leads to intermediate structures in which some of the heterocycles adopt a *cisoid* conformation. It is interesting to note that the activation energy determined by NMR corresponds roughly to the energy required to form two *cisoid* conformers. This suggests that interconversion is a stepwise process in which stereoelectronic repulsions are minimized, rather than *via* the full unwinding of the structure into a linear strand followed by formation of the opposite enantiomer.

Conclusion and perspectives

The results described herein demonstrate the generality of the present approach to helicity induction in chains of alternating pyridine–pyrimidine heterocycles according to the principles outlined previously. Extension towards even longer helices, or helices with larger interior voids are being pursued. Furthermore, the present design principles also apply to polyheterocyclic strands

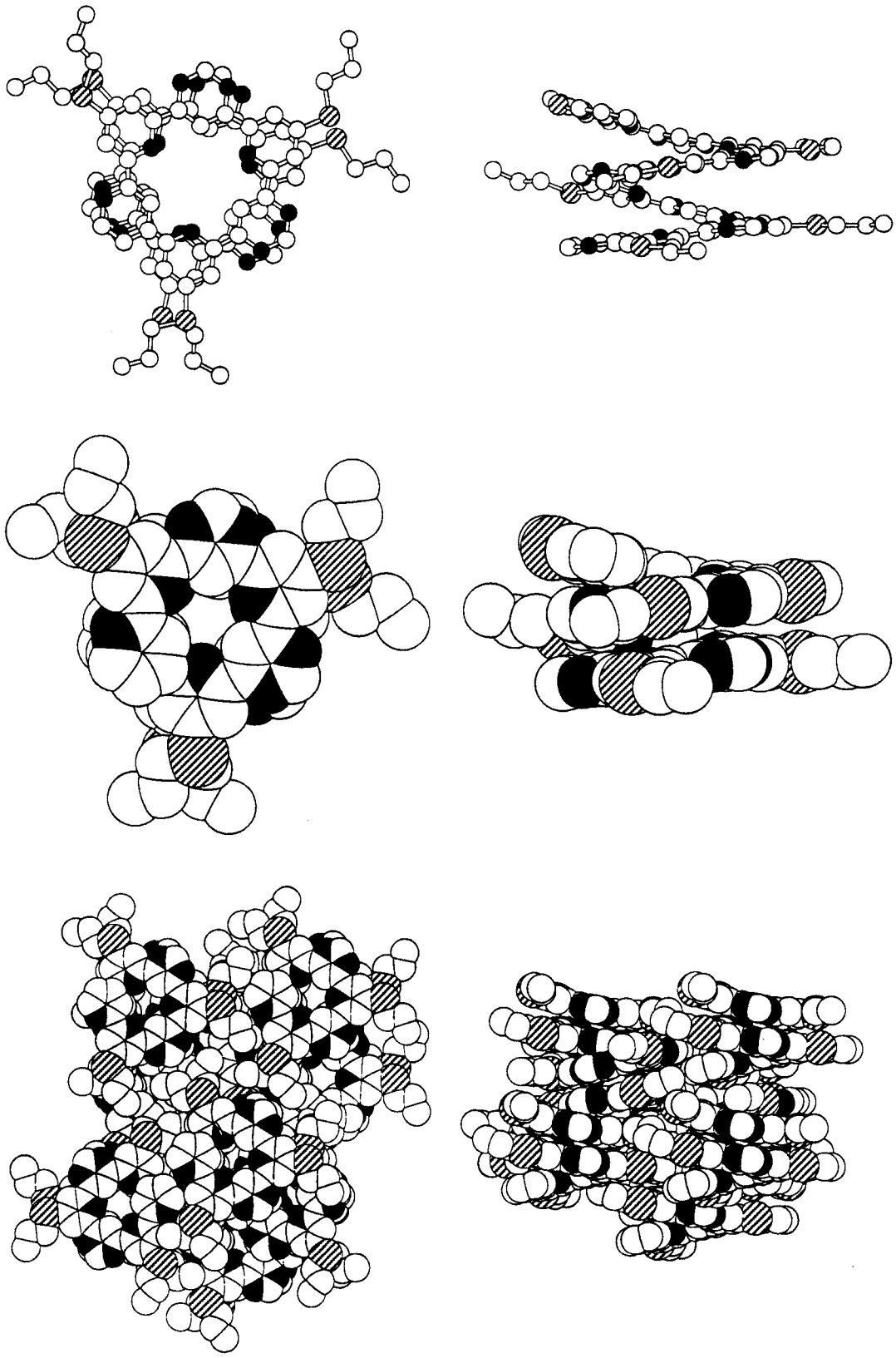
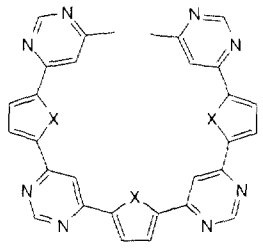
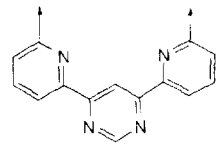


Fig 5. Ball-and-stick and space-filling representations of the crystal structure of **3** showing an individual molecule (top and center) and ball-and-stick representation of the packing (bottom) of the molecules along a central axis viewed along the axis (left) and from the side (right). Hydrogen atoms are omitted for clarity. See [6] for crystal structure data.

incorporating other subunits such as pyrazine, pyridazine, thiophene, thiazole, isothiazole etc (see structure **11** as an example), thus offering an even wider range of structural and functional (optical, electronic, etc) features.



11 X = S, O



12

The spontaneous formation of a helical superstructure represents a *molecular self-organization* process directed by the structural and conformational information encoded in the polyheterocyclic strand and operating through intramolecular non-bonded interactions, in the same way as *supramolecular self-organization* is based on intermolecular recognition events and non-covalent interactions [3]. One may envisage to combine intra- and intermolecular information and interactions for inducing the self-organization of complex chemical architectures of various shapes and sizes on both molecular and supramolecular levels. The (hetero)cyclic components may in addition be decorated with various functional groups so as to generate entities possessing specific physicochemical (optical, electronic) properties as well as potential molecular recognition features.

It is important to note that heterocyclic sequences such as those based on pyridine (py) and pyrimidine (pym) units connected through the positions α to the nitrogens, represent structural fragments that allow the introduction of specific angular bends into a chain. Thus they provide a general approach to geometry induction into a molecular framework. For instance, a py–pym–py sequence will generate a 180° bend as shown in structure **12**.

When compared to biopolymers such as proteins, the (py, pym) sequences, the bends, and the helical structures of the polyheterocyclic strands find analogy in the aminoacid sequences, the β-turns, and the α-helix features respectively; in addition, the organisational process itself corresponds to the protein-folding phenomenon. One may consider combining in a hybrid structure heterocyclic units and biocomponents (aminoacids, sugars, nucleotides, etc) so as to take advantage of the self-organizing power of the polyheterocyclic sequences for inducing biomimetic molecular architectures of desired geometry and of potential biological activity.

Experimental section

General procedures

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC200 instrument at 200 and 50 MHz, respectively, in $CDCl_3$ using the residual solvent peak as reference. Variable temperature, ROESY, and COSY experiments were performed on a 400 MHz Bruker AM400 instrument. Fluorescence spectra were recorded on an SLM Aminco Series 2 spectrophotometer. THF was dried over Na/benzophenone and distilled prior to use. DMF and DMSO were dried over molecular sieves. Sodium hydride (95%, Aldrich) and other reagents were used as received without further purification. Chromatography was carried out on Merk 60 silica gel (0.040–0.200 mm), or Merk activity II–III alumina (0.063–0.200 mm). *Trans*-bis(triphenylphosphine)palladium(II) chloride was prepared in 95% yield from palladium(II) chloride and triphenylphosphine by shaking a stoichiometric mixture in DMSO. 4,6-Diacetylpyrimidine [11], 3,3-bis(*n*-propylthio)-1-(2-pyridyl)prop-2-en-1-one **5a** [8], and 1-ethoxyvinyltributyltin [17] were prepared according to published procedures.

• *4-Acetyl-6-chloropyrimidine*

Tributyl-(1-ethoxyvinyl)tin (72.20 g, 0.20 mol), 4,6-dichloropyrimidine (25.00 g, 0.17 mol), *trans*-bis(triphenylphosphine) palladium(II) chloride (3.8 g, 5.4 mmol) and DMF (200 mL) were combined in a 500 mL round-bottom flask. The mixture was purged with argon and stirred at 80 °C for 16 h. The resulting dark solution was allowed to cool and poured into a flask containing KF (20 g) in 200 mL water. Diethyl ether (200 mL) was then added and the mixture stirred vigorously for 30 min, filtered, and the solid washed well with ether. The organic phase was collected, washed with water, and the solvent evaporated on a rotary evaporator to yield a dark oil which was purified by column chromatography (silica, hexane/acetone (10% v/v) eluent). The fractions containing the product were combined, and the solvent removed to yield an orange solid which was recrystallized from hexane to yield 20.82 g of 4-chloro-6-(1-ethoxyvinyl)pyrimidine as white needles. The latter was dissolved in 100 mL of acetone, 25 mL of 2 N HCl was added and the solution stirred overnight at room temperature, followed by 2 h of reflux. The solution was cooled, poured into 200 mL water, and extracted with chloroform. The organic phase was washed once with aqueous $NaHCO_3$, and the solvent removed on a rotary evaporator. The resulting solid was purified on a short silica column (eluent: dichloromethane) to yield 4-acetyl-6-chloropyrimidine (14.50 g, 0.09 mol) as a white powder in 55% yield. ^{1}H NMR: δ 2.75 (s, 3H), 7.95 (s, 1H), 9.10 (s, 1H).

• *4-Acetyl-6-(1-ethoxyvinyl)pyrimidine* **4**

4-Acetyl-6-chloropyrimidine (5.30 g, 0.034 mol), tributyl-(1-ethoxyvinyl)tin (14.55 g, 0.040 mol), *trans*-bis(triphenylphosphine)palladium(II) chloride (0.50 g, 0.7 mmol) and DMF (100 mL) were combined in a 250 mL flask and reacted as described above to yield an off-white solid that was further purified by sublimation (50 °C/0.1 Torr, then sealed) yielding **4** (5.72 g, 0.03 mol) as colourless plates in 88% yield.

^{1}H NMR: δ 1.46 (t, J = 12 Hz, 3H), 2.75 (s, 3H), 4.00 (q, J = 12 Hz, 2H), 4.58 (d, J = 4 Hz, 1H), 5.75 (d, J = 4 Hz, 1H), 8.20 (s, 1H), 9.22 (s, 1H).

^{13}C NMR: δ 9.76, 13.69, 14.40, 25.68, 63.93, 88.68, 111.59, 111.79, 156.26, 158.08, 159.71, 162.55, 199.42.

Anal calc for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.68; H, 6.27; N, 14.59.

• *4,6-Bis[3,3-bis(n-propylthio)-1-oxoprop-2-en-1-yl]-pyrimidine* **5b**

A solution of diacetylpyrimidine (3.55 g, 0.022 mol) in 20 mL DMSO was added to a 250 mL round-bottom flask equipped with an argon inlet and septum containing a stirred suspension of NaH (1.13 g, 0.047 mol) in 150 mL DMSO. The suspension was stirred 45 min at room temperature

and CS_2 (3.40 g, 0.045 mol) was added dropwise via a syringe. The dark red mixture was stirred 1 h and *n*-propyl iodide (7.61 g, 0.45 mol) was added dropwise. After 1 h, a second portion of NaH (1.13 g, 0.047 mol) was added in small portions. The dark yellow mixture was stirred 45 min, and *n*-propyl iodide (7.61 g, 0.45 mol) was then added dropwise. The resulting dark red mixture was stirred overnight, poured into 200 mL of 1 N HCl, and extracted with chloroform. The organic phases were combined, washed twice with water and the solvent removed on a rotary evaporator. The dark solid was purified by column chromatography (silica, dichloromethane), followed by recrystallization from ethanol to yield **5b** (6.51 g, 0.014 mol) as a yellow powder in 62% yield.

^{1}H NMR: δ 1.08 (m, 12H),1.62 (m, 8H), 3.08 (m, 8H), 7.57 (s, 2H), 8.72 (s, 1H), 9.33 (s, 1H).

^{13}C NMR: δ 13.73, 20.97, 22.37, 33.69, 36.34, 108.26, 115.76, 157.86, 163.03, 170.27, 181.91.

Anal calc for $C_{22}H_{32}N_2O_2S_4$: C, 54.51; H, 6.65; N, 5.78. Found: C, 54.44; H, 6.45; N, 5.68.

• *4,6-Bis[4-(n-propylthio)-6-(pyrid-2-yl)pyrid-2-yl]-pyrimidine* ***1b***

To a stirred solution of potassium *tert*-butoxide (2.29 g, 20.46 mmol) in 100 mL THF under argon was added 2-acetylpyridine (2.81 g, 23.20 mmol). To the resulting milky suspension was added **5b** (1.90 g, 3.93 mmol) in 50 mL THF. The red solution was stirred 16 h at room temperature after which acetic acid (20 mL) and ammonium acetate (9 g) were added. The mixture was refluxed 90 min, cooled, poured into 200 mL water, and the product extracted with chloroform. The organic phases were combined, washed once with $NaHCO_3$ (saturated) solution, and the solvent removed on a rotary evaporator. The product was isolated by column chromatography (alumina, chloroform) as an off-white solid that was then recrystallized from acetone to afford **1b** (1.40 g, 2.61 mmol) as a white powder in 66% yield.

^{1}H NMR: δ 1.14 (t, J = 8 Hz, 6H), 1.78 (m, 4H), 3.19 (m, 4H), 7.37 (m, 2H), 7.83 (t, J = 6 Hz, 2 Hz), 8.38 (s, 2H), 8.43 (s, 2H), 8.72 (m, 4H), 9.43 (s, 1H), 9.68 (s, 1H).

^{13}C NMR: δ 13.72, 21.96, 32.91, 114.13, 118.03, 118.84, 121.30, 123.94, 136.47, 149.04, 152.27, 152.60, 154.86, 155.51, 158.23, 163.41.

MS (FAB+): m/z 537.2 (100%, M^+).

Anal calc for $C_{30}H_{28}N_6$: C, 67.14; H, 5.26; N, 15.66. Found: C, 67.15; H, 5.20; N, 15.59.

• *2-(4-Acetylpyrimid-6-yl)-4-(n-propylthio)-6-(pyrid-2-yl)pyridine* ***6***

To a stirred solution of potassium *tert*-butoxide (1.97 g, 16.00 mmol) in 100 mL THF under argon was added **4** (3.00 g, 15.63 mmol). After 15 min, a solution of **5a** (4.50 g, 16.00 mmol) in 15 mL THF was added. The red solution was stirred 16 h at room temperature after which acetic acid (15 mL) and ammonium acetate (5 g) were added. The mixture was refluxed 90 min, cooled, poured into 200 mL water, and the product extracted with chloroform. The organic phases were combined, washed once with $NaHCO_3$ (saturated) solution, and the solvent removed on a rotary evaporator. The dark oil was purified by column chromatography (alumina, chloroform): the first fraction was collected, and the solvent removed on a rotary evaporator. Deprotection was achieved by stirring in 100 mL of acetone containing 25 mL of 2 N HCl for 12 h, followed by refluxing for 90 min. The suspension was neutralized with aqueous $NaHCO_3$ and extracted with chloroform. Removal of the solvent by rotary evaporation and purification of the dark solid by chromatography (alumina, chloroform), followed by trituration with acetone afforded **6** (1.44 g, 4.11 mmol) as a tan powder in 26% overall yield.

^{1}H NMR: δ 1.12 (t, J = 8 Hz, 3H), 1.82 (m, 2H), 2.80 (s, 3H), 3.19 (t, J = 8 Hz, 2H), 7.36 (m, 1H), 7.88 (t, J = 4 Hz, 1H), 8.35 (s, 1H), 8.42, (s, 1H), 8.55 (d, J = 6 Hz, 1H), 8.63 (d, J = 4 Hz, 1H), 9.01 (s, 1H), 9.40 (s, 1H).

^{13}C NMR: δ 13.62, 21.97, 25.97, 32.92, 113.85, 118.44, 118.63, 119.44, 119.62, 121.75, 124.29, 137.15, 149.21, 152.22, 152.62, 155.27, 155.67, 158.54, 158.80, 159.94, 165.16, 199.70.

• *4-[6-(4-(3,3-Bis(n-propylthio)-1-oxoprop-2-en-1-yl)pyrimid-6-yl)-4-(n-propylthio)pyrid-2-yl]-6-[6-(pyrid-2-yl)-4-(n-propylthio)pyrid-2-yl] pyrimidine* ***7***

To a stirred solution of potassium *tert*-butoxide (0.53 g, 4.71 mmol) in 100 mL THF under argon was added **6** (1.50 g, 4.29 mmol) dissolved in 15 mL THF. The solution was stirred 15 min, and **5b** (2.07 g, 4.30 mmol) in 30 mL THF was added. The red solution was stirred 16 h at room temperature after which acetic acid (5 mL) and ammonium acetate (5 g) were added. The mixture was refluxed 90 min, cooled, poured into 200 mL aqueous $NaHCO_3$ solution, and extracted with chloroform. The solvent was removed on a rotary evaporator and the dark oil purified by chromatography (silica, chloroform). The second yellow band was collected and the solvent removed by rotary evaporation to afford **7** (1.48 g, 2.00 mmol) as yellow powder in 47% yield.

^{1}H NMR: δ 1.15 (m, 12H), 1.88 (m, 8H), 3.20 (m, 8H), 7.31 (m, 2H), 7.68 (s, 1H), 8.40–8.40 (m, 5H), 9.00 (d, J = 4 Hz, 1H), 9.32 (s, 1H), 9.35 (s, 1H), 9.40 (s, 1H), 9.68 (s, 1H).

• *2,6-Bis[4-(4-n-propylthio-6-(pyrid-2-yl)pyrid-2-yl)pyrimid-6-yl]-4-(n-propylthio)pyridine* ***2b***

To a stirred solution of potassium *tert*-butoxide (0.40 g, 3.60 mmol) in 100 mL THF under argon was added 2-acetylpyridine (0.43 g, 3.81 mmol). To the resulting milky suspension was added **7** (1.10 g, 1.49 mmol) in 20 mL THF. The red solution was stirred 16 h at room temperature after which acetic acid (5 mL) and ammonium acetate (5 g) were added. The mixture was refluxed 90 min, cooled, poured into 200 mL water, and the product extracted with chloroform. The organic phases were combined, washed once with $NaHCO_3$ (saturated) solution, and the solvent removed on a rotary evaporator. The product was isolated by column chromatography (alumina, chloroform) as an off-white solid that was then washed with acetone to afford **2b** (0.89 g, 12 mmol) as a white powder in 78% yield.

^{1}H NMR: δ 1.18 (t, J = 8 Hz, 9H), 1.59–1.75 (m, 6H), 3.15 (m, 6H), 6.67–6.88 (m, 4H), 8.17 (s, 2H), 8.22 (d, J = 6 Hz, 2H), 8.28 (d, J = 4 Hz, 2H), 8.34 (s, 2H), 8.42 (s, 2H), 9.32 (s, 2H), 9.76 (s, 2H).

^{13}C NMR: δ 13.67, 22.03, 32.99, 114.54, 117.99, 119.07, 121.46, 123.62, 135.73, 148.40, 152.09, 152.73, 153.05, 153.31, 154.50, 155.34, 158.41, 163.52, 163.89.

MS (FAB$^+$): m/z 766.3 (100%, M^+).

Anal calc for $C_{42}H_{39}N_{98}S_3$: C, 65.86; H, 5.13; N, 16.46. Found: C, 65.87; H, 5.19; N, 16.25.

• *2-[4-(3,3-Bis(n-propylthio)-1-oxopropen-1-yl) pyrimid-6-yl]-6-[4-(1-ethoxyvinyl)pyrimid-6-yl]-4-(n-propylthio)pyridine* ***8***

To a solution of **4** (1.00 g, 5.21 mmol) in 25 mL DMSO under argon was added dropwise a solution of potassium *tert*-butoxide (0.62 g, 5.30 mmol) in 25 mL DMSO. The resulting red solution was stirred 10 min and added dropwise

over a 5 min period to a 250 mL flask, equipped with a septum and argon inlet, containing a solution of **5b** (2.00 g, 4.13 mmol) in 150 mL of a 2:1 THF/DMSO solution. The dark red solution was stirred 16 h at room temperature after which acetic acid (10 mL) and ammonium acetate (5 g) were added. The mixture was refluxed 90 min, cooled, poured into 200 mL water, and the product extracted with chloroform. The organic phases were combined, washed once with $NaHCO_3$ (saturated) solution, and the solvent removed on a rotary evaporator. The dark oil was purified by chromatography (alumina, dichloromethane), followed by recrystallization from acetone to afford **8** (1.06 g, 1.80 mmol) as a light yellow solid in 44% yield.

^{1}H NMR: δ 1.15 (m, 9H), 1.63 (t, J = 10 Hz, 3H), 1.72–1.93 (m, 6H), 3.10 (m, 6H), 4.07 (q, J = 9 Hz, 2H), 4.58 (d, J = 2.5 Hz, 1H), 5.65 (d, J = 2.5 Hz), 7.62 (s, 1H), 8.43 (s, 2H), 8.85 (s, 1H), 9.24 (s, 2H), 9.34 (s, 1H).

^{13}C NMR: δ 13.63, 13.70, 14.62, 21.01, 21.89, 22.37, 32.94, 33.62, 36.34, 64.16, 88.16, 108.45, 112.82, 115.28, 119.66, 119.72, 153.02, 153.58, 157.15, 157.99, 158.17, 162.00, 162.26, 163.16, 164.25, 169.64, 182.29.

• *4-[6-(4-Acetylpyrimid-6-yl)-4-(n-propylthio)pyrid-2-yl]-6-[6-(pyrid-2-yl)-4-(n-propylthio)pyrid-2-yl] pyrimidine* ***9***

To a stirred solution of potassium *tert*-butoxide (1.23 g, 10.35 mmol) in 150 mL THF under argon was added 2-acetylpyridine (1.30 g, 10.71 mmol). To the resulting milky suspension was added **8** (4.00 g, 6.88 mmol) in 20 mL THF. The red solution was stirred 16 h at room temperature after which acetic acid (15 mL) and ammonium acetate (8 g) were added. The mixture was refluxed 90 min, cooled, poured into 200 mL water, and the product extracted with chloroform. The organic phases were combined, washed once with $NaHCO_3$ (saturated) solution, and the solvent removed on a rotary evaporator. The dark oil was triturated with acetone and the light yellow powder collected by filtration to afford 2.20 g of crude product. Deprotection was achieved by refluxing in 100 mL of acetone containing 25 mL of 2N HCl for 2 h, followed by neutralization with aqueous $NaHCO_3$ and extraction with chloroform. Removal of the solvent by rotary evaporation and purification of the dark solid by chromatography (alumina, chloroform), followed by trituration with acetone afforded **9** (1.43 g, 2.47 mmol) as a tan powder in 36% overall yield.

^{1}H NMR: δ 1.17 (t, J = 6.6 Hz, 6H), 1.88 (m, 4H), 3.20 (m, 4H), 7.40 (m, 1H), 8.28 (t, J = 7.3 Hz, 1H), 8.45 (s, 1H), 8.49 (s, 2H), 8.52 (s, 1H), 8.69 (d, J = 4 Hz, 1H), 8.84 (d, J = 7 Hz, 1H), 9.13 (s, 1H), 9.30 (s, 1H), 9.49 (s, 1H), 9.58 (s, 1H).

^{13}C NMR: δ 13.72, 22.0, 25.90, 32.88, 113.36, 113.48, 118.37, 119.22, 119.59, 119.95, 121.82, 124.18, 138.32, 142.92, 148.80, 152.00, 152.29, 152.63, 152.95, 153.43, 155.12, 155.50, 158.06, 158.47, 159.72, 162.63, 163.72, 164.27, 198.76.

• *4-[4-(4-(3,3-Bis(n-propylthio)-1-oxoprop-2-en-1-yl)pyrimid-6-yl)-4-(n-propylthio)pyrid-2-yl]-6-[4-[6-(4-n-propylthio-6-(pyrid-2-yl)pyrid-2-yl) pyrimid-6-yl]-4-(n-propylthio)pyrid-2-yl] pyrimidine* ***10***

To a stirred solution of potassium *tert*-butoxide (33 mg, 0.29 mmol) in 30 mL THF under argon was added **9** (150 mg, 0.26 mmol) dissolved in 10 mL THF. The solution was stirred 5 min, and **5b** (36 mg, 0.28 mmol) in 20 mL THF was added. The red solution was stirred 16 h at room temperature after which acetic acid (5 mL) and ammonium acetate (2 g) were added. The mixture was refluxed 90 min, cooled, poured into 100 mL aqueous $NaHCO_3$ solution, and extracted with chloroform. The solvent removed on a rotary evaporator and the dark oil was purified by chromatography (alumina, chloroform). The second yellow band was collected and the solvent removed by rotary evaporation to afford **10** (117 mg, 0.12 mmol) as yellow powder in 46% yield.

^{1}H NMR: δ 1.22 (m, 15H), 1.68–1.93 (m, 10H), 2.90–3.28 (m, 10H), 6.62 (m, 2H), 6.95 (s, 1H), 7.87 (s, 1H), 7.94 (s, 1H), 8.00 (d, J = 7.2 Hz, 1H), 8.07 (s, 1H), 8.20 (d, J = 2.7 Hz, 1H), 8.26 (s, 1H), 8.29 (s, 1H), 8.36 (s, 1H), 8.76 (s, 1H), 8.82 (s, 1H), 9.22 (s, 2H), 9.61 (s, 1H), 9.70 (s, 1H).

^{13}C NMR: δ 13.68, 13.87, 20.89, 22.00, 22.19, 33.14, 33.40, 36.50, 107.32, 114.77, 114.99, 117.80, 118.46, 119.10, 119.38, 121.34, 123.44, 135.69, 148.36, 151.71, 152.70, 152.84, 153.03, 153.25, 153.80, 154.58, 157.50, 157.80, 158.43, 160.82, 162.80, 164.38, 168.14, 180.34.

• *4,6-Bis[4-n-propylthio-6-(4-(4-n-propylthio-6-(4-(4-n-propylthio-6-(pyrid-2-yl)pyrid-2-yl)-pyrimid-4-yl)pyrid-6-yl)pyrimid-4-yl)pyrid-2-yl] pyrimidine* ***3***

A 100 mL round-bottom flask fitted with a reflux condenser and an argon inlet was charged with **10** (179 mg, 0.31 mmol), **9** (200 mg, 0.21 mmol), 18-crown-6 (100 mg, 37 mmol), and 30 mL of THF. The solution was brought to reflux, and a solution of potassium *tert*-butoxide (69 mg, 0.62 mmol) in 20 mL of THF was added dropwise over a period of 3 h using a syringe pump. The purple solution was further refluxed for 2 h and allowed to cool. Acetic acid (5 mL) and ammonium acetate (2.5 g) were then added. The mixture was refluxed 90 min, cooled, poured into 100 mL aqueous $NaHCO_3$ solution, and extracted with chloroform. The solvent was removed on a rotary evaporator and the solid obtained purified by column chromatography (alumina, chloroform). The product was recovered by washing the column with 5% methanol solution in chloroform and recrystallized from THF to afford **3** (144 mg, 0.10 mmol) as an off-white powder in 47% yield.

^{1}H NMR: δ 1.22 (m, 18H), 1.85 (m, 12H), 3.20 (m, 12H), 6.26 (t, J = 6.3 Hz, 2H), 6.67 (m, 2H), 7.63 (s, 2H), 7.78 (d, J = 4.5 Hz, 2H), 7.83 (s, 2H), 7.96 (s, 2H), 7.99 (s, 2H), 8.13 (s, 2H), 8.19 (s, 2H), 8.25 (d, J = 2.3 Hz, 2H), 8.52 (s, 1H), 9.10 (s, 2H), 9.21 (s, 2H), 9.32 (s, 2H), 9.44 (s, 1H), 9.72 (s, 2H).

^{13}C NMR: δ 13.85, 13.90, 21.81, 21.86, 29.79, 32.99, 33.08, 33.15, 114.11, 114.47, 117.09, 118.19, 118.49, 118.65, 119.15, 121.05, 123.39, 135.18, 148.32, 151.75, 152.11, 152.42, 152.73, 152.83, 153.83, 154.09, 158.12, 158.31, 161.55, 162.46, 162.61, 162.70, 162.77.

MS (FAB$^+$): m/z 1454 (100%, M$^+$).

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