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Facile Iterative Synthesis of 2,5-Terpyrimidinylenes as Nonpeptidic α-Helical Mimics

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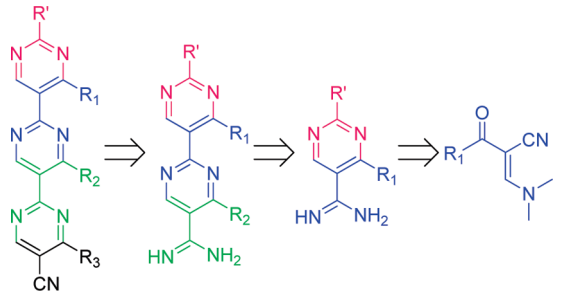

A facile iterative synthesis of 2,5-terpyrimidinylenes that are structurally analogous to α-helix mimics is presented. Condensation of amidines with readily prepared α,β-unsaturated α-cyanoketones gives 5-cyano-substituted pyrimidines. Iterative transformation of the 5-cyano group into an amidine allows synthesis of 2,5-terpyrimidinylenes with variable groups at the 4-, 4′-, and 4″-positions. These compounds are designed to mimic the *i*, *i* + 4, and *i* + 7 sites of an α-helix.

Protein−protein interactions (PPIs) are involved in several cellular processes, and the specific modulation of these interactions will boost our understanding of them.[1,2] Furthermore, PPI inhibitors can be the basis of important therapeutic interventions.[3−8] PPIs are typically shallow surface interactions that occur over relatively large surface areas to accrue sufficient interactions between the protein surfaces and stabilize their specific interaction with each other.[9−12] Thus, the development of specific PPI inhibitors is a challenging task as compared to enzyme inhibitors, which typically have relatively small and deep binding pockets.

Several different secondary and tertiary structures can be involved in the PPI, and one that is the focus of this manuscript is the α-helix. Hamilton et al. have discovered α-helix mimics that act as submicromolar inhibitors of the Bcl-xL interaction with the Bak peptide and the MDM2 interaction with the p53 peptide derived from the p53 N-terminus.[13,14] The Hamilton group has reported several α-helix mimics, but none of them have been more active than the best reported 1,4-terphenylene scaffolds against the same targets in the same in vitro assays.[15−19]

Rebek et al. recognized the importance of Hamilton's α-helix mimic approach and published several examples of more polar versions of the original Hamilton 1,4-terphenylene scaffold[20−24] including a tetrameric heterocyclic α-helix mimic scaffold designed to position four side chains in the *i*, *i* + 4, *i* + 7, and *i* + 11 positions of an α-helix.[24] Recently, Hamilton's group has also published a repetitive heterocyclic scaffold approach.[25] The intense efforts of these research groups to develop repetitive heterocyclic scaffolds to mimic α-helices illustrates the very strong potential importance of this class of compounds.

With the seminal work from the Hamilton group on the 1,4-terphenylene scaffold as a guide, we have developed a facile iterative synthesis of 2,5-terpyrimidinylenes as structurally analogous α-helix mimics.[26,27] Figure 1 shows an overlay of octa-alanine in an idealized α-helical conformation with its *i*, *i* + 4, and *i* + 7 methyl groups highlighted as gold spheres and a 4,4′,4″-trimethyl-2,5-terpyrimidinylene with its methyl groups highlighted as green spheres.

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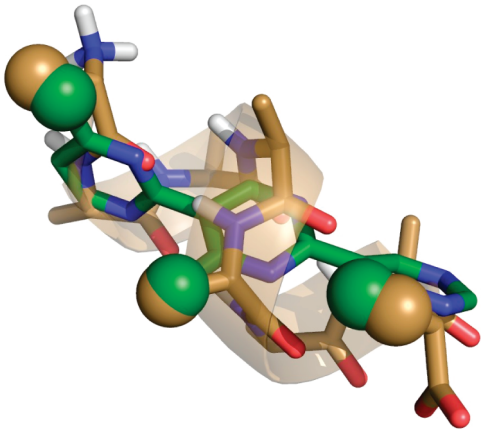


FIGURE 1. A tube representation of an idealized α-helix of octaalanine (gold with transparent ribbon) with the i, $i+4$, and $i+7$ methyl groups highlighted as spheres. An overlay with a 4,4′,4″-trimethyl-2,5-terpyrimidinylene with its methyl groups highlighted as green spheres is shown above. The rmsd for the highlighted methyl groups is 0.68 Å. For clarity, only polar hydrogens are shown. The details of these calculations can be found in Supporting Information.

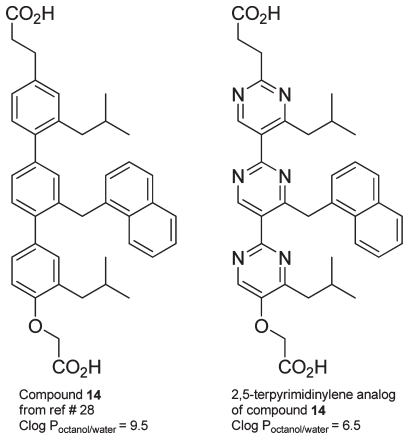
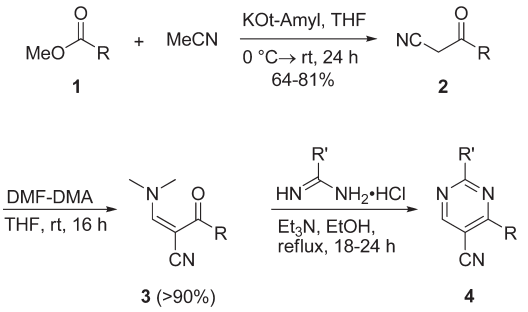


FIGURE 2. QikProp calculations for the most active terphenyl-based Bcl-xL-Bak inhibitor. The analogous terpyrimidine-based analogue shows improved hydrophilic character.

As seen with the Hamilton designed 1,4-terphenylene scaffold,[16] there is a good overlap of these positions, both in orientation and distance. Residues at the $i+4$ position are one turn plus 40°, and $i+7$ residues are 20° less than two turns of an α-helix from the i position. Our 2,5-terpyrimidinylene scaffold essentially replaces the phenyl rings of Hamilton's 1,4-terphenylene scaffold with pyrimidine rings, but these changes make the synthesis of pyrimidine-based derivatives much easier because the pyrimidine synthetic chemistry is more convergent and amenable to an iterative synthetic approach.

In addition, the pyrimidine for phenyl replacement gives the resulting analogous pyrimidine scaffold improved hydrophilicity according to QikProp calculations summarized in Figure 2 and Table 1, Supporting Information A. Structurally analogous 1,4-terphenylene and 2,5-terpyrimidinylene scaffolds show the calculated log $P_{\text{octanol/water}}$ values ranging from hydrophobic behavior for the Hamilton 1,4-terphenylene scaffold[28] to within the desirable range for hydrophilic character for the analogous 2,5-terpyrimidinylene scaffold (see Table 1 Supporting Information A)

SCHEME 1. Representative Synthesis of Pyrimidines 4



When R=Bn

Compound	R'	Yield (%)
4-1	NH_2	83
4-2	H	39
4-3	Me	63
4-4	Ph	91

Pyrimidine monomers **4** were obtained in a few steps through the condensation of commercially available amidines with readily prepared α,β-unsaturated α-cyanoketones **3** (Scheme 1). For instance, ester **1** was reacted with acetonitrile in anhydrous THF in the presence of KO-*t*-amyl to obtain α-cyanoketone **2**.[29,30] These reactions were also carried out in presence of other bases, including NaOMe,[31] KO-*t*-Bu, and LDA (data not shown). While the desired α-cyanoketone was obtained from the reactions with these bases, the isolation and purification was tedious, resulting in lower yields. KO-*t*-amyl afforded the products in good yields with simpler purification conditions.

Treatment of compound **2** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in THF gave **3** in excellent yield.[32] The efficiency of this step allowed us to obtain several α,β-unsaturated α-cyanoketones bearing hydrophobic alkyl, aryl, and heteroaromatic groups for introducing diversity in the 4-position of pyrimidines. As shown in Scheme 1, monomers **4-1** and **4-4** were isolated in higher yields, and no further purification was required since these compounds precipitated from the reaction mixtures, whereas **4-2** and **4-3** required additional purification. Encouraged by the excellent yields and purities obtained when R′ = Ph, we next focused on the iterative synthesis of the dimeric and trimeric 2,5-pyrimidines.

Compounds **5** and **6** were synthesized via conversion of the 5- or 5′-cyano group to a 5- or 5′-carboxamidine salt (Scheme 2). Several methods for this conversion have been reported,[33,34] such as the Pinner,[35] the thio-Pinner,[36] or treatment with Na or LiHMDS followed by aqueous hydrolysis,[37] but none of

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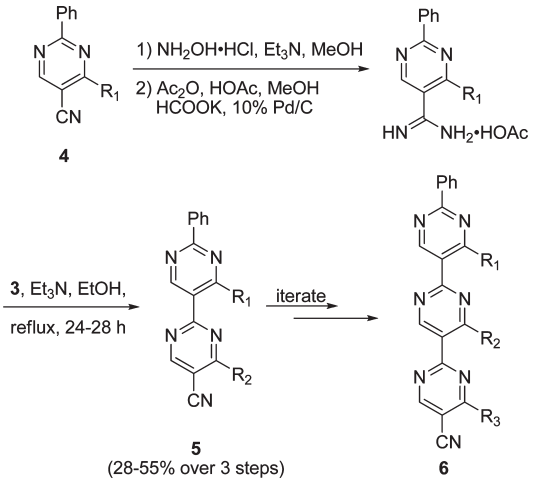
SCHEME 2. Synthesis of Dimeric and Trimeric 2,5-Pyrimidines



Compound	R_1	R_2	R_3	Yield (%) over 3 steps
6-1	*i*-Bu	Bn	*i*-Pr	41
6-2	*i*-Bu	methyl(2-naphthyl)	*i*-Bu	40
6-3	*i*-Bu	Bn	*i*-Bu	37
6-4	*i*-Bu	methyl(1-naphthyl)	*i*-Bu	38
6-5	Bn	methyl(1-naphthyl)	*i*-Bu	31

these alternatives were superior to the two-step hydroxylamine route.[38,39]

The extensive literature on nitrile to amidine conversion suggests that the difficulty of such a conversion can be attributed to the *ortho* substitution on the pyrimidine ring.[40] We found excess hydroxylamine followed by an in situ reduction of the resulting amidoxime was the best route to obtain the intermediate amidine salts. The *N*-hydroxylamine mediated transformation of *ortho*-substituted arylnitrile groups to arylcarboxamidines has been reported[41] but has not been used previously to prepare oligo-2,5-pyrimidines. The resulting intermediate amidine salts were reacted with an α,*β*-unsaturated α-cyanoketone to yield dimers **5**.

Dimers as well as trimers were isolated. The R_1, R_2, and R_3 groups of the 2,5-terpyrimidinylene scaffold were selected to mimic hydrophobic groups found to play important roles in binding similar to the Hamilton terphenylene compounds.[28]

The ORTEP diagram of the 4′-benzyl-4-(1-methylethyl)-4″-(2-methylpropyl)-2″-phenyl-2,5′,2′,5″-terpyrimidinylene-5-carbonitrile (**6-1**) crystal structure is shown in Figure 3. This conformation places the three hydrophobic groups on the same side of the long axis of the molecule, which is the conformer needed to mimic the *i*, *i* + 4, and *i* + 7 residues of an α-helix.

In conclusion, a series of compounds based on novel 2,5-terpyrimidinylenes was obtained through a facile iterative condensation between amidines and α,*β*-unsaturated α-cyanoketones in the presence of a base. This scaffold is being explored as α-helical mimics for the disruption of various protein−protein interactions; our efforts in this direction will be reported subsequently.

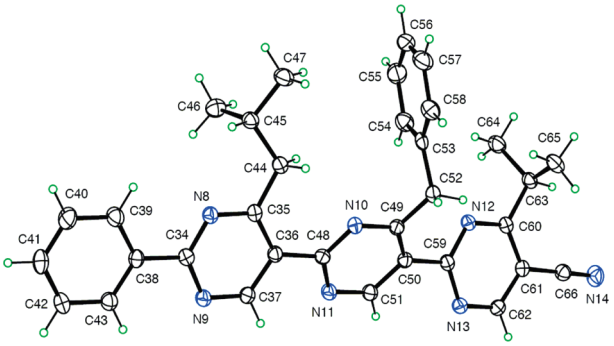


FIGURE 3. ORTEP diagram of compound **6**−**1**.

Experimental Section

See Supporting Information for the complete series.

5-Methyl-3-oxohexanenitrile (2a). A mixture of potassium *tert*-pentylate (∼1.7 M in toluene, 136 mmol, 80 mL) and anhydrous THF (20 mL) was cooled at 0 °C in an ice bath under an argon atmosphere. Anhydrous acetonitrile (136 mmol, 7.14 mL) and methyl ester **1a** (90 mmol, 10.57 g, 12 mL) were added simultaneously to the cold solution. The reaction mixture was allowed to warm to room temperature and stirred under an argon atmosphere for 22 h. A precipitate was formed within a few minutes (3−5 min) of stirring, and the reaction mixture remained cloudy until completion. The reaction was monitored by TLC and was stopped when the TLC indicated the consumption of the ester (**1a**). The mixture was filtered, and the filtered cake was washed thoroughly with hexanes (80 mL). The filtered residue was then transferred to a separatory funnel and acidified to pH ∼2−3 with saturated aq $KHSO_4$ solution (180 mL). An equal volume amount of DCM (180 mL) was used to extract the desired compound (**2a**). The organic layer was collected and washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield **2a** in 73% yield, as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 0.8 Hz, 3H), 0.97 (d, J = 0.8 Hz, 3H), 3.43 (s, 2H), 2.11−2.25 (m, 1H), 2.49 (d, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 24.7, 32.6, 51.1, 113.9, 197.2.

(*E*)-2-((Dimethylamino)methylene)-5-methyl-3-oxohexanenitrile(3a). α-Cyanoketone **2a** (65.9 mmol, 825 mg) was dissolved in dry THF (3 mL) under an argon atmosphere. *N*,*N*-Dimethylformamide dimethyl acetal (85.6 mmol, 11.5 mL) was added, and the mixture was stirred at room temperature. Progress of the reaction was monitored by TLC until complete consumption of starting material **2a** was observed (16 h). The solvent was evaporated under reduced pressure, and the desired compound was obtained as an $E \gg Z$ isomeric mixture. Isolated yield: 98%, pale yellow solid, mp 43−45 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 1.5 Hz, 3H), 0.96 (d, J = 1.5 Hz, 3H), 2.13−2.25 (m, 1H), 2.54 (dd, J = 7.0 Hz, 2H), 3.24 (s, 3H), 3.40 (s, 3H), 7.82 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 25.8, 39.0, 48.1, 48.8, 80.8, 120.6, 157.6, 195.4. HRMS (ESI) calcd for $C_{10}H_{16}N_2O$ $[M + H]^+$ 181.1341, found 181.1333. **Note:** If a precipitate forms during the reaction, the mixture is cooled to 0 °C and then filtered and rinsed with cold THF to isolate the desired compound.

4-Isobutyl-2-phenylpyrimidine-5-carbonitrile(4-5). Method A: A mixture of compound **3a** (1.66 mmol, 300 mg) and benzamidine hydrochloride (3.33 mmol, 521 mg) in ethanol (absolute, 10 mL) was stirred under reflux until TLC indicated completion

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of the reaction. The mixture was brought to room temperature, and the precipitate formed was filtered and rinsed with ice-cold ethanol (3 × 5 mL). Compound **4-5** was isolated in 70% yield as colorless crystals, mp 68−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, J = 6.7 Hz, 6H), 2.39 (m, 1H), 2.93 (d, J = 7.2 Hz, 2H), 7.49−7.59 (m, 3H), 8.50−8.53 (m, 2H), 8.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 28.9, 45.7, 106.7, 115.8, 129.0, 129.4, 132. 4, 136.4, 160.4, 165.7, 173.3. HRMS (ESI) calcd for $C_{15}H_{15}N_3$ $[M+H]^+$ 238.1344, found 238.1337. **Method B:** Microwave-assisted reactions were also done in the presence of base (e.g., Et_3N or NaOEt) to obtain the desired pyrimidines. For example, to a mixture of compound **3a** (1.11 mmol, 200 mg) and benzamidine hydrochloride (2.22 mmol, 350 mg) in ethanol (5 mL) was added sodium ethoxide (1.11 mmol, 75.5 mg) suspended in ethanol (1 mL). The reaction mixture was placed in a microwave reactor for 40 min at 120 °C. A colorless precipitate was formed upon cooling to room temperature. The precipitate was filtered and rinsed with ice-cold ethanol (2 × 3 mL) to isolate compound **4-5** in 83% yield.

4-Benzyl-4′-isobutyl-2′-phenyl-2,5′-bipyrimidine-5-carbo nitrile (5-1). Step 1. To a mixture of compound **4-5** (4.21 mmol, 1000 mg) and hydroxylamine hydrochloride (10.53 mmol, 720 mg) in methanol (12 mL) was added triethylamine (10.53 mmol, 1.46 mL). The reaction mixture was stirred under reflux until TLC indicated the consumption of starting material **4-5**. The solvent was removed under reduced pressure to obtain a white crude solid. The crude was dissolved in DCM (50 mL), washed with water (40 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain intermediate amidoxime, which was used in the next step without further purification.

Step 2. The intermediate from step 1 (0.92 mmol, 250 mg) was dissolved in glacial acetic acid (1 mL) and acetic anhydride (1.01 mmol, 0.1 mL). After stirring for 5 min, potassium formate prepared in situ from K_2CO_3 (5 mmol, 690 mg) and formic acid (10 mmol, 0.37 mL) in methanol (2.5 mL) was added to the mixture followed by the addition of 10% Pd/C (10 mol %, 98 mg). The reaction mixture was stirred at room temperature until the TLC indicated the consumption of starting material. The crude was filtered through Celite (1500 mg) and rinsed with methanol (3 × 3 mL). The filtrate was concentrated under reduced pressure to obtain a yellow crude residue. To this residue was added DCM (6 mL), and the white precipitate that formed was removed by vacuum filtration. The filtrate was concentrated under reduced pressure to obtain the crude acetate salt of carboxamidine as a yellow solid, which was used without further purification in the next step.

Step 3. To the crude carboxamidine salt dissolved in ethanol (0.8 mL) were added compound **3a** (0.69 mmol, 147 mg) and triethylamine (1.38 mmol, 0.19 mL). The reaction mixture was stirred under reflux for 2 h and then at room temperature for 18 h. A white precipitate was formed, which was filtered and rinsed with cold ethanol (5 mL) to yield dimer **5-1** in 28% yield after three steps as a white solid, mp 144−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 6.7 Hz, 6H), 2.24−2.35 (m, 1H), 3.19 (d, J = 7.1 Hz, 2H), 4.39 (s, 2H), 7.27−7.39 (m, 5H), 7.43−7.56 (m, 5H), 9.02 (s, 1H), 9.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 28.4, 43.4, 44.9, 106.3, 115.2, 127.6, 127.8, 128.8, 129.0, 129.2, 129.5, 131.5, 135.8, 137.4, 160.0, 160.7, 164.7, 165.8, 170.3, 172.0. HRMS (ESI) calcd for $C_{26}H_{23}N_5$ $[M+H]^+$ 406.2032, found 406.2049.

5″-Cyano-4,4″-diisobutyl-4′-(2-phenylmethyl)-2-phenylterpyrimidine (6-1). Repeat steps 1−3 as in synthesis of dimer **5-1** starting with **5-1**. Isolated yield = 37% after three steps, white solid, mp 188−189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.7 Hz, 6H), 1.02 (d, J = 6.7 Hz, 6H), 2.22−2.36 (m, 2H), 2.95 (d, J = 7.2 Hz, 2H), 3.20 (d, J = 7.1 Hz, 2H), 4.77 (s, 2H), 7.17−7.25 (m, 5H), 7.49−7.54 (m, 3H), 8.52−8.58 (m, 2H), 9.03 (s, 1H), 9.38 (s, 1H), 9.52 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 22.6, 22.8, 28.5, 29.2, 42.3, 44.7, 45.8, 107.6, 115.0, 126.8, 127.4, 128.56, 128.7, 128.8, 128.8, 129.3, 131.1, 137.8, 138.3, 159.6, 160.1, 160.3, 164.2, 164.6, 164.8, 169.0, 170.0, 173.8. HRMS (ESI) calcd for $C_{34}H_{33}N_7$ $[M+H]^+$ 540.2876, found 540.2869.

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Supporting Information Available: Experimental procedures, spectroscopic data for new compounds, and crystal structure of compound **6-1**. This material is available free of charge via the Internet at http://pubs.acs.org.