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Intramolecular hydrogen bonding allows simple enaminones to structurally mimic the *i*, *i* + 4, and *i* + 7 residues of an α-helix

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Abstract—An intramolecularly hydrogen bonded enaminone scaffold was designed and synthesized in order to mimic the *i*, *i* + 4, and *i* + 7 residues of an α-helix. The resonance stabilized vinylogous amide group serves as an aromatic ring isostere and allows the positioning and angular projection of the R-groups in a manner similar to an α-helix.

The design of oligomers that adopt well-defined secondary structures has received much attention over the past decade due to their numerous applications ranging from mimetics of protein secondary structural motifs to chemical sensors and switches.[1,2] Among the various classes of oligomers, foldamers that adopt helical structures or that can mimic α-helices are of particular interest due to their potential use as inhibitors of protein–protein interactions.[3–7] Within this class of α-helical mimicking oligomers,[8] the most common include the β-[4,5] and γ-[7] peptides and peptoids.[6] However, more recently nonpeptidic organic molecules are receiving added attention due to the wide variety of functional groups available to organic chemists that can help tune the physical properties of the molecules synthesized.[1,3,9,10]

We have previously shown that a trispyridylamide foldamer scaffold (**1**) adopts a bifurcated hydrogen-bond stabilized conformation where all three of its alkoxy groups (R^1, R^2, R^3) are projected on the same face of the molecule.[3] This arrangement of functionality allowed derivatives of **1** to mimic the spatial orientation of the *i*, *i* + 3 or 4, and *i* + 7 residues of an α-helix (Fig. 1A). In addition, a terphenyl scaffold (**2**) whose inherent propensity to adopt a staggered confirmation because of steric interactions of the *ortho*-substituents has also been reported (Fig. 1B).[11,12] Much like the trispyridylamide **1**, the R-groups of **2** can project on one face of the molecule. Prompted by the success of the trispyridylamide and terphenyl scaffolds in mimicking residues of an α-helix and disrupting protein–protein interactions, we sought to identify a new generation of α-helix mimicking foldamers with greater synthetic accessibility.

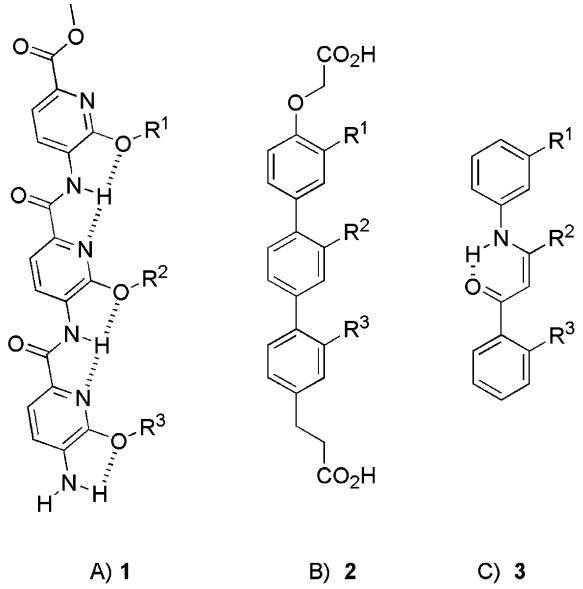

Figure 1. (A) Structure of a trispyridylamide scaffold **1**. (B) Structure of terphenyl scaffold **2**. (C) Structure of enaminone scaffold **3**.

In an earlier work, we have shown that significant synthetic simplicity yet structural rigidity can be imparted

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to a scaffold through six-membered ring hydrogen bonding functional groups.[13–16] This is clearly demonstrated by bisanthranilamide **4** which takes up a linear strand conformation stabilized by two intramolecular hydrogen bonds between adjacent –NH and –CO groups (Fig. 2A). This was confirmed by an X-ray structure (Fig. 2B) and solution NMR data consistent with hydrogen bonded –NH groups.[14,17] In **4**, the six-membered H-bonded rings rigidify the strand and can be viewed as isosteric with a linked biaryl derivative (Fig. 2C). In seeking to simplify the terphenyl scaffold in **2**, we realized that the central phenyl might be replaced by a more polar and hydrogen bonding ring, as in **4**.

While anthranilamides are not suitable for steric reasons, an equivalent and isosteric replacement would be the diphenyl enaminone (**3**) shown in Figure 1.[18] These derivatives use a six-membered intramolecularly hydrogen bonded core to rigidify the molecule in a specific conformation that is further stabilized by the O=C–C=C–NH π-conjugated system.[19,20]

Like the terphenyl and trispyridylamide compounds, the enaminone scaffold can project its R^1, R^2, and R^3 substituents in the same spatial orientation as the *i*, *i* + 4, and *i* + 7 residues of an α-helix. Computational modeling showed that the superimposition of an energy-minimized structure of **3a** (where $R^1 = R^2 = R^3 = Me$) overlayed on the α and β positions of the *i*, *i* + 4, and *i* + 7 methyl side chains on a polyalanine α-helix gives an RMSD value of 0.73 Å, suggesting good spatial similarity between the two compounds (Fig. 3). The aryl-vinylogous amide torsion angles for **3a** in this conformation were calculated at 44.2° (for the aryl-N) and 63.0° (for the aryl-CO) which positions the methyl group side chains in close correspondence with those of the α-helix.

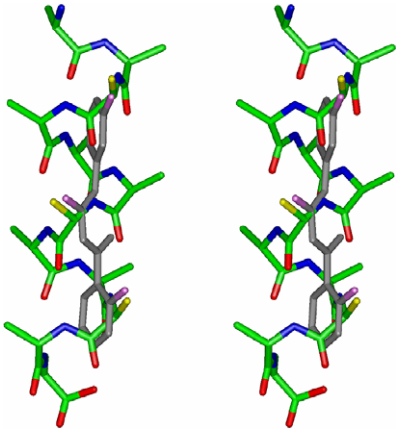


Figure 3. Stereoview of the RMS difference overlay of a polyalanine α-helix (green with the *i*, *i* + 4, and *i* + 7 positions highlighted in yellow) and enaminone **3a** (gray with methyl groups highlighted in pink).

The synthesis of the enaminone derivatives is straightforward and a representative route to **3a** is shown in Scheme 1. Claisen condensation of 2′-methylacetophenone **5** with ethyl acetate gave the diketone **6**. Reaction of the resulting diketone with $BF_3{\cdot}OEt_2$ afforded the 1,3-diketonatoboron difluoride **7**. Following a previously reported procedure by Stefane and Polanc,[21] reaction of **7** with *m*-toluidine gave the final enaminone product **3a** in high yield.

Enaminones can exist as *E*- or *Z*-isomers and in one of three tautomeric forms: a ketoamino, an iminoenol, and in an oxoimino form (Fig. 4).[22,23] The oxoimino form of **3a** is distinguished from the ketoamino and the iminoenol forms by the presence of two methylene protons versus a single vinylic proton. In the ^1H NMR spectra of all the enaminones prepared in $CDCl_3$, the existence of a single vinylic resonance around 5 ppm and a

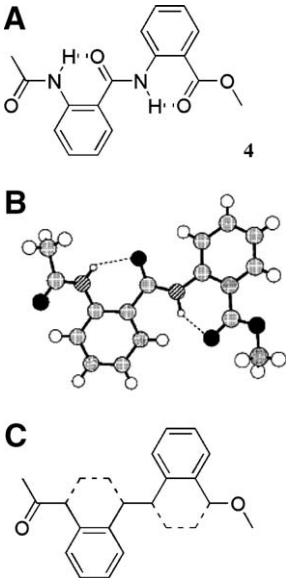
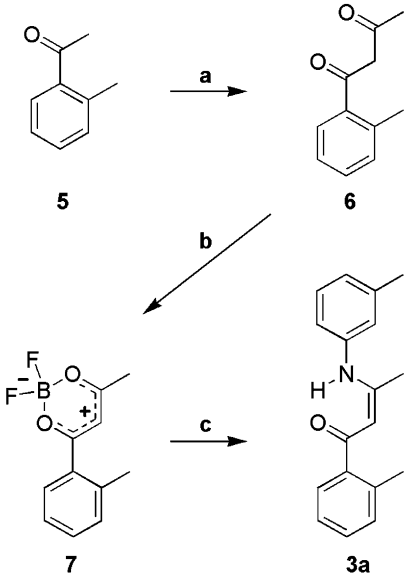


Figure 2. (A) Structure of anthranilamide **4**. (B) X-ray crystal structure of anthranilamide **4**. (C) Isosteric role of hydrogen bonded rings.



Scheme 1. Reagents and conditions for the synthesis of **3a**. (a) NaH, EtOAc, EtOH, ether; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (c) *m*-toluidine, CH_3CN.

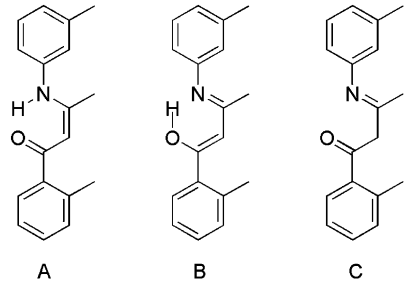


Figure 4. Tautomers of **5**: (A) ketoamino, (B) iminoenol, and (C) oxoimino.

H-bonded proton around 13 ppm suggested the presence of the ketoamino or iminoenol tautomer of the *Z*-enaminone. Extensive ^{1}H and ^{17}O NMR studies on intramolecularly hydrogen bonded *Z*-enaminone compounds have shown that the ketoamino tautomer is preferred even when the alternative iminoenol form would benefit from additional resonance stabilization as in the case of **3** (Fig. 4B).[19,24]

^{1}H NMR NOE-difference experiments were performed on a model enaminone **3b** (where R^1, $R^2 = Me$, $R^3 = H$) in order to confirm the regioselective formation of the enaminones due to the possibility of forming regioisomers in going from **7** to derivatives of **3** in Scheme 1 (Fig. 5). Regioisomer **8** would, like **3b**, have a characteristic vinylic and H-bonded resonance at around 5 and 13 ppm, respectively. However, saturation of the vinylic methyl protons in **3b** showed enhancement of the vinyl proton and *ortho*-aromatic protons. This is in agreement with the enaminone structure of **3b** instead of **8**, where only the vinyl proton would have been enhanced. This was further confirmed with an X-ray crystal analysis of **3a** which crystallized as the ketoamino tautomer with an intramolecular hydrogen bond between the –NH and the carbonyl oxygen atom having an interatomic –H···O distance of 1.82 Å (–N···O distance of 2.62 Å) and an –N–H···O angle of 140.5°. The structure also showed that the resulting six-membered hydrogen bonded enaminone group has a planar deviation of 0.02 Å, making the vinylogous amide functionality a suitable aromatic ring analogue (Fig. 6).

Additional ^{1}H NMR studies of enaminone **3b** were done in order to probe the existence of an intramolecular hydrogen bond. Enaminone **3b** showed very little change in the amine –NH resonance in both $CDCl_3$ ($\delta = 13.00$ ppm, $\Delta\delta = 0.002$ ppm) and DMSO ($\delta = 13.14$ ppm, $\Delta\delta = 0.009$ ppm) when the concentration of the sample was varied between 0.005 and 0.5 M. This suggests that the enaminones are intra- rather than intermolecularly hydrogen bonded even in polar solvents like DMSO. The temperature dependence coefficients of **3b** were determined from VT-NMR in both $CDCl_3$ ($\Delta\delta/\Delta T = 1.5$ ppb K^{-1}) and DMSO ($\Delta\delta/\Delta T = 2.0$ ppb K^{-1}). These results fall within the range of intramolecular hydrogen bonded amide –NH···O=C interactions found for small peptides in DMSO (<3.0 ppb K^{-1})[17] also suggesting that the enaminone proton is intra-molecularly hydrogen bonded.

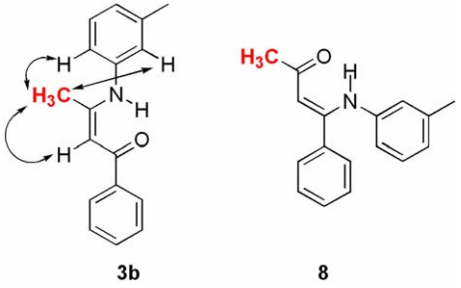


Figure 5. NOEs observed for **3b**, and regioisomer **8**.

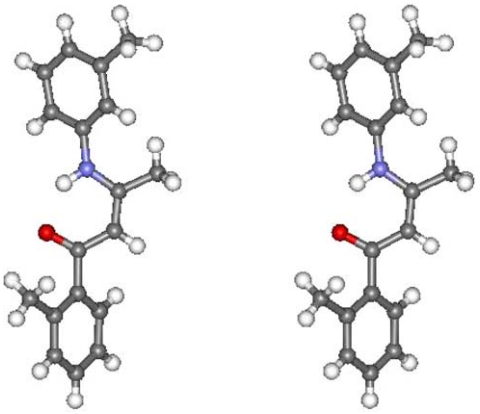


Figure 6. Stereoview of an X-ray crystal structure of **3a**.

In summary, a new scaffold based on an intramolecularly hydrogen bonded enaminone core was designed to mimic the *i*, $i+4$, and $i+7$ residues of an α-helix. Further derivatization of the R-groups in **3**, will allow us to target important α-helix mediated protein–protein interactions.

Acknowledgement

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Supplementary data

Supplementary data, including X-ray crystallographic data, experimental procedures, characterizations, and spectra of all compounds associated with this article can be found, online at, doi:10.1016/j.tetlet.2006.08.048.

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