**ABSTRACT**

Base-promoted 5-exo-dig cyclizations of aza-propargylglycinamides provided N-amino-imidazolin-2-one peptide mimics, which exhibited turn geometry in X-ray crystallographic and NMR spectroscopic analyses. Sonogashira coupling prior to cyclization afforded N-amino-imidazolin-2-ones with diverse 4-position aromatic substituents with potential to serve as Phe and Trp mimics.

Identification of biologically active conformers is critical for developing therapeutics based on peptide structures, because precise folding is essential for function. Geometrically restricted analogs are thus valuable tools, because they may reduce energetic costs for folding into binding conformations and, thereby, improve potency, selectivity, and stability.1

To constrain backbone geometry and induce turn conformations, α-amino-γ-lactams,2 so-called Freidinger–Veber lactams, have been commonly introduced into peptide sequences; however, their lack of side-chain functions may translate into loss of affinity and activity. Aza analogs of amino acids possess a nitrogen atom in place of the CHR. A variety of side chains have been installed onto these semicarbazide structures, which when introduced into azapeptides restrict the backbone φ and ψ dihedral angles, due to the lone pair–lone pair electronic repulsion of the adjacent nitrogen and urea planarity, respectively.2 A strategy has now been devised to induce peptide turn geometry by combining the covalent constraints of α-amino-γ-lactams with the electronic restrictions and side-chain diversity of aza-amino acids through the synthesis of substituted N-amino-imidazolin-2-ones (Figure 1).


receptor antagonists,\textsuperscript{6,7} antioxidants,\textsuperscript{8} and unnatural base pairs.\textsuperscript{9} To the best of our knowledge, however, the synthesis and biological evaluation of 5-amino-imidazolin-2-one has not been explored.

Previously, the submonomer approach for azapeptide synthesis surmounted issues of hydrazine chemistry to give access to side chains inaccessible by traditional methodology, including propargyl, allyl, and (hetero)aryl moieties.\textsuperscript{10,11} The aza-propargylglycine side chain was later reacted in copper-catalyzed 1,3-dipolar cycloadditions to make aza-1,2,3-triazole-3-alanyl peptide mimics.\textsuperscript{12} Aza-propargylglycine-based receptors,\textsuperscript{6,7} antioxidants,\textsuperscript{8} and unnatural base pairs.\textsuperscript{9} To the best of our knowledge, however, the synthesis and biological evaluation of N-aminimidazolin-2-one has not been explored.

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subsequent NaH-promoted 5-exo-dig cyclization gave imidazolin-2-one 9 in 78% yield with 10% racemization (see SI). Olefin migration occurred upon hydrazone removal, using hydroxylamine hydrochloride in pyridine,9 to afford N-amino-imidazoline hydrochloride which, without further purification, was treated with 4-methoxybenzoyl chloride to provide N-acyl dipeptide amide 10 in 56% overall yield.

Crystals were grown by slow diffusion of hexanes into an ethyl acetate/chloroform solution of 10. X-ray diffraction revealed two turn conformations in the solid state (Figure 2): 10a exhibiting a type Π′ β-turn with an intramolecular ten-membered hydrogen bond between residues i and i+3, and 10b showing a seven-membered hydrogen bonded conformer in an inverse γ turn. The X-ray structures for 10 deviate primarily by rotation of the ψi+2 dihedral angle, as shown by comparison of their φ and ψ dihedral angles with an ideal turn geometry and crystal structures of azapeptide and α-amino-γ-lactams, which adopted a turn geometry (Table 1).21–23 In contrast to amino lactams, the planar geometry of the N-amino-imidazoline causes the ψi+1 dihedral angle to deviate by 33°–46° from that of an ideal type Π′ β-turn, the geometry of which is contingent on the stereochemistry of the C-terminal residue (i.e., Phe).

Scheme 2. Synthesis of N-(p-Methoxybenzamido)imidazolin-2-one Isopropyl Amide (10)

Measurement of the amide chemical shift values of 10 as a function of DMSO-d6,6 % (1 to 100%) in CDCl3 indicated relatively little variation (0.45 ppm) for the isopropanamide NH signal compared to the benzamide chemical shift (1.21 ppm; see SI), consistent with solvent-shielded (hydrogen-bonded) and exposed hydrogens,24 as found in the X-ray structure.

To access constrained Phe, Trp, and His mimics, Sonogashira couplings were performed on dipeptide 1, using various aryl iodides, Pd(PPh3)2Cl2, and CuI in a 1:1 DMF/Et3NH mixture (Scheme 3, Table 2). Electron-rich and -poor aryl iodides as well as N-protected indole and imidazole iodides all reacted in the coupling reaction to furnish aza-arylpropargylglycines 14 in 50–93% yields.

Exposure of 14 to the NaH-promoted 5-exo-dig cyclization produced mixtures possessing endo- and exocyclic double bonds. For example, imidazolin-2-ones 15a and 16a were isolated as isomeric mixtures in 69% yield. Although either Z or E geometry were possible for 15, a

Table 1. Structures 10–13 and Their ϕ and ψ Dihedral Angles (in degrees) from Crystal Analyses Compared with Ideal Turns

<table>
<thead>
<tr>
<th>type of turn</th>
<th>ϕi+1</th>
<th>ψi+1</th>
<th>ϕi+2</th>
<th>ψi+2</th>
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<tbody>
<tr>
<td>β-II</td>
<td>60</td>
<td>−120</td>
<td>−80</td>
<td>0</td>
</tr>
<tr>
<td>inverse γ</td>
<td>n/a</td>
<td>n/a</td>
<td>−70</td>
<td>60</td>
</tr>
<tr>
<td>10a</td>
<td>58.9</td>
<td>−153.3</td>
<td>−69.1</td>
<td>−4.6</td>
</tr>
<tr>
<td>10b</td>
<td>62.1</td>
<td>−166.1</td>
<td>−71.7</td>
<td>65.7</td>
</tr>
<tr>
<td>11</td>
<td>−60</td>
<td>120</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>−55.4</td>
<td>120.9</td>
<td>89.3</td>
<td>17.8</td>
</tr>
<tr>
<td>13</td>
<td>−42</td>
<td>133</td>
<td>89</td>
<td>−6.9</td>
</tr>
<tr>
<td></td>
<td>−40</td>
<td>116</td>
<td>96</td>
<td>−97</td>
</tr>
</tbody>
</table>


through-space interaction between the vinyl proton and the methylene of imidazolidinone 15c in a 2D NOESY experiment revealed an exclusive exocyclic Z double bond geometry. Acid cleavage of the tert-butyl ester promoted double bond migration inside the five-membered ring to furnish 17a (Scheme 3).25

In the NaH-promoted 5-exo-dig cyclization, the fluorine p-substituent was well tolerated and gave 15c in 64% yield (Table 2). Substrates 14 with electron-withdrawing substituents (i.e., trifluoromethyl) reacted rapidly giving complete consumption of the starting material, albeit with lower yields due to decomposition. In contrast, electron-rich aza-p-methoxypropargylglycinamide 14b afforded N-amino-imidazolin-2-one 15b in only 10% yield with recovered starting material. Imidazolyl alkyne 14g failed to react and was exclusively recouped. In contrast, N-Boc-3-indolyl alkyne 14f underwent base-promoted cyclization to afford constrained tryptophan mimic imidazolin-2-one 15f in 40% yield with recovered starting material.

4-Substituted N-amino-imidazolin-2-ones have been prepared as hybrids of the covalent and electronic constraints of α-amino-γ-lactams and aza-amino acids. Opportunity for adding side-chain functionality was demonstrated by using a Sonogashira arylation prior to NaH-promoted 5-exo-dig cyclization of aza-propargylglycinamide to afford 4-substituted N-amino-imidazolin-2-one mimics. The propensity of the N-amino-imidazolin-2-one subunit to induce turn conformations was confirmed using X-ray crystallography and NMR spectroscopy of model peptide 10. Considering their conformational preferences and potential for their diversification, N-amino-imidazoliones represent a promising class of geometrically restrained mimics for studying peptide structure.

Incorporation of N-amino-imidazoliones into a biologically active peptide sequence is currently under investigation and will be reported in due time.

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Note Added after ASAP Publication. The Table 1 graphic contained an error in the version published ASAP August 14, 2012. The correct version reposted August 22, 2012.

Supporting Information Available. Experimental procedures, compound characterization data, and NMR spectra for new compounds. Crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.