N-Aminoimidazol-2-ones peptide mimics

Yousra Hamdane, Pradeep S. Chauhan, Suresh Vutla, Darince Truong, Mukandila Mulumba, Huy Ong and William D. Lubell
Department of Chemistry, Université de Montréal, Montréal, Canada

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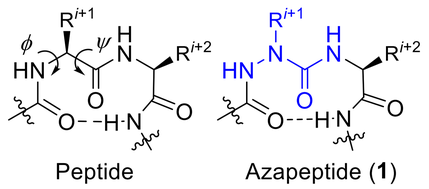
Abstract

N-Aminoimidazol-2-one (Nai) residues adopt peptide β- and γ-turns. 4-, 5- and 4,5-Substituted Nai-peptides were synthesized using a common route featuring proline-catalyzed condensations of aldehydes and ketones onto azopeptides. The bioactive conformer of a cluster of differentiation 36 receptor (CD36) modulator has been identified using Nai-peptide ligands.

Introduction: Nai peptide conception

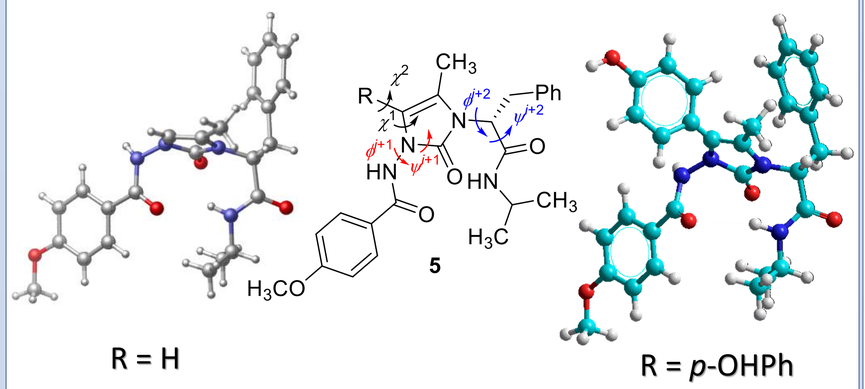
Peptide turns warrant mimicry to study implications in molecular recognition. **Aza-** and **lactam-peptides 1** and **2** favor turn geometry by way of stereo-electronic and covalent effects [1, 2]. Combining such properties, substituted *N*-aminoimidazol-2-one (**Nai**, **3**) residues offer potential to mimic turn backbone and side chain geometry and function [3].

Approaches for β-Turn mimicry



Nai residues induce turn geometry

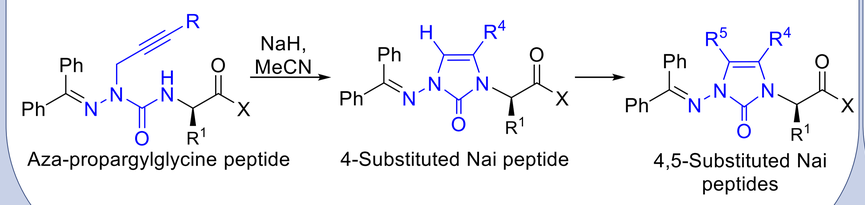
In model peptides, 4- and 4,5-substituted Nai residues induced turn geometry as observed by NMR spectroscopy, X-ray crystallography, and computational analysis [5,6,10]. 4-Methyl, 5-aryl Nai residues replicate natural side chain orientation on β-turn conformations [5,6,10].



Peptide	Φ^{i+1}	Ψ^{i+1}	Φ^{i+2}	Ψ^{i+2}	χ^1	χ^2
Ideal type II' β-turn	60	–120	–80	0	-	-
p-MeOBz-4-Me-Nai-D-Phe-NH*i*Pr (**4**)	58.9	–153.3	–69.1	–4.6	-	-
p-MeOBz-4-Me,5-*p*-HOPh-Nai-D-Phe-NH*i*Pr (**5**)	48.6	–143.7	–62.4	33.6	–41.1	76.0

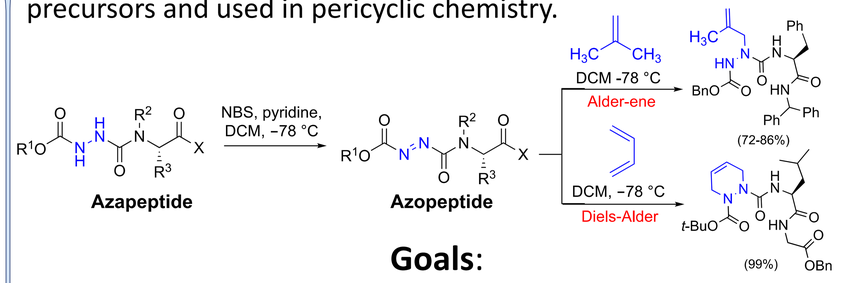
Earlier Nai syntheses

4-Methyl Nai residues were made from azaPra peptides by base-promoted 5-*endo-dig* cyclization and olefin isomerization. Embellishment by Sonogashira (R^4 = CH_2Ar), Pd-catalyzed arylation (R^5 = Ar) and Vilsmeier–Haack formylation (R^5 = CHO) chemistry gave various 4- and 4,5-substituted Nai analogs [4-7,10]. Ester epimerization during alkaline-mediated cyclization was supressed using amide and acid counterparts [6,7,10].



Azopeptide synthesis and pericyclic chemistry [8]

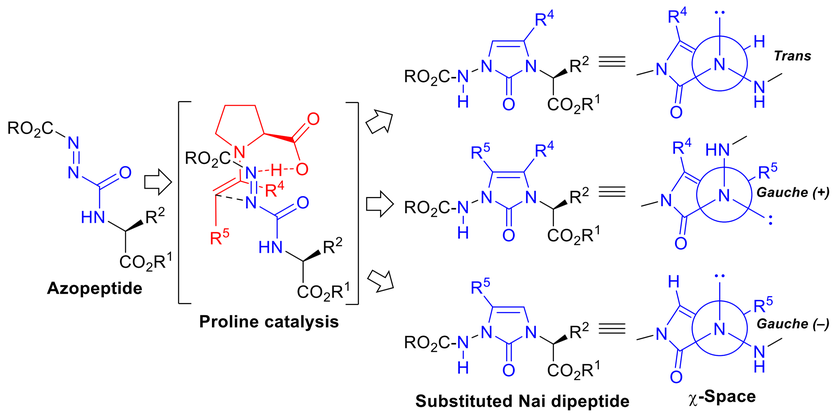
Azopeptides have been synthesized by oxidation of aza-glycine precursors and used in pericyclic chemistry.



Goals:

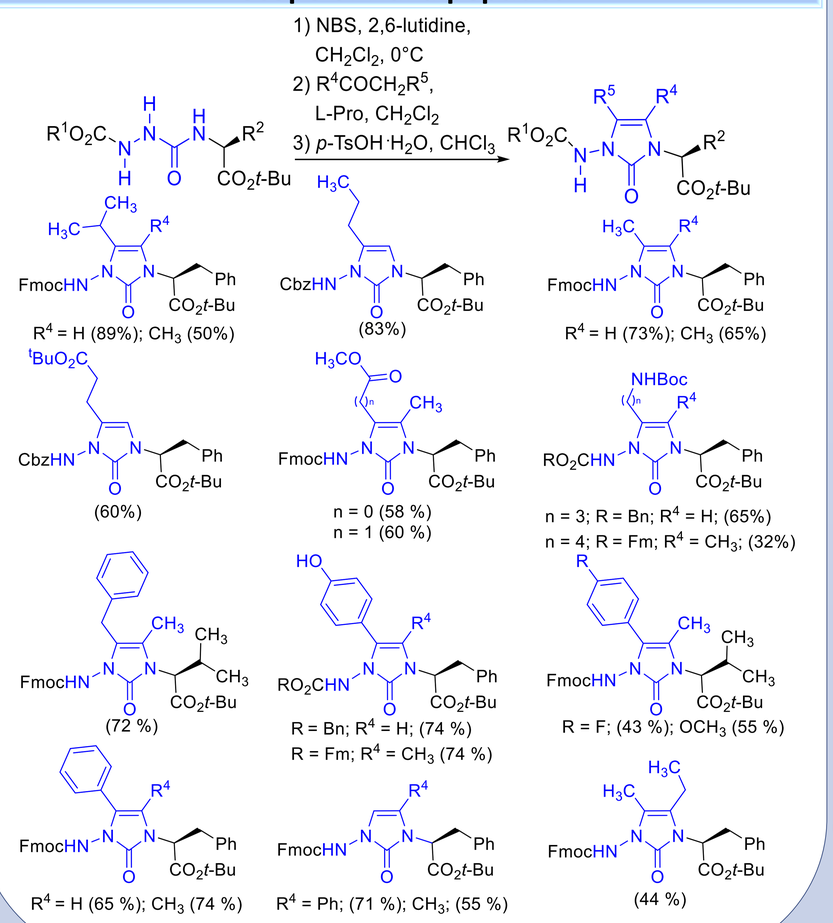
- Synthesis of 4-, 4,5- and 5-substituted Nai residues from a common azopeptide approach
- Biomedical application of Nai-peptides

Azopeptide approach to substituted Nai residues [9-11]



A common azopeptide approach features organocatalyzed reactions with carbonyl components. Proline-catalyzed enamine addition onto azopeptides gives selectively α-nitrogen alkylation to provide γ-oxo aza-amino amides. Subsequent, intramolecular cyclative acid-mediated dehydration gives diverse 4-, 5- and 4,5-substituted Nai-dipeptides with potential to respectively explore *gauche* and *trans* side chain orientations [9-11].

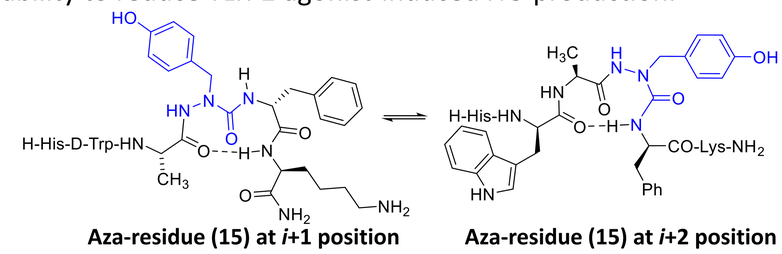
Scope of Nai dipeptides

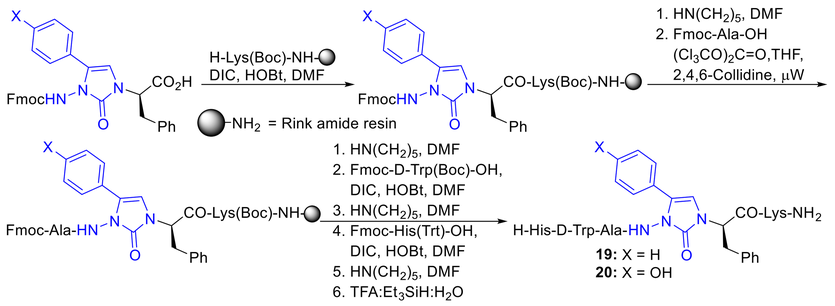


[5-Aryl-Nai[4]]GHRP-6 Analogs CD36 modulation

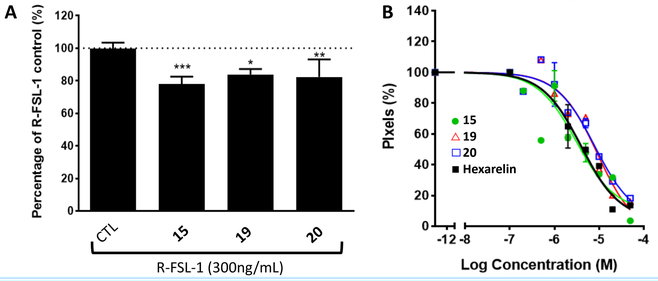
H-His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2; **GHRP-6**
H-His-D-Trp-Ala-azaTyr-D-Phe-Lys-NH_2; [aza-Tyr[4]]-GHRP-6 (**15**)

Azapeptide analogs of GHRP-6 have been pursued as selective CD36 modulators [9,10,12]. For example, azapeptide **15** exhibits relatively high CD36 binding affinity, curbs macrophage-driven inflammation and mitigates angiogenic and atherosclerotic pathology [9,10,12]. The bioactive conformer of azapeptide **15** was studied by the solid-phase synthesis of [5-Aryl-Nai[4]]GHRP-6 analogs **19** and **20** and examination of CD36 binding affinity and ability to reduce TLR-2 agonist-induced NO production.





5-Aryl-Nai analogs **19** and **20** had similar effects on NO production (**A**) and bound CD36 with 2.6- to 3.2-fold lower affinity (**B**) as azapeptide **15** indicating a likely common β-turn conformer with the aza-residue in the *i*+1 position and side chain in *gauche* chi-space.



Conclusions

- 4-, 4,5- and 5-Substituted Nai β-turn mimics were synthesized from azopeptides by a common proline-catalyzed route.
- 5-Aryl-Nai residue incorporation into CD36 modulator **15** indicates bioactive β-turn backbone and side chain geometry.

References

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