SUBSTITUTED *N*-AMINOIMIDAZOL-2-ONE MIMICS OF PEPTIDE TURN BACKBONE GEOMETRY AND SIDE CHAIN FUNCTION

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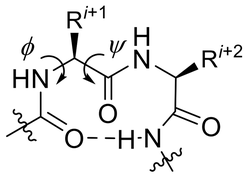
Abstract

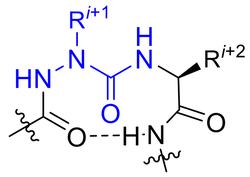
N-Aminoimidazolone (Nai) residues adopt β- and γ-turn conformers in model peptides. Notably, 5-substituted Nai peptides show promise for mimicry of both turn backbone and side chain function and geometry. Regioselective synthesis of 5-susbstituted Nai residues has now been achieved by a route featuring proline-catalyzed condensations of azopeptides and aldehydes.

Introduction: Nai peptide conception

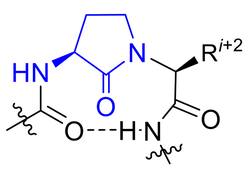
Mimicry of peptide turn geometry has warranted focus due to implications in molecular recognition. Replacement of an amino amide residue by a semicarbazide in so called **azapeptides (1)** has favored turn geometry and improved duration of action by way of stereo-electronic effects due to hydrazine nitrogen lone pair-lone pair repulsion and urea planarity [1]. α-Amino-γ-lactam (**Agl**, **2**) residues, so-called Freidinger-Veber lactams, have been employed to restrict covalently backbone ψ- and ω-dihedral angles to favor turn geometry [2]. Combining properties of aza and Agl constraints, *N*-aminoimidazolone (**Nai**, **3**) residues were conceived to promote peptide turn conformations with potential to introduce and restrain side chain function at the heterocycle 4- and 5-positions [3].



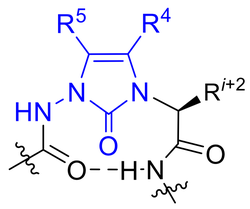
Peptide



Azapeptide (**1**)



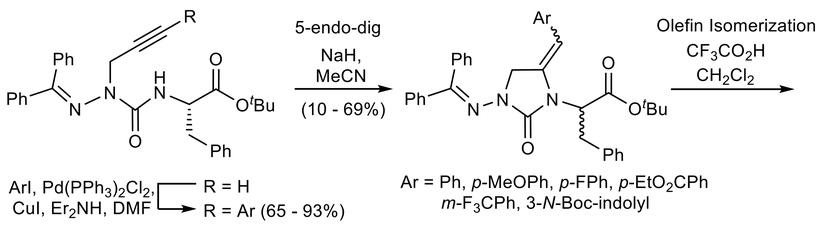
Agl-peptide (**2**)

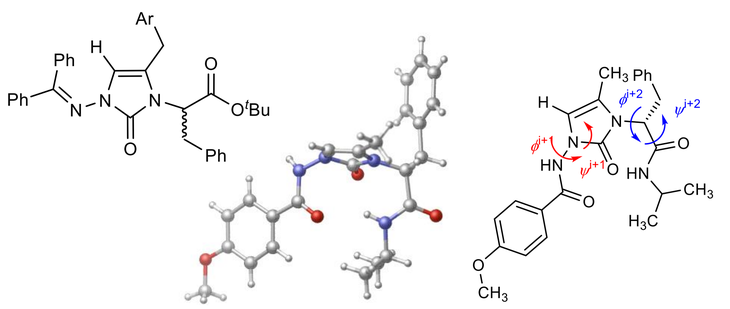


Nai-peptide (**3**)

4-Substituted Nai synthesis

Model 4-substituted Nai dipeptides exhibit turn geometry in X-ray and NMR spectroscopic analyses. They have been synthesized by routes featuring Sonogashira couplings on azaPra residues, base-promoted 5-*endo-dig* cyclization and olefin isomerization, but ester epimerization occurred during alkaline-mediated cyclization [4,5].

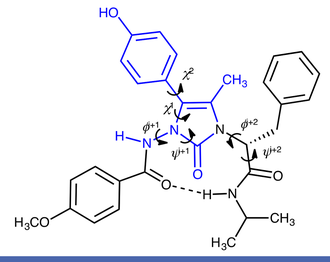


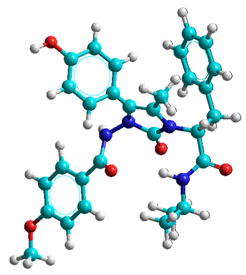


Peptide	Φ^{i+1}	Ψ^{i+1}	Φ^{i+2}	Ψ^{i+2}
Ideal type II' β-turn	60	–120	–80	0
p-MeOBz-4-Me-Nai-D-Phe-NHiPr	58.9	–153.3	–69.1	–4.6

4,5-Disubstituted Nai synthesis

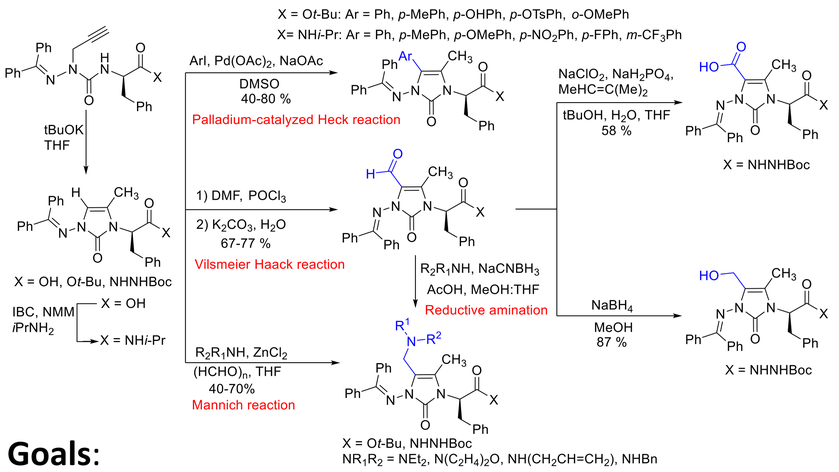
Computational analysis of 4-methyl,5-aryl Nai residues indicated replication of natural side chain orientation and β-turn conformation [6].





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-NHiPr	58.9	–153.3	–69.1	–4.6	-	-
p-MeOBz-4-Me,5-*p*-HOPh-Nai-D-Phe-NHiPr	48.6	–143.7	–62.4	33.6	–41.1	76.0

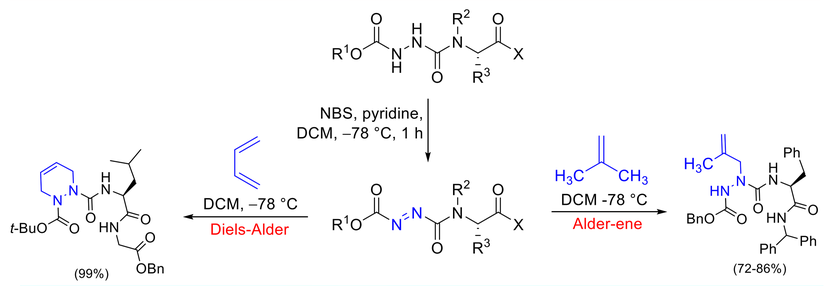
5-Substituted (4-Me)Nai analog synthesis used Pd-catalyzed arylation and Vilsmeier–Haack formylation chemistry [6, 7]



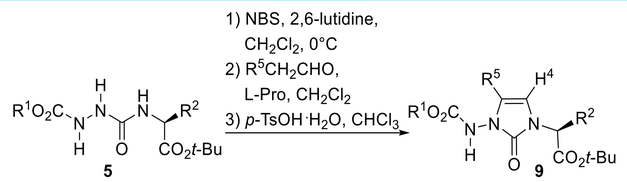
Goals:

- Synthesis of 5-substituted Nai residues
- Diversification of 5-substituted Nai side chains
- Incorporation into biologically active peptide

Azopeptide synthesis and pericyclic chemistry [8]



Synthesis of 5-substituted Nai derivatives [9]

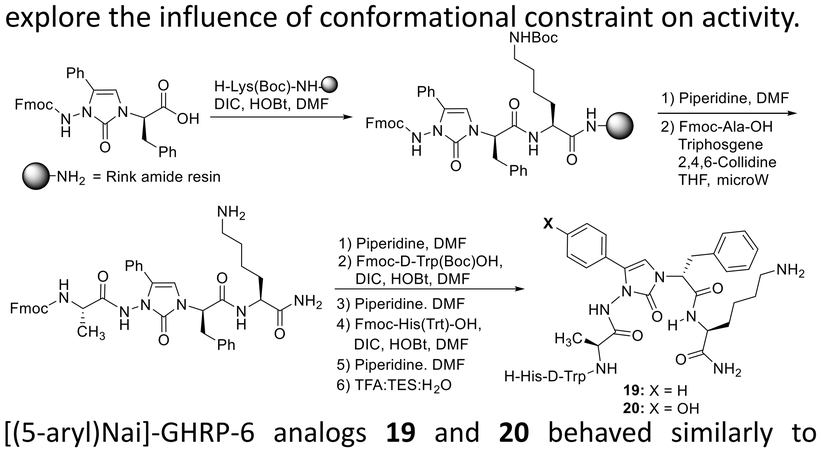


9	R^1	R^5	R^2	(%)
a	Bn	*i*-Pr	Bn	85
b	Fm	*i*-Pr	Bn	89
c	Bn	Me	Bn	91
d	Fm	Me	i-Pr	83
e	Fm	Me	Bn	73
f	Bn	Et	Bn	65
g	Fm	Et	Bn	80
h	Bn	*n*-Pr	Bn	83
i	Fm	Ph	Me	68
j	Fm	Ph	Bn	65
k[a]	Fm	Ph	Bn	43
l	Bn	*p*-(HO)Ph	Bn	74
m[a]	Fm	*p*-(TBSO)Ph	Bn	44
n	Bn	$(CH_2)_2CO_2t$-Bu	Bn	60
o	Bn	$(CH_2)_2$NHBoc	Bn	65

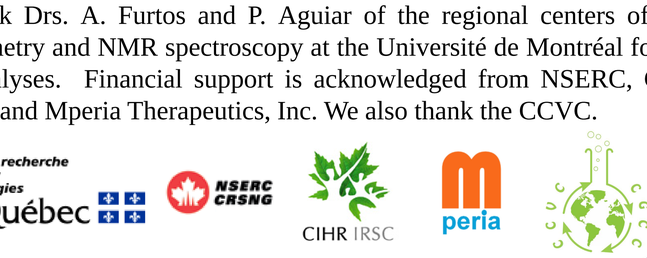
[a]D-Isomer

Synthesis and biomedical application of Nai peptides: [5-Aryl-Nai[4]]GHRP-6

GHRP-6 (HwAWfK) is a synthetic peptide that binds to the GHS-R1a and CD-36 receptors. Replacement of Trp[4] with aza-Tyr[4] provided a CD-36 selective azapeptide with antiangiogenic and anti-inflammatory activities in animal models [10]. [5-Aryl-Nai[4]]GHRP-6 analogs **19** and **20** have been synthesized to explore the influence of conformational constraint on activity.



[(5-aryl)Nai]-GHRP-6 analogs **19** and **20** behaved similarly to [azaTyr[4]]-GHRP-6 (**15**) exhibiting (A) ability to reduce TLR-2 agonist-induced NO production and (B) CD36 binding affinity (μM IC_{50}) in a competition assay with photoactivatable ^{125}I-Tyr-Bpa-Ala-hexarelin: hexarelin (4.0), ■; 15 (3.1), ●; 19 (8.1), □; 20 (10.0), Δ. A common turn conformer may account for their similar activity.



Conclusions

- 5-Substituted Nai synthesis provides mimics of β-turn backbone and side chain geometry and function.
- Various 5-position substituents were introduced by using different aldehyde partners in proline-catalyzed condensations with azopeptides.
- Incorporation of 5-aryl Nai residues into GHRP-6 analogs indicates a bioactive β-turn geometry with aza-residue in *i*+1 position with *gauche* side chain orientation.

References

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