Proceedings of the 37th European Peptide Symposium
Michal Lebl, Editor
European Peptide Society, 2024
http://doi.org/10.17952/37EPS.2024.P1052

N-Aminoimidazol-2-one Peptide Mimic Tools for Deciphering Active Conformations

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Introduction

Peptide mimics serve as tools for studying structure-activity relationships in biomedical applications to improve selectivity and pharmacokinetic properties.[1-3] Among peptide mimics (Figure 1), *N*-aminoimidazolidin-2-one (Aid, **3**)[4] and *N*-aminoimidazol-2-one (Nai, **4**)[5] residues combine properties of the covalent constraint found in α-amino-γ-lactam (Agl, **1**)[6] residues and the stereoelectronic effects of azapeptides (**2**).[7] The Nai residues enable potential for adding ring substituents to mimic amino acid side chains in constrained χ-dihedral angle orientations to improve activity and selectivity.[5]

Results and Discussion

The synthesis of 4-substituted Nai residues was first investigated by a *5-endo-dig* cyclisation of aza-propargylglycine analogs (e.g., **5**, Figure 2).[8] 4,5-Disubstituted Nai analogs were next prepared by diversification of the 5-position using palladium catalysis and Vilsmeier chemistry to install respectively aryl and formyl groups (e.g., **7** and **8**).[9,10] Organic catalysis using azoglycine residues gave later 5-substituted Nai residues which were used to study peptide ligands of the cluster of differentiation-36 receptor (CD36).[11] For example, oxidation of Fmoc-azaGly-Phe-O*t*-Bu (**9**) using *N*-bromosuccinimide gave azopeptide **10**. Subsequent reaction of the azopeptide with aryl acetaldehydes and proline as organocatalyst, followed by acid-mediated dehydration gave 5-aryl Nai dipeptides **11a** and **11b** (Figure 3), which after ester deprotection, were installed into peptides **14a** and **14b** by conventional solid-phase synthesis.[11]

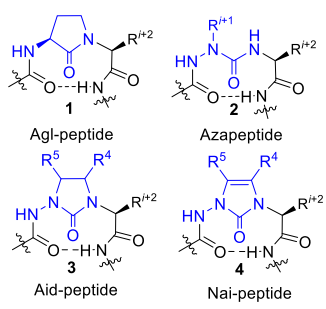

Fig. 1 Agl, aza-, Aid and Nai peptide mimics.

X-ray and computational analyses of model Nai peptides have demonstrated preferences for the *i* + 1 residue of type II' β- and γ-turns as well as potential to mimic side chain function and χ-space orientation contingent upon ring substituent position.[5]

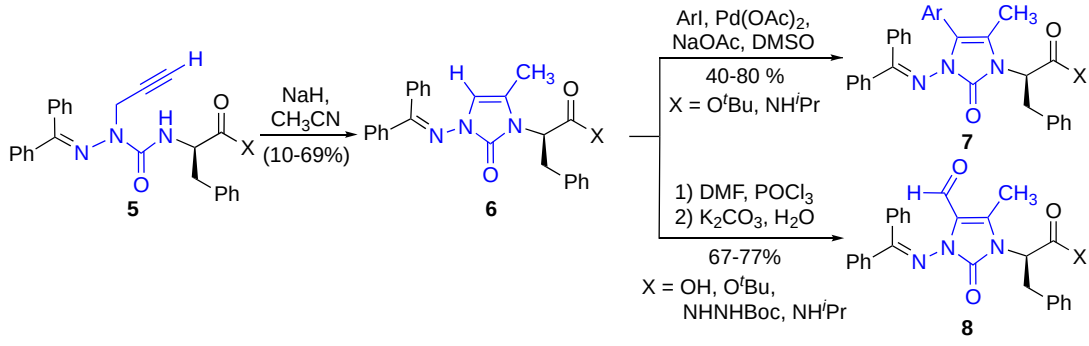

Fig. 2. Synthesis of Nai analogs by way of 5-endo-dig cyclisation of aza-propargylglycines.

Previously, [(5-Ar)Nai[4]]-GHRP-6 analogs **14a** and **14b** exhibited relatively high CD36 binding affinity and reduced NO production by macrophages exposed to a toll-like receptor-2 agonist. The *N*-amino cyclic urea of **14a** and **14b** adopted likely the *i* + 1 residue of a type II' β-turn with aryl substituent in *gauche* χ-space.[11]

With interest to further explore the active conformer, 4,5-disubstituted Nai peptides (e.g., **15**) are under investigation. For example, treatment of azopeptide **10** with 1-phenylpropan-2-one and proline, followed by acid catalyzed dehydration gave (4-Ph,5-Me)Nai **12** in 74% yield from azaGly **9**. Insertion of disubstituted Nai **12** into GHRP-6 analog **15** is now being pursued to detail the active conformation for CD36 modulation towards prototypes for mitigating macrophage-driven inflammation.

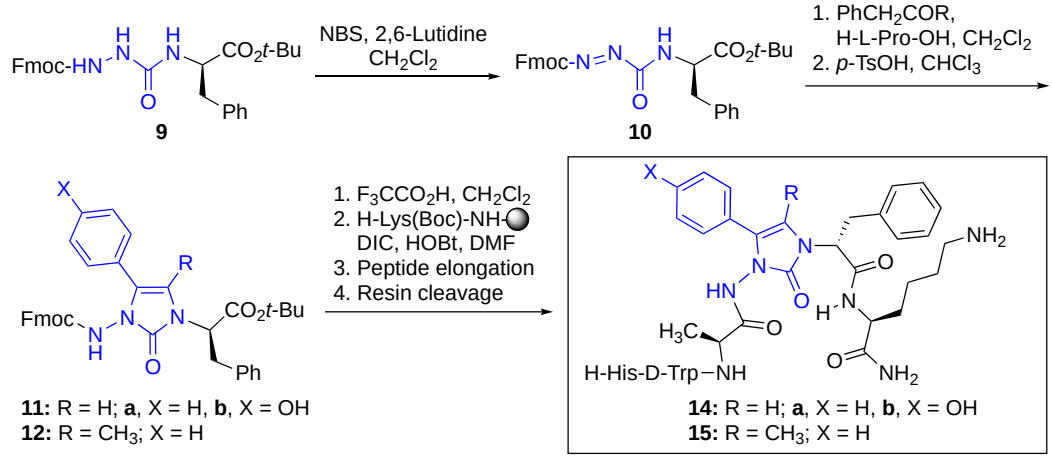

Fig. 3. Organocatalytic approach for Nai peptide synthesis for applications as CD36 modulators.

Acknowledgments

We are grateful for funding from the Natural Sciences and Engineering Research Council of Canada (NSERC, Discovery Research Project RGPIN-2019-04079), the Canadian Institutes of Health Research (CIHR, Project PJT-186296), and the Fonds de Recherche du Québec - Nature et Technologie (FRQNT, CGCC, FRQNT-2020-RS4-265155-CCVC). Assistance is acknowledged from members of the Université de Montréal facilities: Dr. P. Aguiar (NMR spectroscopy) and Dr. A. Fürtös (mass spectrometry).

References

1. Lubell, W. D. *Preface*, In *Peptidomimetics I*; Lubell, W. D., Ed.; Springer International Publishing: Cham, **2017**, v–xiv.
2. Robertson, N. S.; Spring, D. R. *Molecules* **2018**, *23*, 959, https://doi.org/10.3390/molecules23040959
3. Qvit, N.; Rubin, S. J. S.; Urban, T. J.; Mochly-Rosen, D.; Gross, E. R. *Drug Discovery Today* **2017**, *22*, 454, https://doi.org/10.1016/j.drudis.2016.11.003
4. Doan, N.-D.; Hopewell, R.; Lubell, W.D. *Org. Lett.* **2014**, *16*, 2232-5, https://doi.org/10.1021/ol500739k
5. Hamdane, Y.; Poupart, J.; Lubell, D. W. *Synthesis* **2022**, *54*, 1518–1526, DOI: 10.1055/s-0040-1719862
6. Freidinger, R. M. *J. Med. Chem.* **2003**, *46*, 5553-5566, https://doi.org/10.1021/jm030484k
7. Proulx, C.; Sabatino, D.; Hopewell, R.; Spiegel, J.; García Ramos, Y.; Lubell, W. D. *Future Med. Chem.* **2011**, *3*, 1139-1164, https://doi.org/10.4155/fmc.11.74
8. Proulx, C.; Lubell, W. D. *Org. Lett.* **2012**, *14*, 4552-4555, https://doi.org/10.1021/ol302021n
9. Poupart, J.; Doan, N.-D.; Berube, D.; Hamdane, Y.; Medena, C.; Lubell, W. D. *Heterocycles* **2019**, *99*, 279-293, DOI: 10.3987/COM-18-S(F)22
10. Poupart, J.; Hamdane, Y.; Lubell, W. D. *Can. J. Chem.* **2020**, *98*, 278-284, https://doi.org/10.1139/cjc-2019-0479
11. Hamdane, Y.; Chauhan, P. S.; Vutla, S.; Mulumba, M.; Ong, H.; Lubell, W. D. *Org. Lett.* **2021**, *23*, 3491-3495, https://doi.org/10.1021/acs.orglett.1c00936