Constrained Glu-Gly and Gln-Gly dipeptide surrogates from γ-substituted α-amino-δ-lactam synthesis

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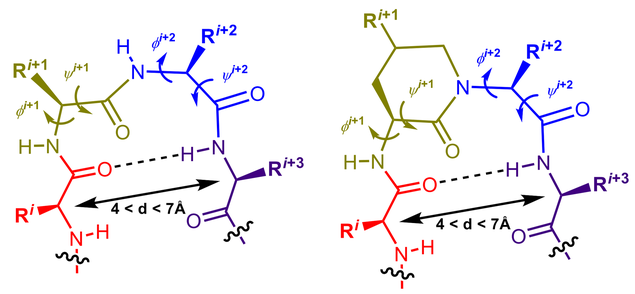
Abstract

α-Amino-δ-lactam (Adl) residues can adopt the *i*+1 position in type II β-turns in peptides. γ-Substituted Adl analogs have utility for mimicry of both turn backbone and side chain function and geometry in peptide-based drug discovery. Enantiomerically pure γ-substituted Adl residues have been synthesized from serine using a route featuring a key Cu-catalyzed allylation.

Introduction: Adl peptides

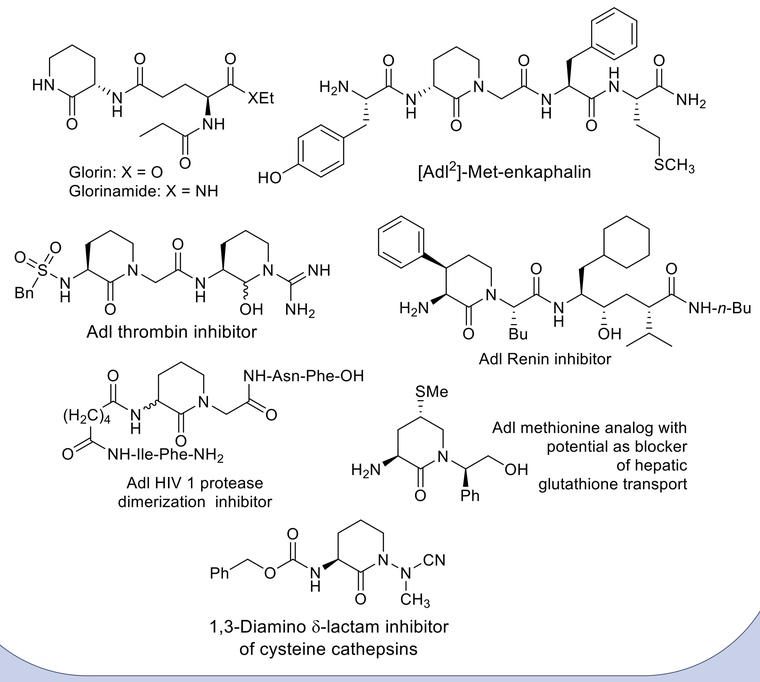
In peptide-based drug discovery, α-amino-δ-lactam (**Adl**) residues have been used as constrained mimics for the stabilization and study of β-turn conformers [1]. Substituted Adl derivatives are tools for studying both backbone and side chain function and geometry.



β-turn **Adl-β-turn mimic**

The natural chemoattractant peptide glorin and glorinamide counterpart contain Adl residues (Figure 1) [2]. Moreover, Adl peptide analogs have been employed to study the conformation of methionine-enkephalin [3], and to prepare inhibitors of thrombin [4] and HIV1-protease dimerization [5]. 4-Phenyl Adl analogs have served in renin inhibitors [6]. In addition, 5-thiomethyl Adl analogs have served as a constrained methionine residues in peptide mimics with potential to act as a blockers of hepatic glutathione transport [7].

Figure 1. Representative Adl analogs exhibiting biological and medicinal utility



Synthesis of γ-Substituted Adl peptides

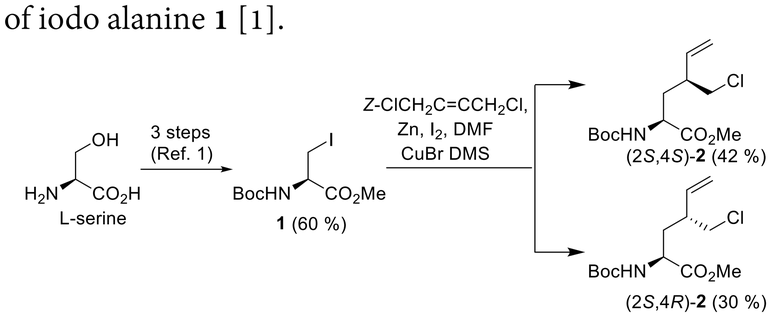
In light of their significant utility, γ-substituted Adl peptides were pursued by a versatile approach. Considering X-ray analyses find respectively Glu (Gln) and Gly residues at the *i*+1 and *i*+2 positions of type II β-turns, Adl-Gly analogs were targeted to furnish building blocks suited for mimicry of the active conformers of Glu-Gly and Gln-Gly peptides.

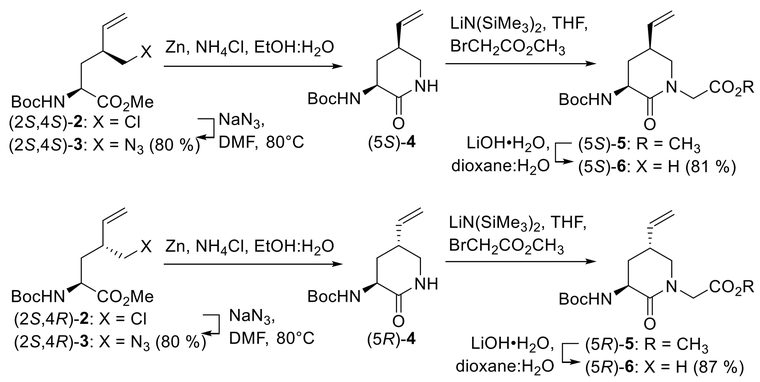
Goals:

- Synthesis of γ-vinyl Adl-Gly dipeptide
- Diversification of γ-vinyl group into carboxylate and carboxamide side chains

γ-Vinyl-Adl-Gly analog synthesis

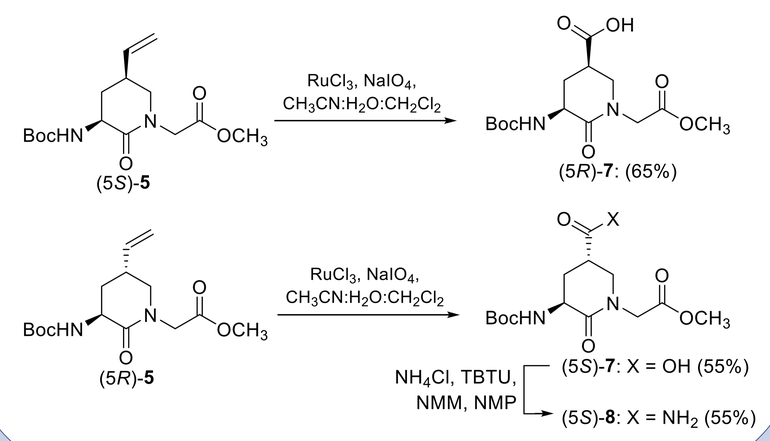
Protected γ-vinyl-Adl-Gly dipeptide **6** was synthesized by an 8 step sequence featuring Cu-catalyzed allylation of iodo alanine **1** [1].





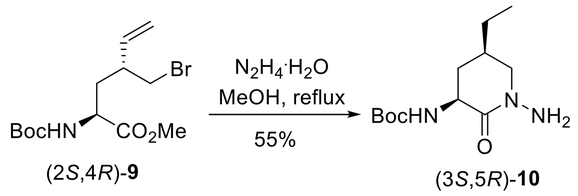
Diversification to Adl Glu-Gly and Gln-Gly analogs

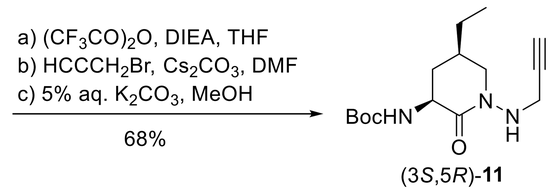
Modification of the olefin of γ-vinyl-Adl-Gly dipeptide **5** by oxidation and peptide coupling has provided 5-(HO_2C)Adl-Gly and 5-(H_2NOC)Adl-Gly analogs **7** and **8** suitable for peptide synthesis [1].



Synthesis of 1,3-diamino δ-lactams for insertion into Adl-azapeptides

1,3-Diamino δ-lactams have been employed in cathepsin inhibitors (Figure 1) [8] and offer interesting potential for insertion into peptides as Adl-aza-dipeptide surrogates. Towards their application, an effective route to 1,3-diamino δ-lactams is being developed from bromide **9** [9].





Conclusions

γ-Substituted Adl analogs were synthesized by effective methods, including constrained Glu-Gly and Gln-Gly dipeptides for mimicry of β-turn backbone and side chain geometry and function.

References

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