# Intramolecular Hydrogen Bonding in Cyclic Peptides and Depsipeptides

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## Introduction

- Utilizing intramolecular hydrogen bonds (IMHBs) (Fig. 1) can affect solubility and permeability of the drugs.
- There are IMHB studies done on molecules beyond Rule of Five[1], levoglucosan derivatives[2] and small-sized pseudo-rings[3] but only a few IMHB studies have been done specifically on cyclic peptides[4,5] (CPs), cyclic depsipeptides (CDPs) or larger pseudo-rings.
- The aim of this MSc project is to assess the therapeutic potential of CPs/CDPs via analyzing their structures and then, testing them with molecular dynamics (MD) to determine their conformational stability.

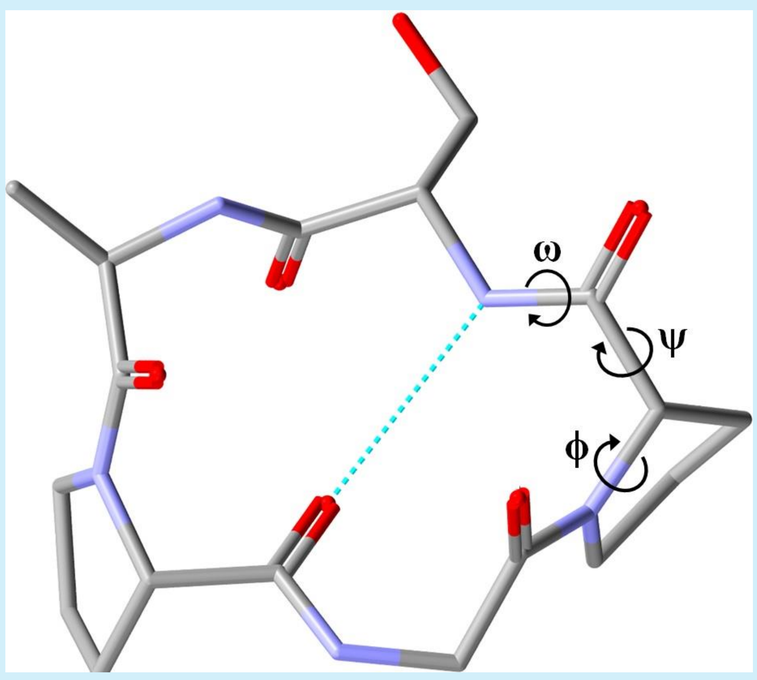


**Figure 1:** An example for CP, containing 1 IMHB (shown with a turquoise dashed line). ω, ψ and ϕ are the torsions, which show the relative rotational angles between groups at both ends of the bonds. CSD code for this cyclic peptide: CGPSAQ

## Data Mining Method

- From tetra- to deca-CP/CDP, crystal structures were searched in Cambridge Structural Database (CSD), using ConQuest. Duplicated entries and metal complexes of the molecules were excluded from this search.
- Using Mercury, structures of every molecule were analysed comprehensively to find the ones with IMHB(s) and molecules with IMHB(s) were collected as data. Then, the sizes of pseudo-rings in cyclic peptides were determined and the frequency of pseudo-ring formation in among all peptides in CSD were searched.
- Finally, torsions of these pseudo-rings were investigated. Only the torsions of two most abundant pseudo-rings are shown.

## Results

- CPs with odd number of amino acids have higher tendency to contain IMHB(s) (Fig. 2) and there are not many crystallized CDPs in CSD (Fig. 3).
- The most abundant pseudo-ring in both collected data and in all peptides in CSD is 10-membered one (Fig. 4-5). This is a result of β-turn in peptides.
- ψ and ϕ torsions prefer certain angular values (Fig. 6-7). Moreover, majority of these torsions prefer *trans* conformation

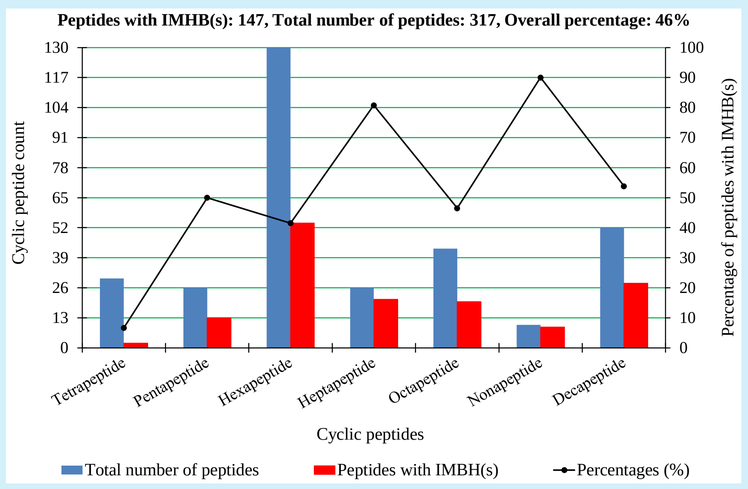


**Figure 2:** Number of CPs with IMHB(s) in the data set

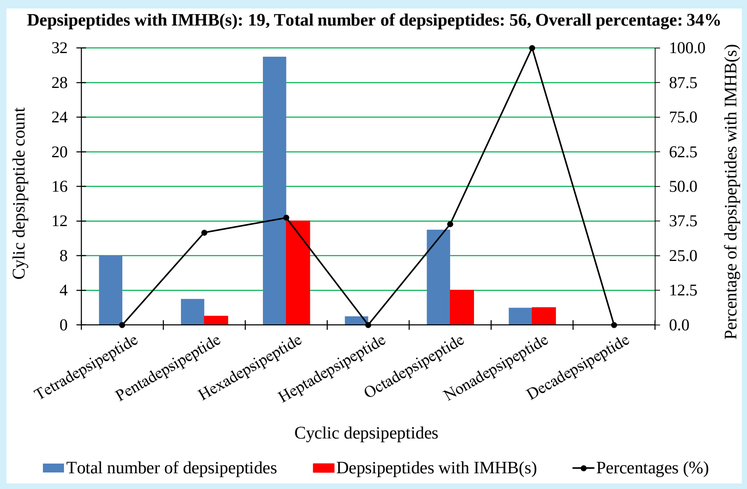


**Figure 3:** Number of CDPs with IMHB(s) in the data set

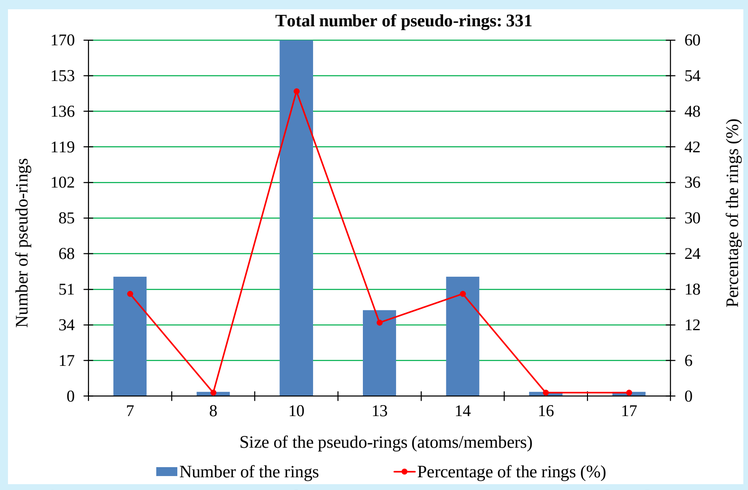


**Figure 4:** Occurrence of IMHB ring sizes in CPs in the data set

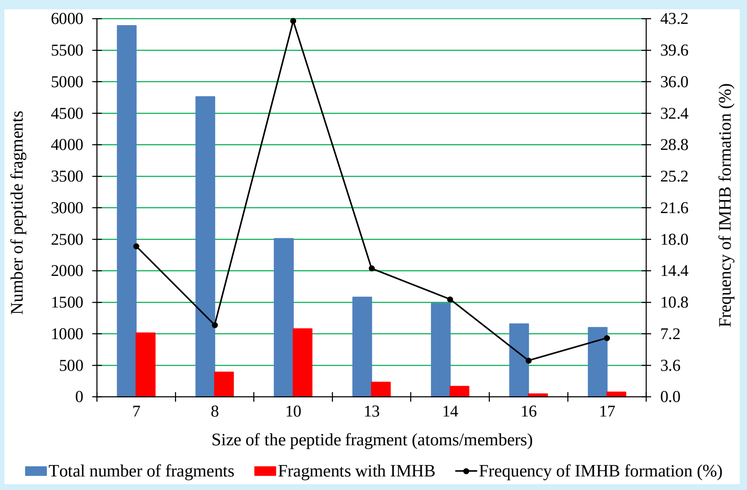


**Figure 5:** Number of peptide fragments in CSD. Red columns show the number of pseudo-rings, which formed with an IMHB

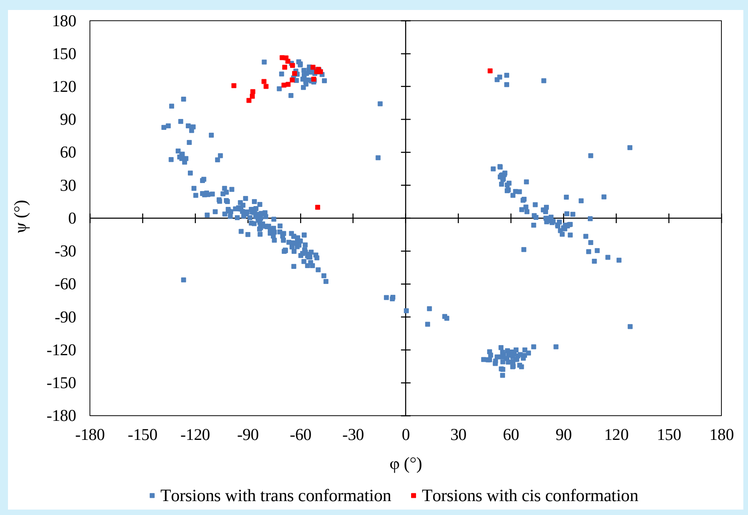


**Figure 6:** Distribution of torsions in 10-membered pseudo-rings

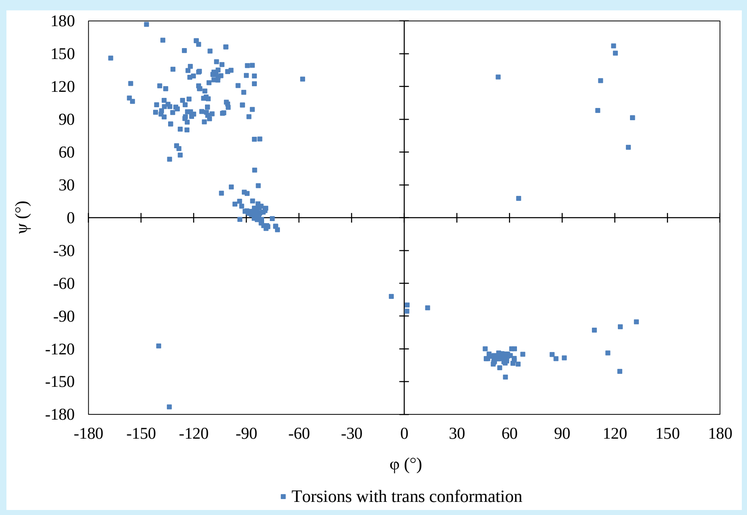


**Figure 7:** Distribution of torsions in 14-membered pseudo-rings

## Conclusion and Outlook

- There are commonly observed shapes for rings with IMHB(s) in cyclic peptides and therefore, they are going to be further tested with MD in GROMACS.

## References

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[2] L. Quiquempoix *et al*, 2017, **22**, 518

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[4] T. Rezai *et al*, J. Am. Chem. Soc. 2006, **128**, 2510-2511

[5] T. Rezai *et al*, J. Am. Chem. Soc. 2006, **128**, 14073-14080