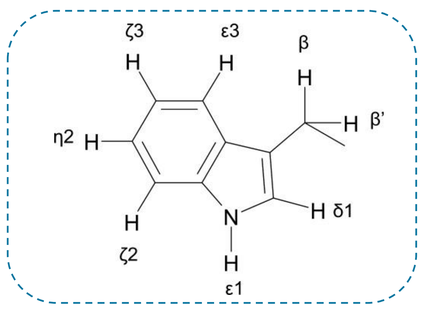
Engineering Robust and Photoswitchable β-turns Through Hydrazide Incorporation

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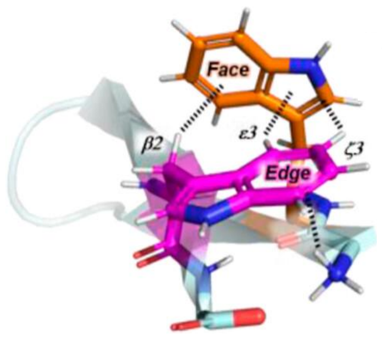
Abstract:

The Tryptophan Zipper (TrpZip) is an iconic folding motif of β-hairpin peptides stabilized by cross-strand tryptophan–tryptophan interactions, each stabilized by an aromatic–aromatic stacking in an edge-to-face geometry. They serve as minimal model systems for understanding protein folding, stability, and hydrophobic interactions. Herein, we report one promising strategy for specifying the conformation of glycine by substituting the alpha carbon with nitrogen, thereby creating an azapeptide which would therefore restrict the conformational landscape as compared to glycine. Further, we set out to enable spatiotemporal control over β-hairpin formation by the introduction of a photosensitive β-turn mimic in the TrpZip backbone. Finally, we anticipate that this mimic will be useful in better deciphering of the roles of β-hairpin structures in protein folding processes, development of peptidomimetic systems, and chemical biology more generally.

Tryptophan as a unique residue



- Tryptophan as a residue has the lowest abundance (~1.4%) amongst all naturally occurring amino acids.



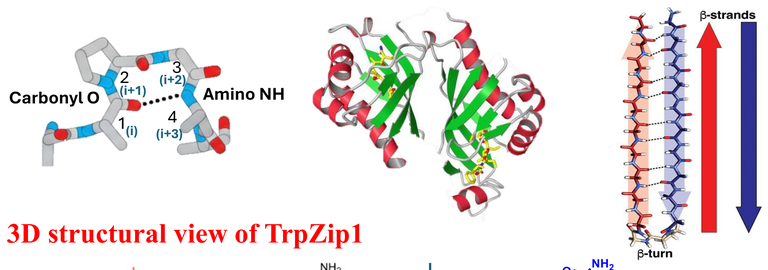
Trp/Trp
Edge-to-Face stacking

- This stacking preference arises from Coulombic interactions between electron-deficient hydrogens and the electron-rich π-cloud.

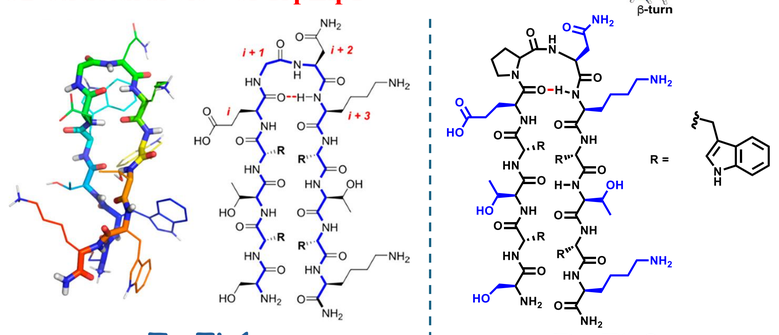
Roche and co-workers, ACS Chem. Biol., **2023**, *18*, 2555-2563

β-turn & β-hairpin

β-turn | β-turn in globular protein | β-hairpin



3D structural view of TrpZip1

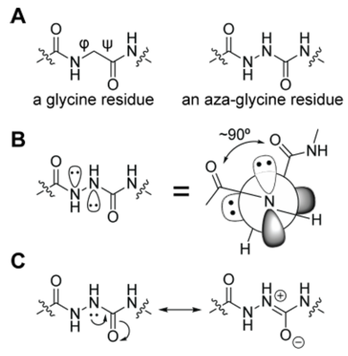


TrpZip1 | TrpZip3

Thomson and co-workers, Org. Lett., **2020**, *22*, 4424-4428

Azapeptide incorporation in TrpZip3

- Aza-glycine restricts the backbone dihedral angles φ and ψ.
- Aza-glycine might stabilize the type I′ turn in Trpzip3, where glycine is present at the i+2 position.



TrpZip3-azGly

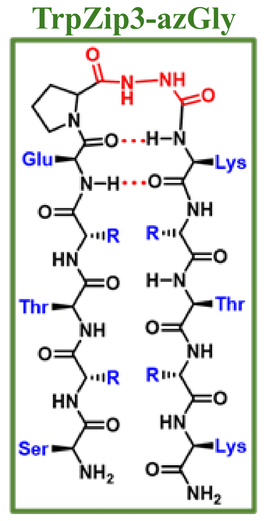


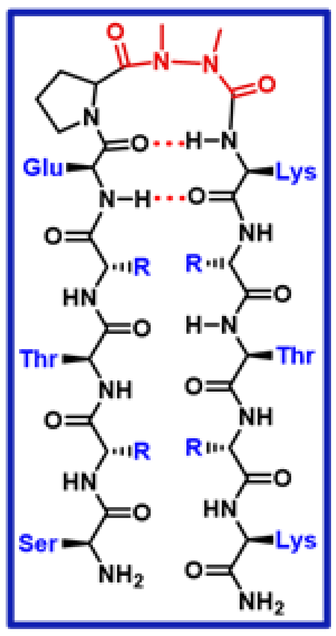
Table 1. Preferred approximate dihedral angles of glycine residues in β-turns

	φ (C′i–1–Ni–Cαi–C′i)	ψ (Ni–Cαi–C′i–Ni+1)
Type I′ β-turn, i+2 position	90°	0°
Aza-glycine conformational minima	±90°	0°/180°

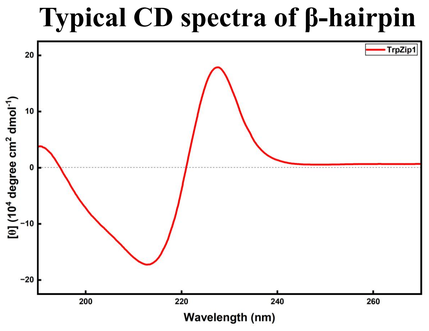
Newberry and co-workers, Chem. Rxiv., **2024**

Can Aza substitution enhance stability?

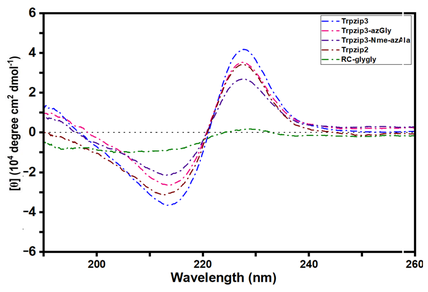
TrpZip3-NMeNme



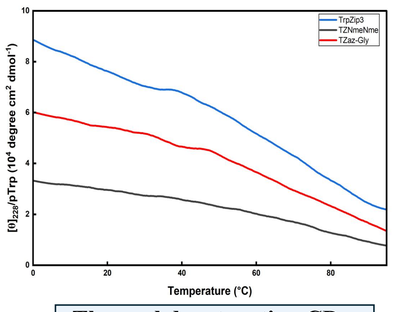
Typical CD spectra of β-hairpin



CD spectra of TrpZip1 (1mg/ml) in 20mM sodium phosphate buffer (at 4°C)



CD spectra in 20mM sodium phosphate buffer (at 4°C)



Thermal denaturation CD monitored at 228nm

Tm (°C)

TrpZip3	65
Tz3aza-Gly	70
Tz3NMeNme	40

Photocontrol of β-hairpin peptide via Hydrazide incorporation

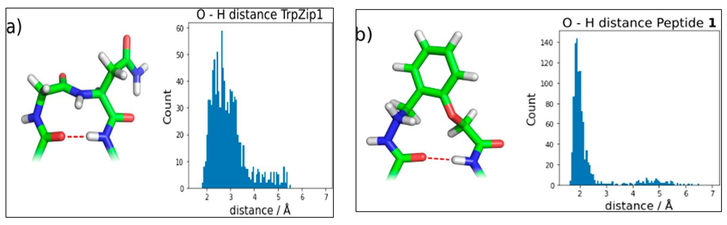


Fig: MD Analysis showing the MD trajectory and a Histogram of the O–H distance for the β-turn hydrogen bond. (a) TrpZip1. (b) Peptide 1.

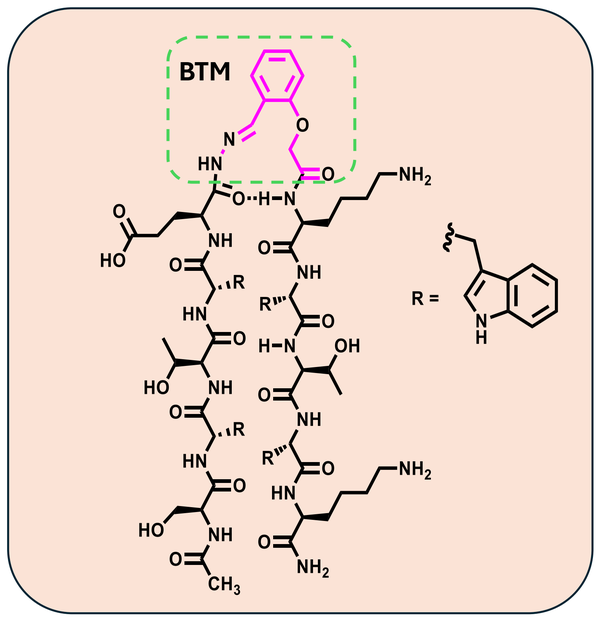
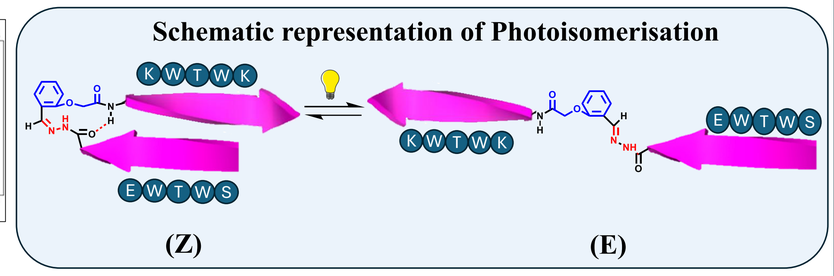
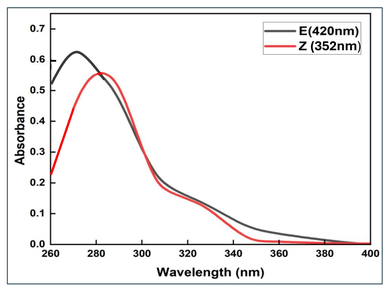
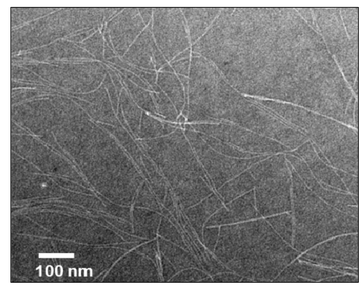


Fig: Introduction of β-turn peptidomimetic in a β-hairpin Tryptophan Zipper 1 (Peptide 1).

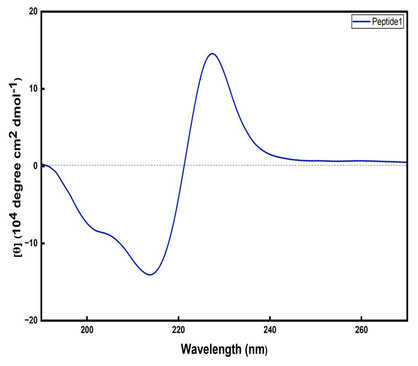




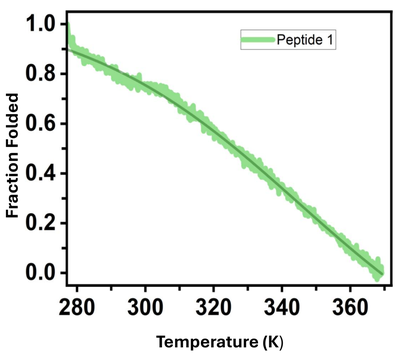
UV-vis absorption spectra of Peptide 1 In DMSO (1×10^{-5} M); $\Delta\lambda_{max}$ 16nm



TEM image of fibrils



CD spectra of Peptide 1 in 20mM Sodium phosphate buffer (at 4°C)



Thermal denaturation CD of Peptide1 monitored at 228nm

Summary and Outlook

1. Aza substitution moderately enhances TrpZip3 stability and may help reduce aggregation in glycine-rich sequences.
2. We successfully incorporated BTM into TrpZip1 to create a photoresponsive peptide and further plan to study its photoisomerization via NMR.

Acknowledgement

JNCASR | SERB INDIA | ज्ञान-विज्ञान विमुक्तये | सत्यमेव जयते Department of Science and Technology (DST) DST

