Conformational Effects of Fluorinated Aminocyclopropane Carboxylic Acids Incorporation in Peptides

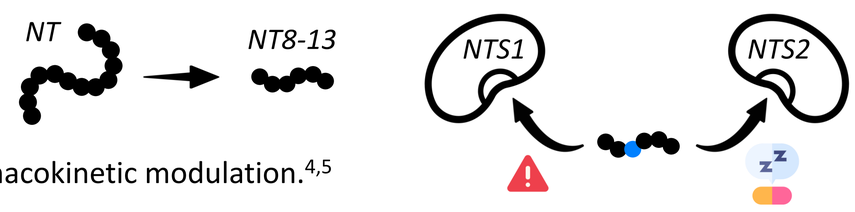
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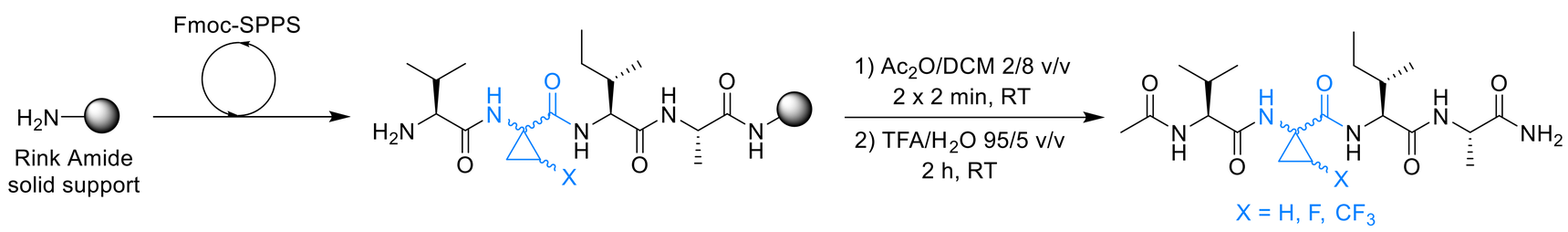
Context of the study

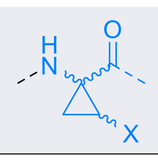
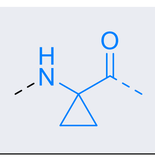
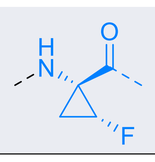
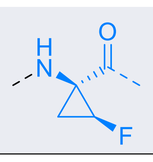
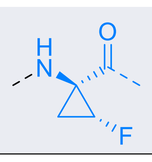
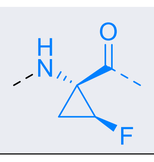
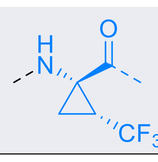
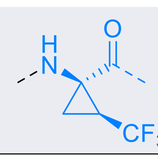
- **Neurotensin** (**NT**), a tridecapeptide with analgesic properties, acts through binding to the NTS2 receptor.[1,2,3]
- NT's poor NTS2/NTS1 receptor selectivity causes undesirable side effects.
- Constrained amino acids, such as α,α-dialkylamino acids, promote specific peptide conformations, aiding pharmacokinetic modulation.[4,5]
- Previous work showed that replacing Pro in the NT8-13 sequence with a fluorinated aminocyclopropane carboxylic acid (**FACC**) improves NTS2/NTS1 selectivity.



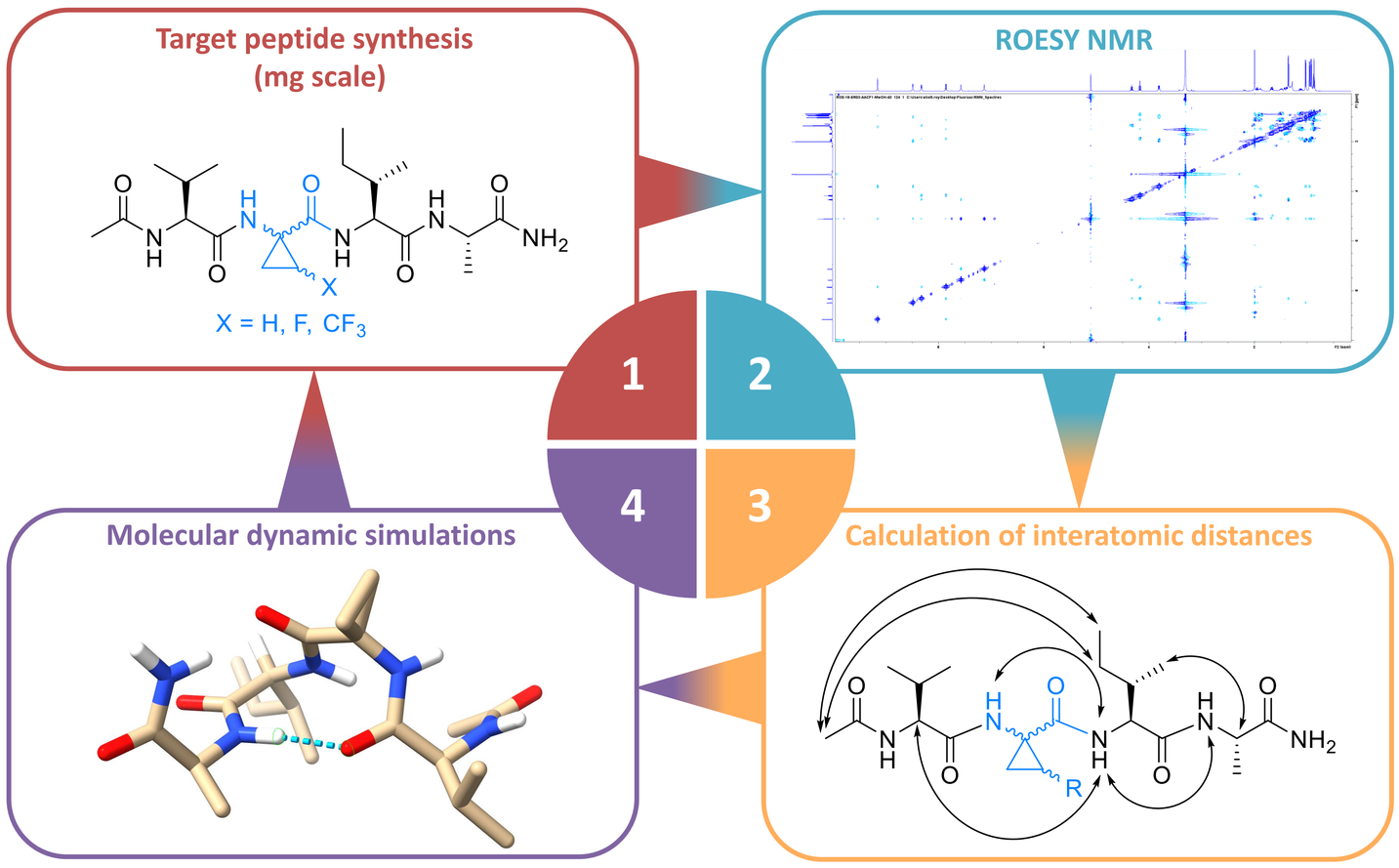
Objectif: Investigate how **FACCs** influence peptide conformation to gain new insights into their **structure-activity relationship** for medicinal applications.

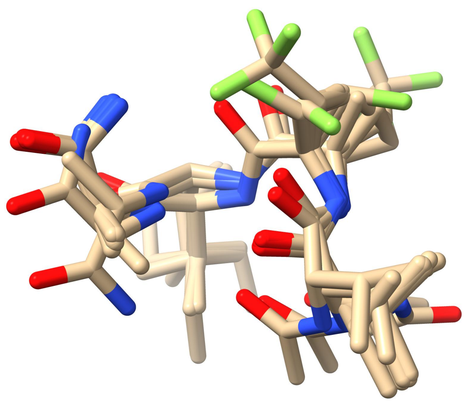
1) Synthesis of model peptides



							
Isolated yield (%)	28	15	42	3	4	5	6

2) Structural analysis





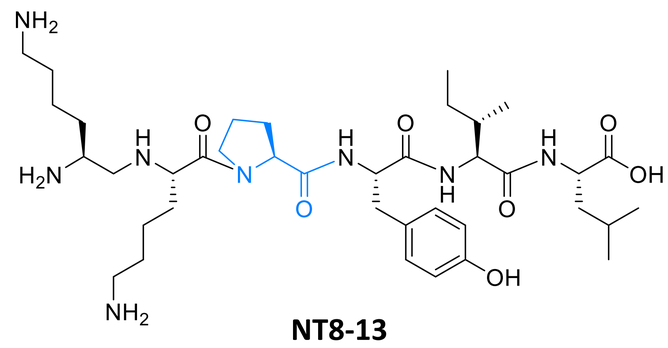
Superimposition of the lowest energy structures of model peptides.

Observations:

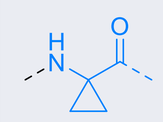
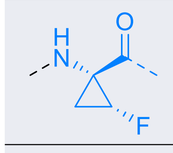
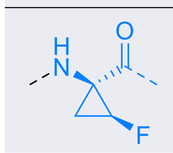
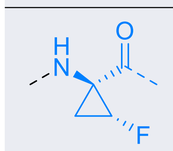
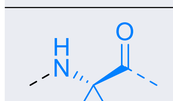
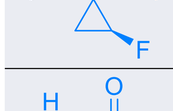
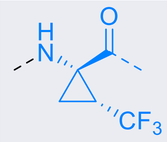
- Cyclopropane substituents seem not to influence peptide conformations.
- Peptide conformations seem only guided by the cyclopropane in a C10 turn.

3) Affinity of NT8-13 analogues

After the synthesis of **Pro[10]FACC NT8-13 analogues**, compounds' affinities toward NTS1 and NTS2 were tested by dose-response displacement of radiolabeled NT.



NT8-13

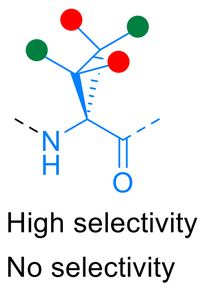
	Isolated yield (%)	Ki ± SEM (nM) hNTS1	Ki ± SEM (nM) rNTS2
	96	786 ± 226	340 ± 191
	65	> 10 000	303 ± 190
	10	2836 ± 986	457 ± 219
	17	> 10 000	226 ± 141
	15	509 ± 103	101 ± 18
	57	1598 ± 450	786 ± 496
	22	> 10 000	117 ± 52

Observations:

- Unsubstituted cyclopropane gives no selectivity.
- Presence of –F or –CF3 substituents on specific positions seems to confer high NTS2/NTS1 selectivity.

Conclusion & Perspectives

- Incorporation of the aminocyclopropane carboxylic acid motif into peptide sequences induces a C10 turn conformation, regardless of cyclopropane substitution.
- However, substitution at only 2 out of the 4 positions on the cyclopropane with hydrophobic substituents confers high NTS2/NTS1 selectivity.
- New FACCs will be tested soon to further decipher the SAR of these residues.



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References:

[1] St-Gelais, F. et al. *Psychiatry Neurosci*. **2006**, *31*, 229.
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