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Synthesis of 5-member heteroaromatics containing peptide backbones: *pro* and *cons* of structural constraints induced by amide bond surrogates

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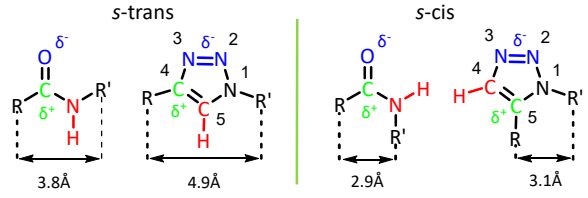
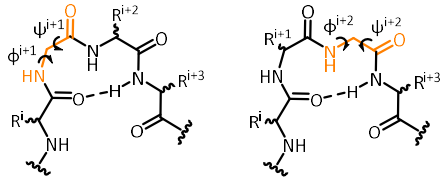
Background

Increasing the stability and bioavailability of short peptides *in vivo* is crucial for the development of peptide-based drugs. The main challenges to address are the low metabolic stability and the high conformational flexibility of peptides, which can lead to inactivation and a decrease in their activity. To avoid these issues, one strategy is the use of peptidomimetics, where the peptide bond is replaced by surrogate bonds with similar structural features (bioisostere).[1] One of the most common bioisostere of the amide bond is the [1,2,3] triazole moiety, which presents structural features similar to the peptide bond, resulting in an improvement in metabolic stability and an increase in structural constraints. Moreover, this moiety is easily obtained by 1,3-dipolar cycloaddition reaction, and proved particularly resistant to several types of cleavage. Finally, an additional benefit of peptidotriazoles is their low toxicity.

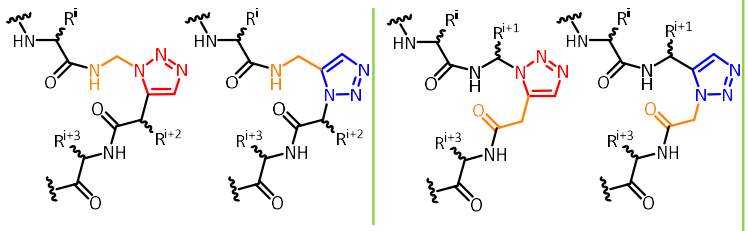


Objectives

The main objective is to develop mimetics of the *s*-cis peptide bond using 1,5-disubstituted [1,2,3] triazole in order to stabilize β-turns where a **glycine** is present in the i+1 or i+2 position. This aims to improve the low rigidity of glycine, thereby increasing the activity and selectivity against specific targets.



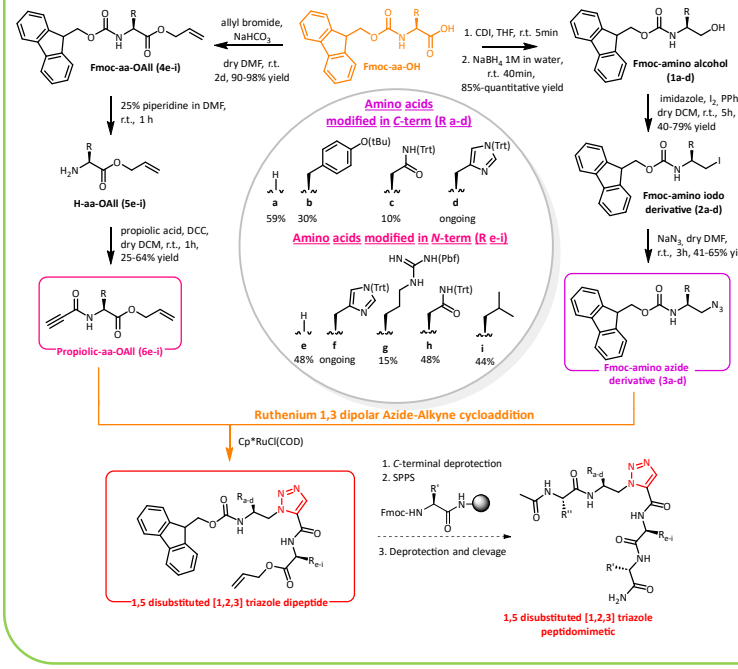
➢ Orientation of heterocycle ←→conformational behavior



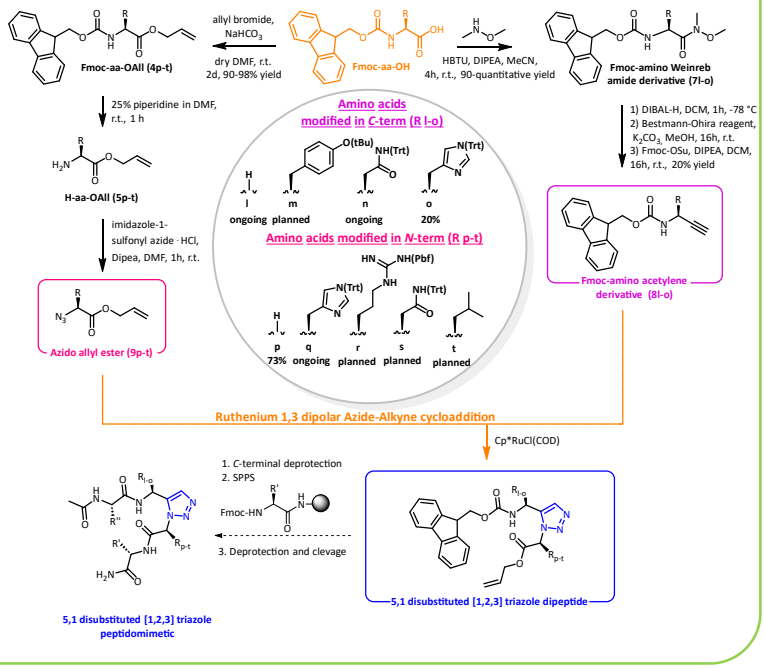
1,5 disubstituted [1,2,3] triazole peptidomimetic
5,1 disubstituted [1,2,3] triazole peptidomimetic

Research and development[2]

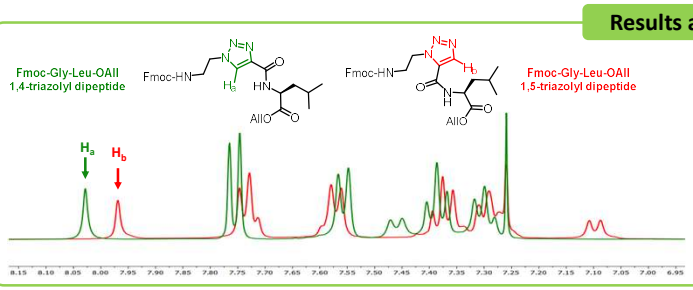
Mimetic containing 1,5 disubstituted [1,2,3] triazole



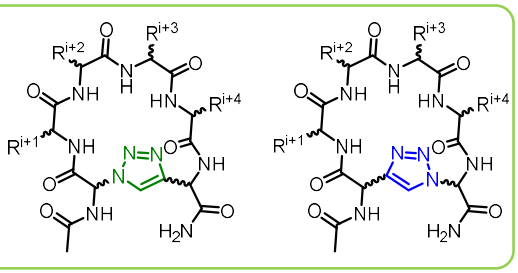
Mimetic containing 5,1 disubstituted [1,2,3] triazole



Results and Future perspectives



- Study of the conformational behavior
- Biological properties
- Comparison with side chain-to-side chain triazolyl bridged peptides[3]



[1]Li, H.; Aneja, R.; Chaiken ,I. *Molecules* **2013**, *18* (8), 9797–9817.
[2]Bruyat, P.; Gautier, A.; Jean, L.; Renard, P. *J. Org. Chem.* **2018**, 83, 13515−13522
[3]Testa, C.; Scrima, M.; Grimaldi, M.; D'Ursi, A. M.; Dirain, M. L.; Lubin-Germain, N.; Singh, A.; Haskell-Luevano, C.; Chorev, M.; Rovero, P.; Papini, A. M. *J. Med. Chem.* **2014**, *57* (22), 9424–9434.