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Isosteric replacement of amide bond with azole rings as a tool for drug design

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Abstract

Post-translational modified amino acid residues with azole ring in place of the C-terminal amide bond have been found in numerous natural peptides. Peptides, in which such unique amino acid residues occur, belong mainly to RiPP (*Ribosomally Synthesized and Post-translationally Modified Peptides*) and are classified into four groups: *Linear azol(in)e-containing peptides* (LAPs) (Arnison, Bibb et al. 2013), *Thiopeptides* (Bagley, Dale et al. 2005), *Cyanobactins* (also called cyanamides) (Kashman, Bishara et al. 2010), and *Bottromycins*. Those peptides reveal antibacterial, antitumor and antimalarial activity (Bagley et al. 2005; Davyt and Serra 2010; Jin 2016; Craveur et al. 2019; Ding et al. 2020). The biological activity and metal-binding properties of proteins and peptides depend on their conformation (Giri Rao and Gosavi 2016). The capability of changing ligand conformation to improve binding affinity in proteins is one of the biomolecular engineering tools crucial for drug discovery and design (Lassila 2010; Gagné et al. 2012; Boehr et al. 2018; Ding et al. 2020; Aguesseau-Kondrotas et al. 2019). Replacement of the main chain peptide bond by azole ring as oxazole, thiazole or imidazole ring constrains the chain's conformational flexibility. Therefore conformational studies on a series of model amino acid residues containing oxazole, thiazole and imidazole rings were performed using theoretical calculations (DFT method) supported by FTIR, NMR, and X-ray methods for synthesized compounds. In addition, the solid-state crystal structure conformations of amino acid residues retrieved from the Cambridge Structural Database were also analysed. The results showed that the studied amino acids tend to adopt the unique conformation β2 (ϕ, $\psi \approx 180°, 0°$), especially in weakly polar environments, stabilized through the formation of the internal N-H···N hydrogen bond, atypical for standard residues. The azomethine nitrogen atom (-N=) is a better hydrogen bond acceptor than the sulfur or oxygen atoms. Interestingly, because the feature of imidazole is that it can be protonated and deprotonated, and it occurs in two tautomeric forms, our research proved that both tautomer and pH change can cause a conformational switch of the studied residues with the C-terminal peptide group replaced by imidazole.

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