Novel furan-containing peptide-based inhibitors of protein arginine deiminase type IV (PAD4)

ABSTRACT

Protein arginine deiminase type IV (PAD4) is responsible for the posttranslational conversion of peptidylarginine to peptidylcitrulline. Citrullinated protein is the autoantigen in rheumatoid arthritis, and therefore, PAD4 is currently a promising therapeutic target for the disease. Recently, we reported the importance of the furan ring in the structure of PAD4 inhibitors. In this study, the furan ring was incorporated into peptides to act as the ñwarheadò of the inhibitors for PAD4. IC50 studies showed that the furan-containing peptide-based inhibitors were able to inhibit PAD4 to a better extent than the furan-containing small molecules that were previously reported. The best peptide-based inhibitor inhibited PAD4 reversibly and competitively with an IC50 value of 243.2 ± 2.4 εm. NMR spectroscopy and NMR-restrained molecular dynamic simulations revealed that the peptide-based inhibitor had a random structure. Molecular docking studies showed that the peptide-based inhibitor entered the binding site and interacted with the essential amino acids involved in the catalytic activity. The peptide-based inhibitor could be further developed into a therapeutic drug for rheumatoid arthritis.

Keyword: Drug design; Peptide-based inhibitors; Protein arginine deiminase IV; Rheumatoid arthritis