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# Discovery of new inhibitor for the protein arginine deiminase type 4 (PAD4) by rational design of α-enolase-derived peptides

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Rheumatoid arthritis (RA) is an inflammatory autoimmune disease affecting about 0.24 % of the world population. Protein arginine deiminase type 4 ( PAD4 ) is believed to be responsible for the occurrence of RA by catalyzing citrullination of proteins. The citrullinated proteins act as autoantigens by stimulating an immune response. Citrullinated α-enolase has been identified as one of the autoantigens for RA. Hence, α-enolase serves as a suitable template for design of potential peptide inhibitors against PAD4 . The binding affinity of α-enolase-derived peptides and PAD4 was virtually determined using PatchDock and HADDOCK docking programs. Synthesis of the designed peptides was performed using a solid phase peptide synthesis method. The inhibitory potential of each peptide was determined experimentally by PAD4 inhibition assay and $IC_{50}$ measurement. PAD4 assay data show that the N-P2 peptide is the most favourable substrate among all peptides . Further modification of N-P2 by changing the Arg residue to canavanine [P2 (Cav)] rendered it an inhibitor against PAD4 by reducing the PAD4 activity to 35 % with $IC_{50}$ 1.39 mM. We conclude that P2 (Cav) is a potential inhibitor against PAD4 and can serve as a starting point for the development of even more potent inhibitors. © 2021 Elsevier Ltd

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Drug design ; PAD4 ; Peptide inhibitor ; Rheumatoid arthritis

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