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Fighting the root cause of rheumatoid arthritis: Discovery of protein arginine deiminase type IV inhibitors

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Protein Arginine Deiminase IV (PAD4) is a promising therapeutic target for Rheumatoid Arthritis (RA). The main objective of this research is to search for potent inhibitors for PAD4. Three approaches were applied in this research: structure-based, ligand-based and peptide-based drug designs. LIDAEUS and Ultrafast Shape Recognition (USR) programs were utilized in virtual high throughput screening. Three out of 22 of the top-ranked water-soluble compounds identified by LIDAEUS program showed significant inhibition to PAD4. The IC50 values were ranged from 1.49±0.03 to 2.96±0.01 mM. The structures of the three compounds showed no resemblance with previously discovered PAD4 inhibitors, nor with existing drugs for RA treatment. A previous reported inhibitor, streptonigrin, was used as a parent compound in ligand-based virtual screening using USR. Five compounds out of 37 compounds screened inhibited PAD4 significantly. The best compound was a moderate inhibitor for PAD4 with IC50 value of 362.67±4.13 μM. The common structural feature of the compounds discovered by LIDAEUS and USR was furan ring. Peptide-based inhibitors incorporated with non-standard amino acid containing furan ring were designed and synthesized. The peptide-based inhibitors have IC50 value of 243.2±2.4 μM which was lower than compounds obtained from LIDAEUS and USR. Inhibitors containing furan ring have high potency in inhibiting PAD4 and the inhibitors discovered in this research could be further developed to a better drug candidate for treatment of rheumatoid arthritis.

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