

Squash inhibitors: From structural motifs to macrocyclic knottins

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Abstract: In this article, we will first introduce the squash inhibitors, a well established family of highly potent canonical serine proteinase inhibitors isolated from Cucurbitaceae. The squash inhibitors were among the first discovered proteins with the typical knottin fold shared by numerous peptides extracted from plants, animals and fungi. Knottins contain three knotted disulfide bridges, two of them arranged as a Cystine-Stabilized Beta-sheet motif. In contrast to cyclotides for which no natural linear homolog is known, most squash inhibitors are linear. However, *Momordica cochinchinensis* Trypsin Inhibitor-I and -II (MCoTI-I and -II), 34-residue squash inhibitors isolated from seeds of a common Cucurbitaceae from Vietnam, were recently shown to be macrocyclic. In these circular squash inhibitors, a short peptide linker connects residues that correspond to the N- and C-termini in homologous linear squash inhibitors. In this review we present the isolation, characterization, chemical synthesis, and activity of these macrocyclic knottins. The solution structure of MCoTI-II will be compared with topologically similar cyclotides, homologous linear squash inhibitors and other knottins, and potential applications of such scaffolds will be briefly discussed. © 2004 Bentham Science Publishers Ltd.

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Proteinase Inhibitors

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