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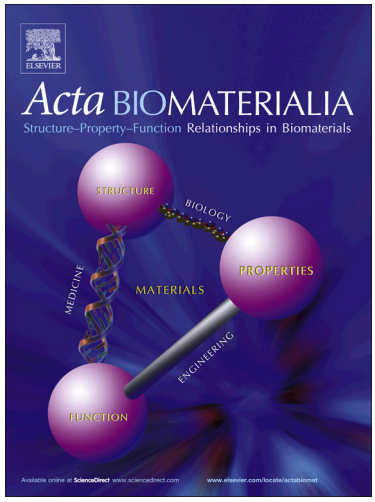

Full length article

Inhibition of the Fibrillation of Highly Amyloidogenic Human Calcitonin by Cucurbit[7]uril with Improved Bioactivity

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Inhibition of the Fibrillation of Highly Amyloidogenic Human Calcitonin by Cucurbit[7]uril with Improved Bioactivity

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Abstract: Protein/peptide fibrillation is an important challenge for biotechnological drug development. Salmon calcitonin (sCT) is currently used in the clinical treatment of bone-related diseases such as osteoporosis and hypercalcemia, but it still has the risk of immune responses. Although human calcitonin (hCT) would be a better choice in terms of immunogenicity, it has a strong tendency to irreversibly aggregate in aqueous solutions and form long amyloid fibrils, which significantly reduces its bioavailability and therapeutic potency. Here, we demonstrate that cucurbit[7]uril (CB[7]) can inhibit hCT fibrillation by supramolecular interaction with its aromatic groups (affinity: Phe16 > Tyr12 > Phe19 > Phe22). The hCT-CB[7] complex exhibits low cytotoxicity, even promotes osteoblast proliferation and osteogenic capacity of MC3T3 cells. Meanwhile the hCT-CB[7] complexes shows higher bioactivity compared to hCT in reducing blood calcium levels in rats, and also decreases the immunogenicity of hCT. These results suggest that CB[7] has the potential to improve the therapeutic potency of amyloidogenic protein/peptide drugs such as hCT.

Keywords: Human calcitonin, Amyloid beta-peptides, Cucurbit[7]uril, Inhibitor, Supramolecular chemistry.