Crystal structure of transthyretin in complex with indomethacin and sulindac.

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Transthyretin (TTR) is a protein found in blood plasma and cerebral fluid. This protein is the secondary carrier of T4 (thyroid hormone). In its native form, TTR forms a tetramer composed of identical subunits of 127 amino acids. In misfolding conditions, such as low pH, the tetramer can dissociate into monomers, followed by structural changes, leading to amyloid fibril formation. The deposition of these amyloid fibrils on tissues is an important factor in several diseases. We have been screening for compounds that would act as potential inhibitors of protein dissociation, which is a step which proceeds aggregation and fibril formation. Here we show that indomethacin and sulindac, two non-steroidal anti-inflammatory compounds, are able to bind to TTR in micromolar concentration. We solved the crystal structure of theses complexes and the mechanism of binding and implications on stabilization of TTR tetramer are discussed.
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