

Design and Synthesis of Transglutaminase Inhibitors

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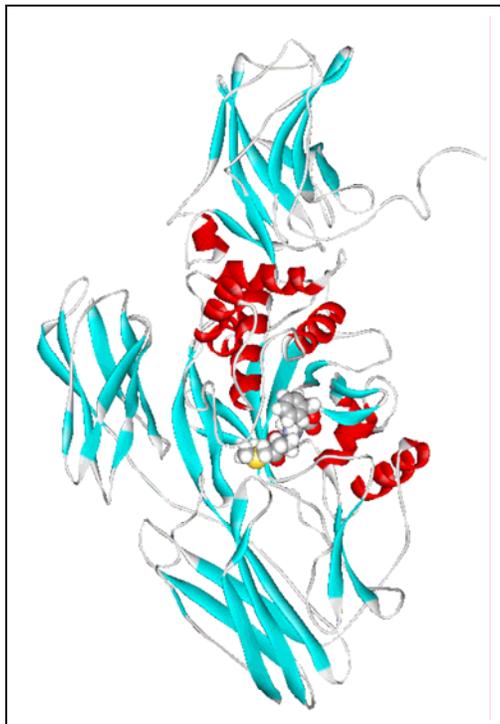
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Transglutaminases (TGases) catalyse the calcium-dependent crosslinking between proteins through formation of a peptidase-stable isopeptide linkage between glutamine and lysine residues on separate protein molecules.^{1,2} This is the heart of a generic biological tissue stabilization process. Blood clot stabilization and wound healing,³ for example, are facilitated by this process. There are occasions, however, when it would be beneficial to block this otherwise natural process. Examples include fibrosis and scarring, thrombosis and neurodegenerative diseases such as Alzheimer's and Huntington's.^{4,5}

The project will involve the computer-aided design, synthesis and biological evaluation of potential transglutaminase inhibitors. Computer models of the different transglutaminase will be prepared from X-ray crystal structures and homology modelling. These will be refined using a combination of molecular dynamics and semi-empirical quantum mechanical geometry optimisations and used as the hosts for *in silico* docking studies with analogues of a class of in-house inhibitors⁶. This will facilitate exploration of the allowable docking space within the active sites of the different TGase family members and will enable the substrate specificities to be delineated beyond that known from biochemical binding experiments so far.

The existing dipeptide-based inhibitors consist of a recognition element (the dipeptide) and a warhead that alkylates a key cysteine residue at the active site. The synthetic part of this project will involve the synthesis of new analogues of the existing inhibitors, including non-peptide small molecule analogues, using the modifications suggested by the modelling studies. These will be tested *in vitro* and the results will be used to guide the optimisation of the inhibitor structures.



References

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