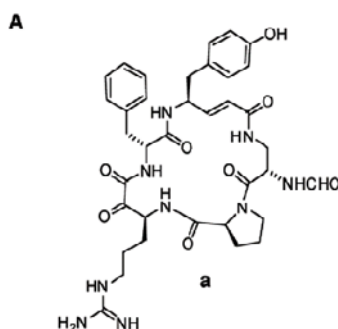
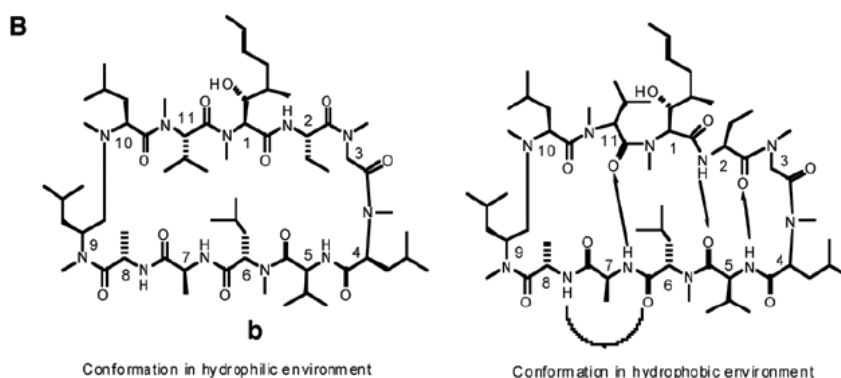


S1 box | **Cyclic peptides in nature and their conformations.**

a | Macrocyclic peptides that can function as classic enzyme inhibitors are represented by the sponge-derived thrombin inhibitor cyclotheonamide A.



b | NMR studies of cyclosporine A (CsA) and derivatives in various solvents have shown that cyclic peptides can change conformation depending on their environment. In polar solvents capable of hydrogen bonding, CsA adopts a conformation where solvent interacts with the amide backbone to satisfy both hydrogen bond donating and accepting groups. In hydrophobic environments, those hydrogen bonds are fully satisfied internally, maximising the macrocycle's lipophilicity and membrane permeability¹. It has been postulated that the amphiphilic nature of CsA improves its bioavailability, despite its overall peptide-like nature^{2,3}. Notably, the bound conformation of tacrolimus is highly similar to the structure of water-soluble analogues, as determined by NMR⁴, analogous to the situation for CsA. Thus, tacrolimus is also a molecule whose functional domains are revealed through conformational rearrangement rather than localisation of polar and apolar functional groups (for example, as found in AmB).



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