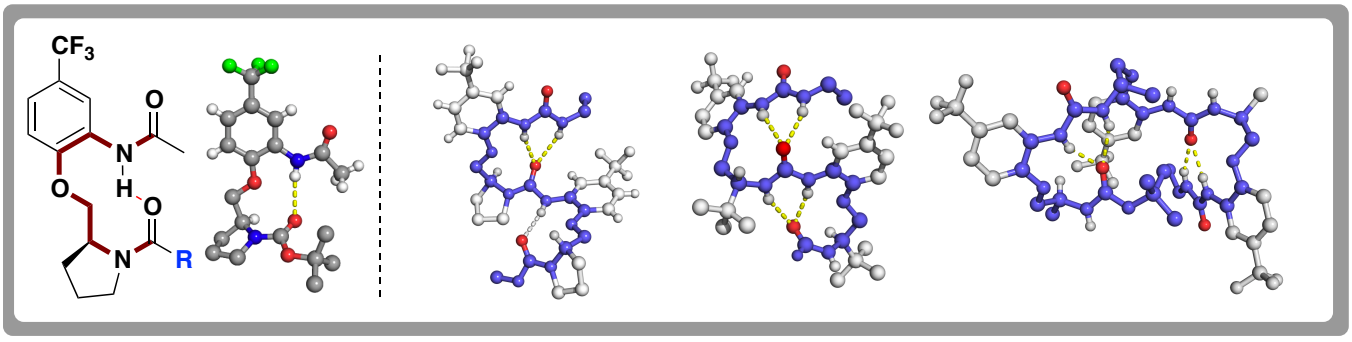
Catfold: Cooperatively enhanced hydrogen bonding catalysis

Introduction: Hydrogen bonding is ubiquitous throughout nature, from its role in maintaining the secondary structure of proteins to assisting in the specific recognition of enzyme substrates. It is known that in nature enzymes utilize specific non-covalent interactions to facilitate efficient catalysis. The presence of specific secondary structures is very important for these enzymes to perform various reactions. Although the number of non-covalent interactions in enzymes are manifold, various small molecules can be designed based on cooperative H-bonding interactions to act as efficient catalysts. The development of small molecule organocatalysis in the last decade has been immense as evident from the recent literature. Transformations mediated by hydrogen-bonding organocatalysts typically require a reactive electrophile due to the low levels of activation on offer and hence there is significant scope for increasing reactivity and efficiency through the design and application of new catalytic entities.

Objectives: Taking a lead from nature, the aim of this project was to exploit the notion of cooperativity – namely that a hydrogen bond *donor* is made stronger if it is also involved as an *acceptor* – to increase catalytic efficiency and facilitate challenging asymmetric transformations. This will require the development and investigation of a series of folded materials, the probing of a series of non-covalent interactions and application of this information to the development of new folded catalysts. The work programme comprises three main interrelated elements.

(i) Development of new folded structures: we have demonstrated that a reverse-turn comprising an amino acid derived alcohol conjoined with an aromatic amine can promote parallel sheet structure in a γ-peptide sequence designed to fold with the aid of C-H···O hydrogen-bonds. In designing this parallel-turn motif, we reasoned that incorporating an *ortho*-amino phenol derivative would restrict the $\psi_{(i+2)}$ torsion to angles consistent with natural β-turns. An *N*-aryl amide proton would also possess a greater hydrogen-bond donor ability than a conventional amide, and the presence of the aryl trifluoromethyl group may offer further conformational control through acidification of the *ortho*-proton, facilitating its participation in a hydrogen-bond with the adjacent carbonyl group (scheme 1)

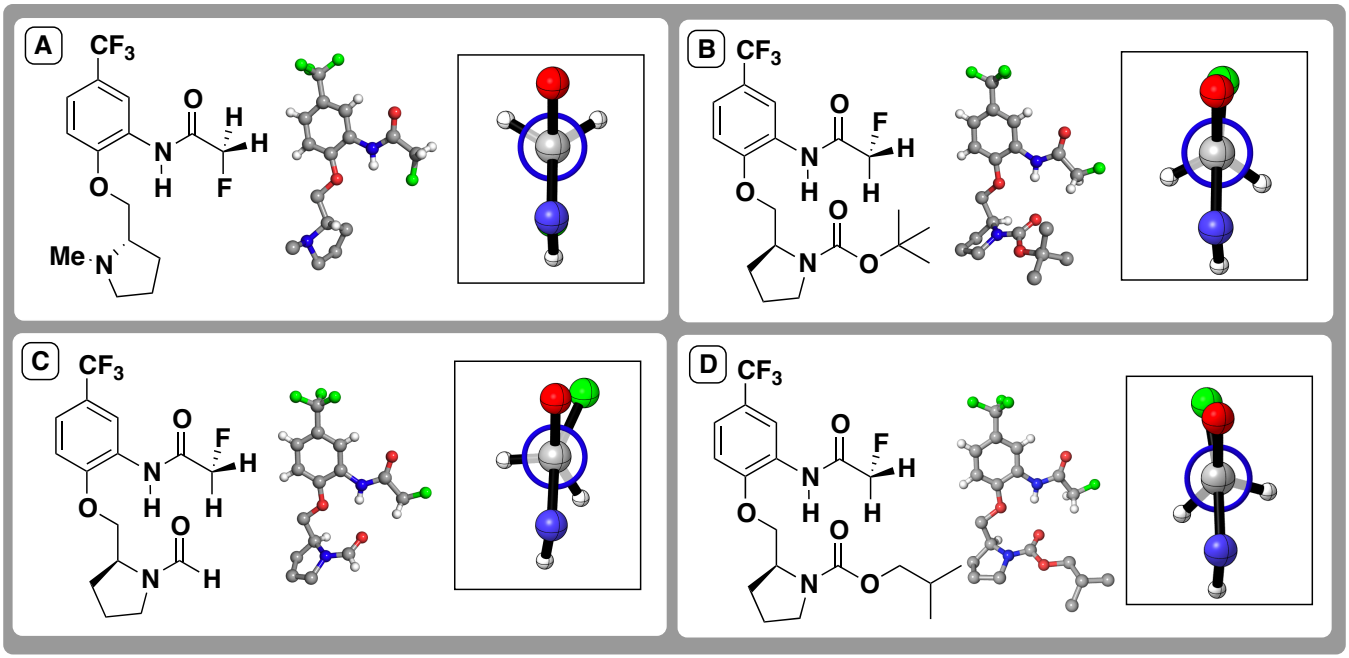


Scheme 1: New materials based around a reverse-turn mimetic

We have made a series of simple turn structures and then extended this to larger, more complex structures with repeat their hydrogen bonding patterns along a chain. As such we have generated materials with repeating turn stuctures stabilized by urea and amide hydrogen bonds, and have also synthesized larger materials containing two isolated turn structures.

(ii) Investigation of the C-H···O interaction: a study of α-fluoro amides: Work from the O'Hagan group has demonstrated that a-fluoro amides adopt a *trans*-planar conformation in the solid state, with a deep potential minimum of *ca.* 7 kcal mol^{-1}, predominantly as a consequence of an interaction between the

fluorine lone pairs and the N-H s* orbital. We rationalized that substituting the α-position of the amide in the our turn motif with electronegative groups such as fluorine would increase the acidity of the α-C-H proton, with a concomitant increase in the hydrogen bond donor ability of this group. This could permit us to generate a series of compounds in which the effects of the α-fluoro amide effect and the C-H···O hydrogen-bond would be in opposition. The benefit of this would be in allowing us to attempt to develop a system where the usually weak C-H···O could be a determinant of conformation. We have synthesized a series of such compounds and investigated their conformational preferences in the solid state (scheme 2).



Scheme 2: Probing the C-H···O interaction

This shows that the introduction of a hydrogen bond donor changes the rotational preference of the C-F bond from the *trans*-planar seen in most α-fluoro amides. Detailed DFT calculations have demonstrated that this is a consequence of a series of non covalent interactions including the C-H···O hydrogen bond (which in the case of difluoroamides can be worth up to 3.5 kcal in the gas phase). As such, this is a rare example fo a system where the conformational preferences of materials are in part determined by the weak C-H···O interaction.

(iii) The development of folded catalysts for asymmetric transformations. We have shown that folded catalysts containing a network of hydrogen bonds accelerate asymmetric hydrogen bond mediated reactions and we have continued to investigate these reaction manifolds. We have generated a series of materials based aroung the turn structure and have investigated their utility in a series of challenging asymmetric reactions. This work is ongoing and will be reported in due course.

(iv) Final results: We have shown that the development of new folding backbones can impact on disparate fields including new materials, the study of non-covalent interactions and asymmetric catalysis. We are in the process of completing three manuscripts based on the work described in this summary and envisage that they will be published in high profile journals, which will benefit the fellow and the PI. These results will form the core of an ongoing series of investigations into the utility of folded structures for information transmission, as scaffolds for the study of non covelent interactions and as building blocks for the development of more efficient asymemtric catalysts.