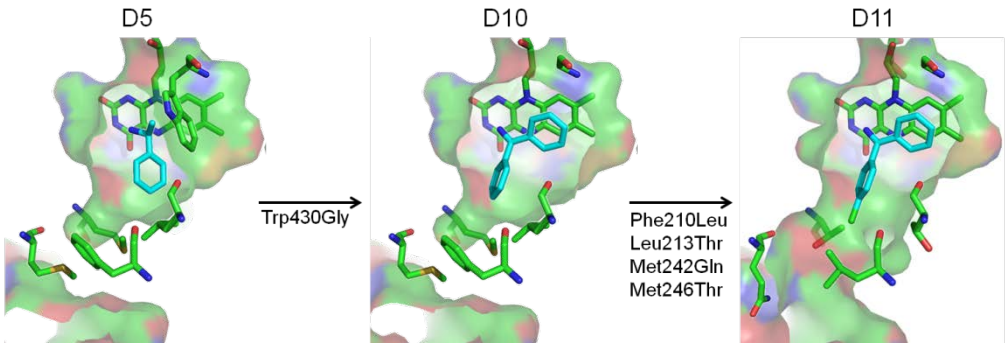
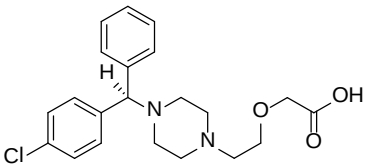
Biocatalytic retrosynthesis - designing new routes to target molecules

Nicholas J Turner, School of Chemistry, University of Manchester, Manchester Institute of Biotechnology, 131 Princess Street, Manchester M1 7DN, UK

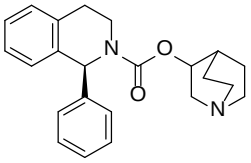
The increased availability of a broad range of biocatalysts that can be applied in organic synthesis has brought into focus the need to rethink the way in which organic target molecules are synthesized in the future. To aid synthetic chemists in identifying where biocatalysts might be usefully applied we recently highlighted the need for rules and guidelines for 'biocatalytic retrosynthesis'.[1] This lecture will describe recent work from our laboratory aimed at developing new toolboxes of biocatalysts for enantioselective organic synthesis.[2] For example, monoamine oxidases (MAO-N) are a family of enzymes that catalyze the oxidation of amines to imines. MAO-Ns can be used as biocatalysts to obtain enantiomerically pure chiral amines by deracemisation or desymmetrisation of substrates. Recently new variants of MAO-N (D5, D10, D11) has now been developed via a combination of directed evolution and rational design in order to broad the enzyme's substrate specificity.[3, 4]



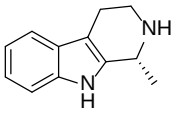
The new mutants have been used for the deracemisation of primary and secondary amines such as (*R*)-4-chlorobenzhydrylamine (building block for the synthesis of levocetirizine), (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (building block for the synthesis of Solifenacin) and the two alkaloids (*R*)-Harmicine and (*R*)-Eleagnine.



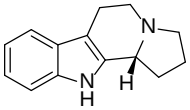
Levocetirizine



Solifenacin



(R)-Eleagnine



(R)-Harmicine

The integration of several biocatalytic transformations into multi-enzyme cascade systems has also been a focus of recent work in our laboratories. In this context MAO-N has been used in combination with other biocatalysts and chemocatalysts in order to complete a cascade of enzymatic reactions. In particular, a biocatalytic tandem reaction combining MAO-N and ATHase has been developed for the deracemisation of 1-methyl tetrahydroisoquinoline, nicotine and 2-substituted pyrrolidine[5] and a combination of MAO-N and either ω-transaminases or imine reductases[6] was employed for a one-pot synthesis of enantiopure 2,5-disubstituted pyrrolidines starting from different 1,4-diketones.[7]

References

[1] E. O'Reilly and N.J. Turner, *Nature Chem. Biol*., **2013**, *9*, 285-288. [2] N.J. Turner, *Nature Chem. Biol*., **2009**, *8*, 567-573. [3] D. Ghislieri *et al*., *J. Am. Chem. Soc*., **2013**, *135*, 10863-10869. [4] J.H. Schrittwieser *et al*., *Angew. Chem. Int. Ed.*, **2014**, *53*, 3731-3734. [5] V. Koehler *et al*., *Nature Chem*., **2013**, *5*, 93-99. [6] F. Leipold *et al*., *ChemCatChem*, **2013**, *5*, 3505-3508. [7]. E. O'Reilly *et al*., *Angew. Chem. Int. Ed*., **2014**, *53*, 2447-2450.