Manipulated enzymes—researchers set milestone in biocatalysis research

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Kathrin Heckenbichler and Rolf Breinbauer and their team managed for the first time ever to 'retrain' an enzyme to build ring-shaped molecular structures instead of performing its natural task of reducing double bonds. Credit: © TU Graz

TU Graz researchers managed for the first time ever to 'retrain' an enzyme to build ring-shaped molecular structures instead of performing

its natural task of reducing double bonds. The work was published in *Angewandte Chemie*, and is relevant for the production of pharmaceuticals and plant protection products.

Biocatalysis uses enzymes to bring about chemical reactions. This kind of 'soft chemistry' replaces the use of poisonous reagents or solvents in existing syntheses to a high degree. However, a major challenge in biocatalysis is extending this concept to completely novel chemical reactions so far not accessible to enzymes found in nature. One such new design was created by a team of researchers at TU Graz led by Rolf Breinbauer, head of the Institute of Organic Chemistry, and Kathrin Heckenbichler, who is pursuing this research in the framework of a doctoral thesis at the Institute of Organic Chemistry. Breinbauer says, "For the first time, we've succeeded in manipulating an enzyme to carry out not its natural function, but rather a much more interesting function in terms of synthesis. Instead of reducing double bonds in a catalytic process, the enzyme now creates molecular structures in the form of small rings. By exchanging only one amino acid in the active centre of the enzyme, we've managed to suppress the natural reaction and facilitated a new reaction course."

The team led by Heckenbichler and Breinbauer was able to produce 'cyclopropanes,' extremely small ring-shaped molecules in the shape of a triangle, using biocatalysis. Such ring systems, also called three-ring systems, occur not only in many biomolecules, they are also an important structural element in plant protection products and in pharmaceuticals such as contraceptive pills, drugs used to treat asthma and AIDS medications. The work has been published in the current issue of *Angewandte Chemie*.

The good and the bad 'hand' of the molecule

Parallel to this, the researchers also managed to master the chirality of

the produced molecule, which is of great importance in the production of medications. Chirality, or the 'handedness' of molecules, describes how two molecules of the same atom can be structured in a mirror-image way—either right handed or left handed. One variant of these enantiomers can be useful and the other damaging, and great value is placed today on using only the curative variant in the production of medications. This ensures that medications work very specifically and that no undesirable side effects occur due to so-called chiral twins. Kathrin Heckenbichler explains the process and result of the biocatalytic implementation of the substrate: "To enable an optimum chiral recognition between enzyme and substrate, we designed a substrate with a large residue. By doing this, we could ideally exploit the spatial conditions in the active centre of the enzyme to produce a cyclopropane in high enantiomeric purity." The researchers managed to produce only the desired enantiomer from the two possible chiral three-ringed molecules.

The research team from TU Graz managed to carry out an important extension of their biocatalytic repertoire to open the door to diverse applications, particularly in the 'green' production of new medications and the economical production of generic pharmaceuticals, aromatic substances and plant protection products. The aim of this so-called green chemistry, to which biocatalysis can be attributed, is to employ mild and environmentally sound reagents, contain environmental pollution, and save energy and costs.

More information: Kathrin Heckenbichler et al, Asymmetric Reductive Carbocyclization Using Engineered Ene Reductases, *Angewandte Chemie International Edition* (2018). DOI: 10.1002/anie.201802962

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