The Key that Fits: New Technique To Trace Disease-Related Agents

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(PhysOrg.com) -- In the development of new drugs, photoaffinity labels (PALs) are a versatile tool to investigate the interaction between a receptor and a drug or a ligand. Researchers working with Stephanie Grond at the University of Tübingen and Paultheo von Zezschwitz at the University of Marburg have now developed a new class of PALs that can be attached to the ligand in a single step, thus causing less modification of its structure, as they report in the *European Journal of Organic Chemistry*. The group has tested the new labels on an enzyme that is linked to osteoporosis and cancer.

When PALs are used to study a specific ligand, the ligand is firstly decorated with a chemical group that can be activated when exposed to ultraviolet light, whereupon it irreversibly binds to the receptor to form a stable complex. This complex can then be thoroughly studied, e.g., by fragmentation of the receptor.

Typically, formation and fragmentation of the ligand-receptor complex is traced by monitoring special tags that are incorporated into the complex. However, these tags are problematic due to high costs and size restrictions, and frequently, the tagged fragments cannot be detected among the vast excess of untagged fragments. Therefore, any potential to study the complexes is lost. Finding new ways to separate the tagged fragments from the untagged ones is one of the major challenges facing scientists today.

Grond and von Zezschwitz, together with the help of their biology

colleagues Markus Huss and Helmut Wieczorek at the University of Osnabrück, have been studying V-ATPase, which is an enzyme that has been linked to osteoporosis and some cancers, to determine its mode of inhibition.

To do so, they have developed a new fluorous photoaffinity label (F-PAL) that can be attached to the ligand in one step, as both the activator and the tag are contained within the same compound. The F-PAL contains a long carbon chain that is fully substituted with fluorine atoms instead of the usual hydrogen atoms. By using a special separation technique that is specific to fluorine-containing compounds, compounds with a high fluorine content can be easily "fished out" from untagged compounds. Once the tagged fragments of the ligand-receptor complexes are isolated, they can be analyzed to unravel the exact function of the drug, which could give scientists some valuable insight into how diseases such as osteoporosis and cancer can be fought.

More information: Stephanie Grond, et al., New Fluorous Photoaffinity Labels (F-PAL) and Their Application in V-ATPase Inhibition Studies, *European Journal of Organic Chemistry*, Permalink: dx.doi.org/10.1002/ejoc.200901463