Navigating the neurochemical space by computer-aided molecular design

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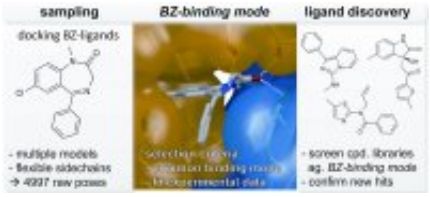

Pharmaceutical scientists from VU University Amsterdam and colleagues from the University of Vienna and Medical University of Vienna have gained new insights into the molecular basis of the GABAA receptors, an important class of brain receptor involved in regulating the excitation of nerve cells. Their results were published online on March 25 in the prestigious journal Nature Chemical Biology.

GABAA receptors are the major inhibitory receptorsin the brain and the site of action of a variety of clinically important drugs against epilepsy, anxiety and sleep disorders. VU scientists Chris de Graaf and Iwan de Esch from the Division of Medicinal Chemistry and their colleagues developed three-dimensional structural models of the GABAA receptor with computer-aided molecular design. They predicted that novel molecules (neurochemicals)canbind to the receptor in the same manner as known drugs like benzodiazepines (Diazepam)can. Based on previously known ligand binding hypotheses, the consortium used

computer simulationst o select a small set of molecules from large chemical libraries. Laboratory experiments confirmed that the predicted novel small molecules can indeed modulate the activity of the GABAA receptor.

Some of these novel neurochemicals are relatively small, making them attractive starting points for so-called Fragment-Based Drug Discovery (FBDD). This methodology has the potential to develop new medicines more efficiently than high-throughput screening. In recent years, the Division of Medicinal Chemistry has set up a dedicated FBDD research line to develop new biologically active compounds. New drug targets are probed by screeningsmall fragments using innovative technologies. The group is tackling drug targets embedded in cell membranes, such as G-protein coupled receptors (GPCRs) and ligand-gated ion channels (LGICs), like the GABAA receptor. The customized computer-aided fragment screening approach used in this study supports the validity of thebinding between GABAAand its ligands. Moreover, it paves the way for efficient structure based drug design and possibly novel drugs against epilepsy, anxiety and sleep disorders.

More information: Richter, L.; et al. Diazepam-bound GABAAreceptor modelsidentify new benzodiazepine binding-site ligands. *Nature Chemical Biology*. dx.doi.org/%2010.1038/Nchembio.917

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