BIOMOLECULAR CHEMISTRY DIRECTED TOWARDS DRUG DEVELOPMENT

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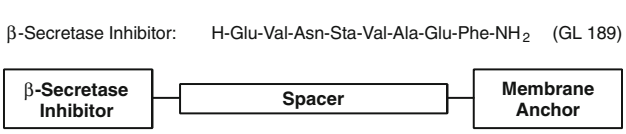
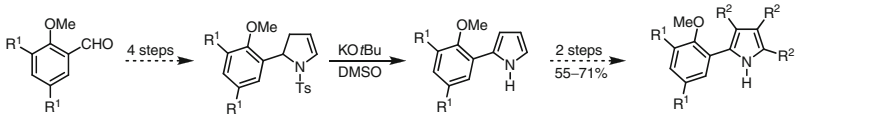
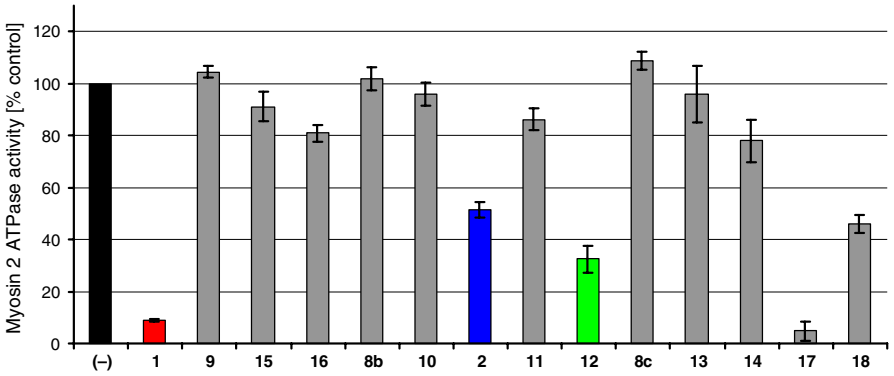
Alzheimer's disease (AD) is a neurodegenerative disorder leading to progressive loss of memory and other cognitive abilities. Currently, there is no treatment for AD available which either stops the progress or can cure the disease. In cooperation with JADO Technologies (Dresden), the Max-Planck Institute for Molecular Cell Biology and Genetics in Dresden and the Laboratory for Molecular Neurobiology at the University Duisburg-Essen, we are developing an approach for the design of potential novel drugs against AD. Characteristic of AD is the formation of extracellular aggregates of β-amyloid peptides, known as amyloid plaques. According to the amyloid cascade hypothesis, β-amyloid peptides are believed to play a key role in the pathogenesis. The β-amyloid peptides are generated from the membrane protein APP (amyloid precursor protein) by sequential cleavages of APP involving first, β-secretase, and subsequently, γ-secretase. Thus, highly efficient inhibition of the β-secretase enzyme should lead to a potential therapy for AD. Amyloidogenic cleavage of APP takes place when APP and β-secretase are co-internalized into the cell via endocytosis. β-Secretase is found in structural microdomains of the cell membrane, known as lipid rafts and cleavage of APP by β-secretase was reported to occur in lipid rafts. Based on these findings, we have designed and synthesized a modified lipophilic β-secretase inhibitor with a tripartite structure, in which each unit exhibits a well-defined function.[1]



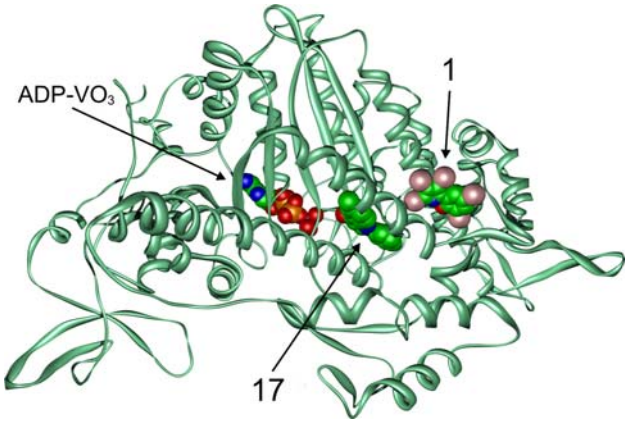
The known β-secretase inhibitor GL 189 (Calbiochem) is a transition state inhibitor showing only a minor effect in cellular assays.[2] However, linking it to a membrane anchor via a spacer of defined length, leads to a tripartite structure which locates the β-secretase inhibitor to lipid rafts. The tripartite structure is transported into the cell by endocytosis and delivered to endosomes where β-secretase is active.[1,3] The first results emphasized that our tripartite structures are more effective compared to nonlipophilic modified inhibitors, by several orders of magnitude—in cell culture as well as in animal models. In a mouse model simulating AD, our novel inhibitor reduced the formation of β-amyloid peptides by 60% in only 4 h, whereas the nonanchored inhibitor showed no effect.



In a further project, we are developing novel inhibitors of myosin ATPase. Based on a silver-mediated pyrrole synthesis described a few years ago,[4] we have elaborated a highly efficient silver-catalyzed route which provided pentabromopseudilin (**1**) and pentachloropseudilin (**2**), halogenated natural products isolated from microorganisms, as well as their synthetic analogs **12** and **14**.[5] These compounds have been identified as novel isoform-specific inhibitors of myosin motor activity. The activities of **1** and **2** are comparable to the known inhibitors (−)-blebbistatin (**17**) and *N*-benzyl-*p*-toluenesulfonamide (BTS) (**18**).[5–7]



An X-ray crystal structure analysis of the complex formed by the *Dictyostelium* myosin-2 motor-domain with Mg^{2+}–ADP–*meta*-vanadate and pentabromopseudilin (**1**) revealed a new allosteric binding site, 7.5 Å away from the allosteric binding site of (−)-blebbistatin (**17**).



The discovery of a novel class of myosin ATPase inhibitors and the identification of a second allosteric-binding site opens up the way for the development of more potent isoform-specific myosin inhibitors based on rational drug design. Specific inhibitors of myosins represent promising candidates for the treatment of a range of diseases, such as cancer and malaria.

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