

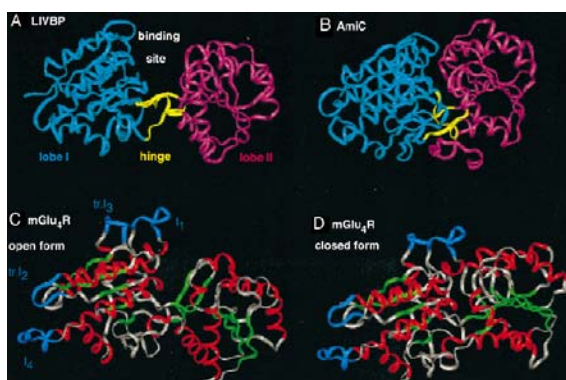
針對結構生物學家及新藥開發人員的蛋白質-配體交互作用應用實例

4a型代謝麩胺酸感受器之細胞外域的3D結構模型：活化過程的新想法

Metabotropic glutamate receptors (mGluRs) belong to the family 3 of G-protein-coupled receptors. On these proteins, agonist binding on the extracellular domain leads to conformational changes in the 7-transmembrane domains required for G-protein activation. To elucidate the structural features that might be responsible for such an activation mechanism, they have generated models of the amino terminal domain (ATD) of type 4 mGluR (mGlu4R). The fold recognition search allowed the identification of three hits with a low sequence identity, but with high secondary structure conservation: leucine isoleucine valine-binding protein (LIVBP) and leucine-binding protein (LB) as already known, and acetamide-binding protein (AmiC). These proteins are characterized by a bilobate structure in an open state for LIVBP/LBP and a closed state for AmiC, with ligand binding in the cleft. ACPT-1, a selective agonist, has been docked in the two models. In the open form, aCPT-1 is only bound to lobe I through interactions with Lys 74, Arg78, Ser159, and Thr182. In the closed form, ACPT-1 is trapped between both lobes with additional binding to Tyr230, Asp312, Ser313, and Lys317 from lobe II. These results support the hypothesis that mGluR agonists bind a closed form of the ATDs, suggesting that such a conformation of the binding domain corresponds to the active conformation.

Three-dimensional model of the extracellular domain of the type 4a metabotropic glutamate receptor: New insights into the activation process

Reference: ANNE-SOPHIE BESSIS et al, *Protein Sci*(2000),9:2200;
Used Module: MODELER, Profiles_3D, Discover



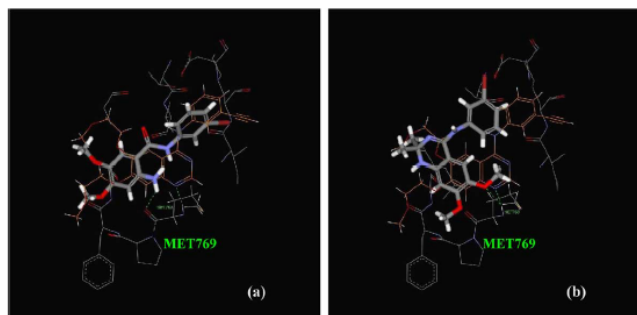
苯甲酰胺和Benzamidines作為EGFR及thyrosin 激酶的專一抑制劑

The benzamides 1 and the benzamidines 2 as well as the cyclic benzamidines 3 were designed and synthesized as the mimics of 4-anilinoquinazolines for an inhibitor of EGFR tyrosine kinase. The specific inhibitions of EGFR tyrosine kinase were observed in the benzamides 1c and 1d, and the benzamidine 2a. According to the docking simulation using the X-ray structure of EGFR kinase domain in complex with erlotinib, the LigScore2 scoring function value of erlotinib was calculated as 5.61, whereas that of the benzamide 1c was 5.05. In a similar manner, the LigScore2 value of the cyclic benzamidine 3a was calculated as 5.10.

Benzamides and benzamidines as specific inhibitors of epidermal growth factor receptor and v-Src protein tyrosine kinases

Reference: Toru Asano et al *Bioorganic & Medicinal Chemistry* 12 (2004) 3529;

Used Module: CHARMM, DS Modeling-SBD



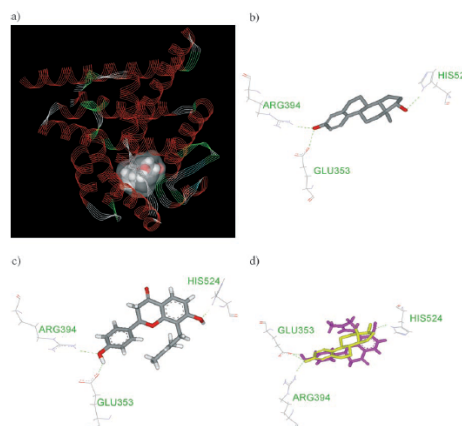
作為非類固醇系Phytoestrogens的 Prenylflavonoids和有關的構造-活性間的關係

In the search for estrogen receptor (ER) modulators, a series of prenylflavonoids were found to be widely distributed amongst tonic herbal medicines and to possess estrogen-like activity in MCF-7/BOS cells, as evaluated by an estrogen-screening assay. Cell-cycle analysis revealed that the stimulatory effects of these compounds toward cell proliferation were elicited at the G1-S checkpoint and could significantly increase the S-phase population of MCF-7 cells under hormone-free conditions. Furthermore, to explore the structure-activity relationship based on the estrogen receptor and detailed molecular mechanisms among the prenylflavonoids, protein-ligand docking simulations were carried out by using the DS-MODELING software package. The binding affinity of each prenylflavonoid toward Era was scored and the receptor-ligand interaction was also analyzed to provide the simulation characteristics of virtual molecular recognition mechanisms. The results of the docking experiment based on the structure of the LBD of Era bound to estradiol provide a molecular view of the binding factors. Based on the biological effects and docking experiments, the docking affinity and receptor-ligand interaction of the compounds clearly contribute to the activation of the estrogen receptor.

Prenylflavonoids as Nonsteroidal Phytoestrogens and Related Structure-Activity Relationships

Reference: Zhi-qiang Wang et al, *ChemMedChem* 2006, 1, 482;

Used Module: DS-Modeling



LigandFit: 根據形狀所做的蛋白質活性站點與配體間高速對位的新方法

Original shape-based method, LigandFit, for accurately docking ligands into protein active sites was reported. The method employs a cavity detection algorithm for detecting invaginations in the protein as candidate active site regions. A shapecomparison filter is combined with a Monte Carlo conformational search for generating ligand poses consistent with the active site shape. The method appears quite promising, reproducing the X-ray structure ligand pose within an RMS of 2 Å in 14 out of the 19 coomplexes. A high-throughput screenign study applied to the thymidine kinase receptor is also presented in which LigandFit, when combined with LigScore, an internally developed scoring function, yields very good hit rates for a ligand pool seeded with known actives.

LigandFit: a novel method for the shape-directed rapid docking of ligands to protein active sites

Reference: C.M. Venkatachalam et al *Journal of Molecular Graphics and Modelling* 21 (2003) 289;

Module: LigandFit/LigandScore

