

針對新藥開發研究者的

Rational Drug Design (RDD) 應用實例

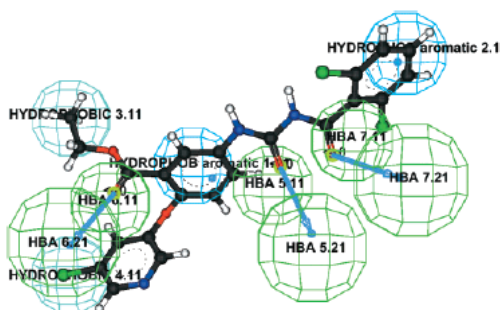
以3D數據庫查尋技術所發現的新的血管系膜細胞增殖抑制劑

A three-dimensional pharmacophore model of mesangial cell (MC) proliferation inhibitors was generated from a training set of 4-methyl-N-benzamide, 2, and its derivatives using the Catalyst/HIPHOP software program. On the basis of the vitro MC proliferation inhibitory activity, a pharmacophore model was generated as seven features consisting of two hydrophobic regions., two hydrophobic aromatic regions, and three hydrogen bond acceptors. Using this model as a three-dimensional query to search the Maybridge database, structurally novel 41 compounds were identified. The evaluation of MC proliferation inhibitory activity using available samples from the 41 identified compounds exhibited over 50% inhibitory activity at the 100nM range. Interestingly, the newly identified compounds by the 3D database searching method exhibited of normal proximal tubular epithelial cell proliferation compared to a training set of compounds.

Discovery of Novel Mesangial cell Proliferation Inhibitors Using a Three-Dimensional Database Searching Method

Reference: Yasuhisa Kurogi et al, *J. Med. Chem.* 44 (2001),2304;

Used Module: catalyst



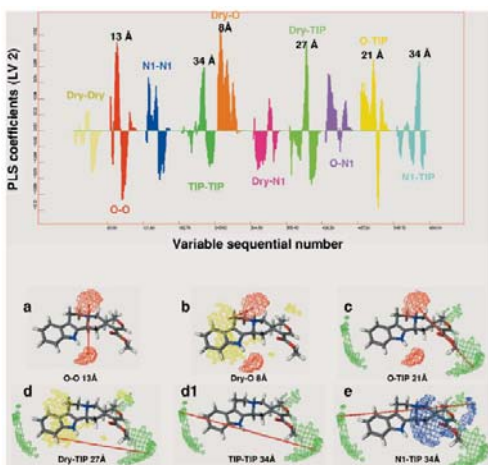
用來尋找CYP2D6可能抑制劑的預測模型

The inhibition of cytochrome P450 2D6 (CYP2D6) by drug candidates is a liability that discovery programmes try to avoid. Computational models for identifying inhibitors of this isoform would be of great utility for helping the correct selection of compound devoid of such issue. The purpose of this study was to develop and evaluate a model for predicting the CYP2D6 inhibition potential based on the molecular structures of drug candidates. The identification of common pharmacophoric features of the CYP2D6 inhibitors under analysis was also an objective of this evaluation.

Predictive Model for Identifying Potential CYP2D6 Inhibitors

Reference: Patrizia Crivori and Italo Poggesi *Basis & Clinical Pharmacology & Toxicology* 96 (2005) 251;

Used Module: Cerius11, Catalyst



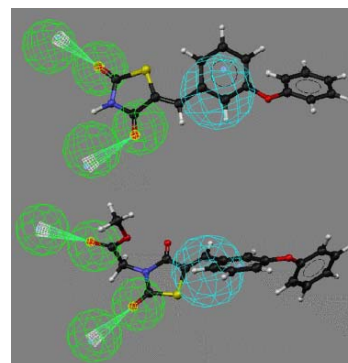
作為醛式糖還原酶抑制劑的5-arylidene-2,4-thiazolidinediones的結構活性關係與分子模型

The structure-activity relationships (SARs) of 5-arylidene-2,4-thiazolidinediones active as aldose reductase inhibitors (ARIs) were extended by varying the substitution pattern on the 5-arylidene moiety and on N-3. In particular, the introduction of an additional aromatic ring or an H-bond donor group on the 5-benzylidene ring enhanced ALR2 inhibitory potency. Moreover, the presence of a carboxylic anionic chain on N-3 was shown to be an important, although not essential, structural requisite to produce high levels of ALR2 inhibition. The length of this carboxylic chain was critical and acetic acids 4 were the most effective inhibitors among the tested derivatives. Molecular docking simulations into the ALR2 active site accorded with the in vitro inhibition data. They allowed the rationalization of the observed SARs and provided a pharmacophoric model for this Class of ARIs.

Structure-activity relationships and molecular modelling of 5-arylidene-2,4-thiazolidinediones active as aldose reductase inhibitors

Reference: Rosanna Maccari et al, *Bioorganic & Medicinal Chemistry* 13 (2005) 2809;

Used Module: Cerius2, Catalyst



以形狀為基礎之虛擬篩選的成功案例：Type I TGF β Receptor Kinase 的強力抑制劑的發現

The authors described the discovery, using shaped-based virtual screening, of a potent, ATP site-directed inhibitor of the T β R1 kinase, an important and novel drug target for fibrosis and cancer. The first detailed report of a T β R1 kinase small molecule co-complex confirms the predicted binding interactions of their small molecule inhibitor, which stabilized the inactive kinase conformation. Their results validate shape-based screening as a powerful tool to discover useful leads against a new drug target.

Successful Shaped-Based Virtual Screening: The Discovery of a Potent Inhibitor of the Type I TGF β Receptor Kinase

Reference: Juswinder Singh et al *Bioorganic & Medicinal chemistry Letters* 13 (2003) 4355;

Module: Catalyst

