

QSAR AND LIBRARY DESIGN IN DISCOVERY STUDIO

The Power of QSAR and Library Design. The ultimate objective of many computational modeling studies is to identify compounds that could potentially become new drugs. With appropriate molecular descriptors, the large quantity of relatively easily available data inherent in chemical libraries can be mined, analyzed and used to select compounds that can become drug leads.

DS QSAR provides easy access to the hundreds of molecular descriptors, proven in biological systems to correlate with activity. The streamlined Discovery Studio® (DS) interface presents these descriptors and advanced modeling and visualization methods in an easy-to-use environment. DS Library Design applies these capabilities together with similarity and diversity methods specifically tailored for chemical library design to guide optimal library design.

ACCELRYS SCIENCE

Extensive Set of Proven Descriptors to Effectively Capture Critical Properties in DS QSAR

- Describe billions of structural features present in molecules using Extended Connectivity Fingerprint (ECFP) descriptors.
- Access traditional descriptors for basic chemical features, physical properties, ADME characteristics, and experimental data.
- Optionally add VAMP and DMol3 for efficient implementations of semi-empirical quantum mechanical methods to rapidly calculate highly accurate electronic properties for thousands of candidate compounds.

Advanced Modeling Tools for Easy Analysis of Complex Data in DS QSAR

- Easily apply modeling techniques such as Bayesian models, multiple linear regression, Partial Least Squares (PLS), Genetic Functional Analysis and more.
- Extend the basic functionality of the package by adding an advanced neural network component and quantum mechanical based descriptors.

Powerful, Customizable, and Easily Accessible SAR Tools in DS QSAR

- Integrated Discovery Studio environment provides easy access to QSAR tools along side library design and other tools.
- Using the Pipeline Pilot Platform, QSAR models can easily be deployed to and shared among large groups of chemists.
- Advanced 3D graphing and molecular data views guide users in drawing conclusions from complex data.

Easily Design Targeted Chemical Libraries with DS Library Design

- Maximize multiple properties simultaneously using Pareto Optimization methods.
- Prioritize chemical libraries using readily accessible metrics for diversity, similarity, and hundreds of physical and chemical properties.
- Interactively customize chemical libraries to optimize the value of each member of a selected set of compounds.

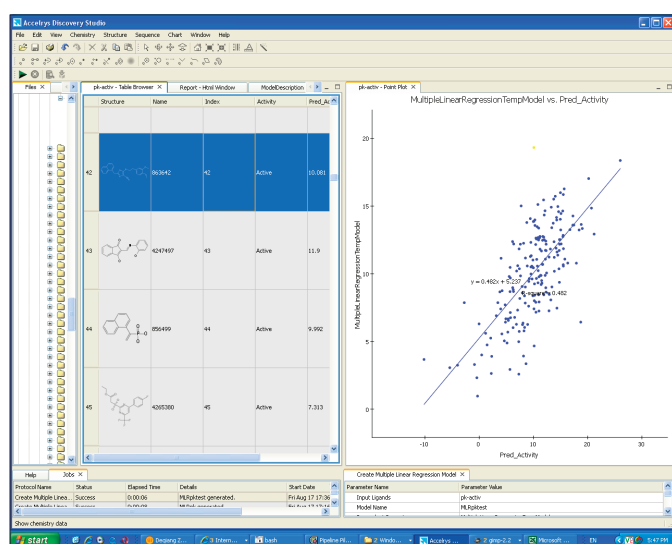


Figure 1: An interactive Multiple Linear Regression QSAR model showing correlation between actual and predicted activities. Selection between the plot and table are synchronized.

THE GOLD STANDARD IN TECHNOLOGY

Comprehensive – The QSAR and library design tools in Discovery Studio include hundreds of useful descriptors, multiple well validated model building techniques and tools specially tailored for custom library selection and design. These packages can easily be augmented with powerful add-ons for rapidly generating quantum mechanical based descriptors and advanced modeling techniques.

Proven history – The core technology has undergone over a dozen years of continuous innovation and customer driven improvement, and has demonstrated dependable performance in the pharmaceutical industry with dozens of publications.

Cutting edge – Accelrys is incorporating new scientific tools to meet current pharmaceutical needs and we are continuously working with our customers to plan for future innovation.

Easy to use interface – DS 2.0 provides a powerful and intuitive user interface. DS 2.0 can be deployed either in a complete standalone solution for individual modelers or as part of an enterprise-level client server installation for easier protocol sharing and administration in larger modeling groups.

Integrated solution – The DS 2.0 environment, based on the Pipeline Pilot™ open operating platform, integrates protein modeling, pharmacophore analysis, and virtual screening as well as third-party applications for an infinitely extensible virtual discovery platform. Well-tested applications including CHARMM, MODELER, Catalyst, and others are accessible in the graphical DS environment, the Pipeline Pilot scripting and protocol development environment and from command-line prompts.

Parallel computing – The DS 2.0 platform is optimized to take advantage of grid and cluster computing as well as multi-core processors to rapidly process large tasks.

ACCELRYS IS YOUR PARTNER IN RESEARCH

User community – Accelrys scientific forums and presentations at scientific meetings world-wide provide opportunities for Accelrys users to exchange ideas and share new research.

Scientific consulting – Accelrys has dozens of experienced Ph.D.s with expertise in implementing scientific solutions for drug design that are available for short or long-term engagements to create tailored solutions or perform modeling experiments.

Customer support – Accelrys customers report a 98% satisfaction rate with our support team.

Committed to innovation – With over 100 Ph.D.s in the field working daily with researchers in industry and academia, Accelrys is committed to delivering cutting-edge technology to our customers

World leading scientific advisors – Through our in-licensing agreements, partnerships, and scientific advisors many of the world's foremost experts in computational drug design are involved in setting our direction.

BIOLOGICAL VALIDATION AND COMPARISON

2007 – Genetic Functional Analysis module used to study fluoroquinolone antibacterials. The results suggest specific chemical modifications and physical properties for future drug design efforts.¹

2006 – Effect of 2-aminothiazole derivatives on Neuro-cell apoptosis studied using a QSAR model that has a 97% correlation to EC50²

2003 – A descriptor-based QSAR model for hOCT1 predicts IC50 values with 95% correlation to observed data.³

To learn more about Discovery Studio, go to accelrys.com/discovery-studio

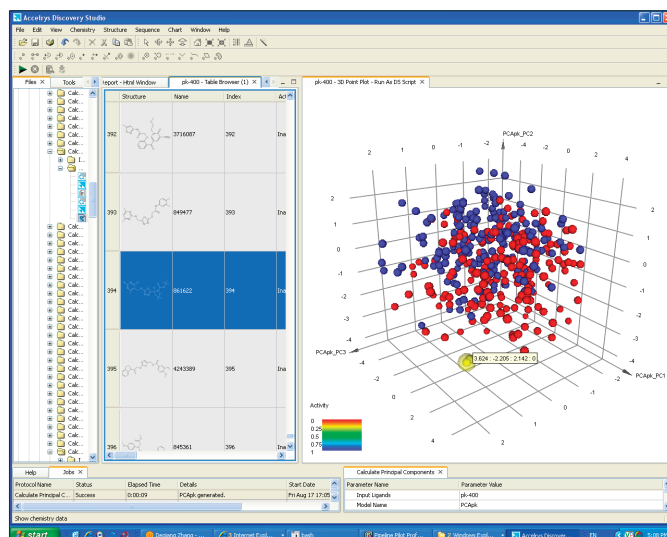


Figure 2. An interactive 3D plot of the first three principal components from a Principal Component Analysis using several molecular descriptors as input. The plot can optionally be colored by a specified property.

REFERENCES:

1. Cheg, D. et al., "Relationship of quantitative structure and pharmacokinetics in fluoroquinolone antibacterials", *World J Gastroenterol*, **2007**, *13*(17), 2496-503
2. Jiang FC., et al., "The design and synthesis of 2-aminothiazole derivatives and their inhibitory activity on apoptosis", *Yao Xue Xue Bao*, **2006**, *41*(8), 727-34
3. Bednarczyk D., et al., "Influence of molecular structure on substrate binding to the human organic cation transporter, hOCT", *Mol. Pharmacol*, **2003**, *63*(3), 489-98