DATASHEET

accelrys®

DISCOVERY STUDIO® SCIENCE PORTFOLIO

From project conception, through to candidate selection, Discovery Studio® delivers a comprehensive portfolio of validated scientific technologies. Built on a set of well-established gold-standard applications backed by years of peer-reviewed publications (e.g., CHARMm, MODELER, ZDock, Delphi, Catalyst, DMol3, TopKat, etc), in combination with novel leading-edge scientific tools, Discovery Studio is ideally positioned to address today's drug discovery challenges.

SCIENTIFIC SOFTWARE PORTFOLIO

The Discovery Studio software portfolio is built on and powered by the enterprise-ready Pipeline Pilot platform. This formidable architecture enables the scientist to effectively and efficiently conduct small and macromolecule research within the following domains:

- **Simulation:** Perform calculations using Molecular Mechanics (MM), Molecular Dynamics (MD), Quantum Mechanics (QM) and hybrid QM/MM
- **Macromolecule Design and Analysis:** Undertake sequence alignments and analysis, 3D structure prediction (MODELER) and validation, structure ionization, predict protein-protein docking (ZDOCK), and even undertake protein engineering and optimization of biophysical properties, including thermal stability and prediction of protein aggregation.
- **Small Molecule Design:** Using a broad portfolio of scientific technologies, calculate ligand properties and ligand efficiency, perform ligand profiling and filtering using well understood characteristics of drugs, including permeability and undesirable feature metrics, and select optimal subsets using either molecular diversity or cluster-based methods. In addition, it includes specialist tools for:
  - **Pharmacophore Modeling:** Specialist tools for small molecule screening and profiling. Includes tools for both pharmacophore generation, validation and virtual screening, as well as ligand profiling.
  - **Receptor-ligand Interactions:** Undertake Structure-Based Design (SBD), including both fast and physics-based ligand docking (also with flexible docking tools for both ligand and receptor side-chains), combinatorial chemistry library design and optimization tools, fragment-based drug-design (FBDD) tools and de novo ligand design.
- **QSAR and ADMET:** Create and validate statistical models against biologically important end-points. Alternatively, make use of our pre-built validated models for a broad range of critical pharmacological end-points, including: aqueous solubility, Blood-Brain Barrier penetration, intestinal absorption, Hepatotoxicity and many more.

Delivered through a single, easy-to-use client interface, all of these scientific technologies can be readily accessed in Discovery Studio® from both Windows and Linux environments.

SIMULATION PRODUCTS

Product	Description
DS CHARMM	Leverage this industry-standard program to study the energetics and flexibility of molecules - from small ligands to multi-component physiological complexes, using the industry standard in force field technology, CHARMM (Chemistry at HARvard Macromolecular Mechanics). DS CHARMm is regularly updated to include the latest functionality developed by the CHARMM scientific community [e.g., Refs 1,2]. DS CHARMM includes the following well-validated force fields (CHARMm, charmm27, charmm22, charmm19) and solvation models such as Poisson-Boltzmann (PB), Generalized Born, Generalized Born with molecular volume (GBMV) or simple switching (GBSW). Examples of application of DS CHARMM include energy minimization and Molecular Dynamics simulations of ligands and/or macromolecules, sampling of protein side-chain and loop flexibility, refinement and calculation of protein-ligand interaction energies and even use in physics-based scoring of ligands in protein active sites. DS CHARMM is scalable for high throughput analysis of large numbers of ligands and can be accessed from Discovery Studio, Pipeline Pilot and via command line for a greater degree of customization and flexibility. ***CHARMM is maintained by the CHARMM Development Project, lead by Prof. Martin Karplus and his lab at Harvard University. To learn more about CHARMM, please visit http://www.charmm.org/***
DS CHARMM Lite	A customized version of CHARMm providing molecular minimization and energy calculation capabilities. For example, with DS CHARMm Lite, perform in situ ligand minimization using the well-validated CHARMm forcefields. DS CHARMm is scalable for high throughput analysis of large numbers of ligands; all jobs can be run in parallel and in background mode.
DS Analysis	Gain new insights into molecular processes by using DS Analysis to animate, graph, and tabulate results of CHARMm molecular dynamics, small molecule docking, or protein modeling. Compute RMSD, hydrogen bonds and contacts for thousands of docked ligand poses in a single job. Analyze and cluster MD trajectories in an intuitive, easy-to-use manner. Calculate RMSD of residues/atoms during the course of a trajectory and display the results in a dendrogram or heat map. Check the quality of the protein structure and analyze regions with abnormalities using the 'Protein Health' toolpanel. Evaluate model quality based on the MODELER DOPE (Discrete Optimized Protein Energy) energy function.
DS DMOL3-MOLECULAR	DMol3 is a modeling program that uses density functional theory (DFT) to simulate chemical processes and predict properties of materials both rapidly and accurately. DMol3 can predict processes in gas phase, solution, and solid environments and is broadly applicable to research problems in chemistry, pharmaceuticals, materials science, and chemical engineering, as well as solid state physics.
DS QUANTUMM	Increase accuracy of protein-ligand modeling during lead optimization by using accurate Quantum Mechanics/Molecular Mechanics (QM/MM) methods that combine the Density-Functional Theory program DS DMOL3 Molecular (QM) and CHARMm (MM). Perform single point energy calculations or geometry optimization using a wide variety of exchange-correlation functionals and basis sets.
DS MMFF	Study the energetics and interaction between macromolecules and ligands with the industry-validated forcefield MMFF94s that has been broadly parameterized for organic and bio-organic systems and for the intermolecular interactions crucial to enzyme binding.
DS CFF	Optimize DNA, RNA, carbohydrates, lipids, proteins, peptides, and small-molecule models with high confidence on accuracy of results. The forcefield parameters in CFF (Consistent Forcefield) were developed by computing the properties of 1,768 different molecules spanning 19,432 molecular structures, resulting in a robust and diverse collection of parameters applicable to most biomolecules and small molecules.

MACROMOLECULE-BASED DESIGN AND ANALYSIS PRODUCTS

Product	Description
DS SEQUENCE ANALYSIS	With DS Sequence Analysis, use the popular BLAST and PSI-BLAST algorithms to identify homologs for protein sequences by searching databases that are either installed locally or available via the internet at NCBI. In addition, access tools for performing phylogenetic analysis and Evolutionary Trace analysis. For Antibody Modeling, use pre-compiled CDR loop databases to automate the process of CDR identification and annotation. A sequence alignment file of the best aligned hits enables automated loop grafting of the CDR regions.
DS Biopolymer	Biopolymer delivers model building and electrostatics analysis tools for use with nucleic acids (DNA, RNA), proteins and peptides. Calculate electrostatic potentials and solvation energies of both large and small molecules using Poisson-Boltzmann electrostatics (DelPhi[3,4]). Calculate the protonation state of titratable amino acids within the protein quickly and accurately, using the Generalized Born model for charge estimation, and accurately predicts pK's, pH titration curves, and overall energy of folding. In the area of X-ray crystallography, build protein models (with X-BUILD technology) and fit ligands (with X-LIGAND technology) into X-ray electron density maps. ***DelPhi is developed and maintained by the lab of Prof. Barry Honig at Columbia University. To learn more about DelPhi, please visit http://wiki.c2b2.columbia.edu/honiglab_public/index.php/Software:DelPhi***
DS MODELER	Automatically and rapidly generate a refined homology model of a protein, given only the sequence alignment to a known 3D protein structure, with the industry-standard MODELLER algorithm[5,6,7,8] for fast homology modeling. With DS MODELER, you can build protein models and mutants with ligands bound, perform loop modeling, perform structure-based alignments, create sequence profiles and perform remote homology modeling searching. DS MODELER also features SALIGN, a method for improving the sequence alignment in low homology cases that uses sequence profile information. In the domain of antibody modeling, additional automation tools are included to facilitate both Full-length (Immunoglobulin G templates for IgG1 and IgG2), and Framework-based model building. ***MODELLER is maintained by the team of Prof. Andrej Sali at the University of California, San Francisco (UCSF). To learn more about MODELLER, please visit http://salilab.org/modeller/***
DS PROTEIN REFINE	Optimize a loop region of a protein structure using an in-house developed algorithm based on CHARMm. Generate multiple energy optimized variants of the loop region and browse through loop structures and chart results. In addition, optimize the side-chain of a protein structure using an in-house developed algorithm based on a systematic searching method and CHARMm energy minimization. Both optimization algorithms have no dependency on initial structure (ab initio approach).
DS PROTEIN HEALTH	Access the validity of a protein structure (or part of the structure) derived from modeling studies or experimental data. Protein Health uses a method called Profiles-3D Verify to evaluate the protein structure by comparing its structural environments with the preferred environments of amino acids. Misfolded protein segments within a protein structure can be identified by this method, indicating where additional consideration should be given to structural packing. In addition, check the quality of the protein structure and analyze regions with abnormalities using the 'Protein Health' tool panel.
DS PROTEIN FAMILIES	Gain a better understanding of the mechanism of protein function at the molecular level by analyzing the sequence conservation patterns within a family of protein sequences, as well as the position of those conserved residues on the 3D structure. Includes tools to align a family of proteins based on sequence or structure, perform phylogenetic analysis and Evolutionary Trace analysis using a hierarchical clustering method and map information onto your 3D structure.

MACROMOLECULE-BASED DESIGN AND ANALYSIS PRODUCTS (continued)

Product	Description
DS PROTEIN DOCKING	Predict protein-protein structure interactions of novel targets rapidly and accurately with DS Protein Docking. Perform rapid rigid body docking with the well-published ZDOCK algorithm[9,10], which employs an FFT-based method using a pair-wise shape complementarity function for identifying docked conformations and scores hits based on atomic contact energies. Increase the accuracy of docked poses using the ZRANK scoring function[11]. Use the RDOCK algorithm[12] to refine ZDOCK hits based on a CHARMm energy minimization and score poses by CHARMm energy and desolvation energy. Narrow the search and identify poses of interest with advanced clustering methods. ***ZDock, ZRank and RDock are developed and maintained by the lab of Dr. Zhiping Weng at the University of Massachusetts Medical School. To learn more about ZDock, ZRank and RDock, please visit http://zlab.umassmed.edu/***
DS Protein Aggregation	Identify the size and location of regions on antibodies prone to aggregation, and then predict mutations leading to improved stability. Uses the spatial aggregation propensity algorithm[13, 14] [WO 2009/155518 A1][15] Additionally, DS Protein Aggregation can be used to identify surface regions on proteins, likely to be involved in protein-protein bindings events[16]. ***The spatial aggregation propensity algorithm is maintained and developed by the lab of Prof. Bernhardt Trout at the Massachusetts Institute of Technology. To learn more about it, please visit http://web.mit.edu/troutgroup/***
DS X-RAY	Contains interactive and semi-automated tools for the model building, analyis and refinement stage of crystallographic (X-ray) structure determination. Capabilities include CNX protocols for structure refinement, water picking, and structure validation. Includes CNX Standalone.

SMALL MOLECULE PHARMACOPHORE PRODUCTS

Product	Description
DS Catalyst Search	Use DS Catalyst Search to carry out rapid database searches with a pre-defined or customized pharmacophore query. Includes the ability to handle a range of match constraints, including partial, minimum number and required feature matches. Results can include. Additionally, can either search compounds using a flexible match, or use multiple pre-computed rigid conformer samples.
DS Catalyst DB Build	Easily create a 3D compound database for querying pharmacophore models and identifying potential lead compounds. With DS Catalyst Build, convert compounds into a 3D database that stores a diverse sampling of all the energetically accessible conformations under physiological conditions for any given structure.
DS Catalyst Conformation	Rapidly calculate conformational models for small molecules that provide diverse representations of all the molecule's energetically accessible conformations. Choose from among three conformation generators (CAESAR, FAST, BEST) to select the algorithm that is best suited to each drug discovery project. Within each algorithm, parameters can be customized to optimize the conformational sampling. From these generated conformers, create pharmacophore hypotheses for querying compound libraries of both rigid and flexible molecules.
DS Catalyst Hypothesis	Automatically create qualitative or quantitative pharmacophore models that identify the essential chemical and structural features required for target binding. Includes capabilities to automatically generate common feature pharmacophore hypotheses from sets of known active ligands (HIPHOP) and also structure-activity relationship-based models when activity data is provided (HypoGen). Model refinements can be delivered with inclusion of exclusion volumes (HIPHOPREFINE and HypoGenRefine, respectively). A further feature is that test sets containing examples of known active and inactive ligands can be used to validate the predictive potential of each pharmacophore model.

SMALL MOLECULE PHARMACOPHORE PRODUCTS (continued)

Product	Description
DS Catalyst SBP	DS Catalyst SBP provides tools for fast and easy creation of structure-based pharmacophore (SBP) models from the putative binding site in a protein, either from receptor-ligand complex, or directly from a structure if no bound ligand information is available. Notably, with DS Catalyst SBP, protein structure pharmacophore features can be combined directly with ligand features to create a more complete model of the features critical for binding.
DS Catalyst Score	Enables hit results from a pharmacophore screen to be evaluated and prioritized. DS Catalyst Score calculates the predicted fit or activity value for each compound. Based on the size of your returned search hit list, have the flexibility to broaden or narrow your search results by specifying the minimum and maximum feature requirements of your pharmacophore model.
DS Catalyst Shape	Expand or refine a search query using a 3D shape representation from a molecule from a specified conformation. Shape queries can be used to identify molecules that possess a similar shape with or without considering specific chemical entities. Because overall shape is considered, the search hits can exhibit a far greater topological diversity than standard 2D searches.
HYPODB	HypoDB is a database of high-quality pharmacophore models from Inte:Ligand containing 1846 individual pharmacophore models from 187 targets. The database can be used to explore the selectivity and specificity of candidate compounds across a wide variety of therapeutically relevant targets. This method of profiling can also help identify potential mechanism of action, potential adverse targets or new targets for candidate drug compounds.

RECEPTOR-LIGAND INTERACTION PRODUCTS

Product	Description
CDOCKER (via DS CHARMM)	Dock ligands using the validated CDOCKER algorithm, a grid-based molecular docking method[17] that employs CHARMm. With CDOCKER, initial ligand conformations are sampled via high temperature molecular dynamics and are also allowed to flex during the refinement (via simulated annealing MD). Crucially, CDOCKER also provides a physics-based scoring function, via the CHARMm energy of the docked complex. CDOCKER has been shown to give highly accurate docked poses[18]. DS CHARMM is scalable for high throughput analysis of large numbers of ligands and can be accessed from Discovery Studio and Pipeline Pilot
DS FLEXIBLE DOCKING	Perform rational flexible docking that combines the strength of CHARMm for accurate receptor sampling with efficient, features-based docking.[19] DS Flexible Docking is a realistic approach to flexible docking in which the docking of small molecules is influenced by existing low-energy conformations of side chains in the active site. DS Flexible Docking can be parallelized in multi-core machines or compute clusters for virtual high-throughput screening.
DS LIBDOCK	Perform efficient docking by using polar and apolar features (hotspots) on the receptor binding site to guide docking. Use the industry-standard Catalyst engine to generate small molecule conformations (DS Catalyst Conformation, optional but strongly recommended) to increase accuracy of docking. DS LibDock can be parallelized in multi-core machines or compute clusters for virtual high-throughput screening.
DS LIGANDFIT	Gain direct insight into the complementary features of ligands and their potential as lead candidates. DS LigandFit lets you easily dock ligands into the binding site of receptors using shape-based searching and Monte Carlo sampling of ligands. Parameters are customizable, and your settings can be saved and shared with other users. DS LigandFit can be parallelized in multi-core machines or compute clusters for virtual high-throughput screening.

RECEPTOR-LIGAND INTERACTION PRODUCTS (continued)

Product	Description
DS LIGANDSCORE	Evaluate ligand-protein interactions with well-validated and trained scoring functions and their individual descriptors. Insight gained with DS LigandScore will help you identify potential problems in a binding mode hypothesis, discriminate between correct and incorrect poses from docking, and prioritize posed ligands for downstream efforts such as screening or synthesis. Parameters are customizable and your settings can be saved and shared with other users. DS LigandScore can be parallelized in multi-core machines or compute clusters for virtual high-throughput screening.
DS LIBRARY DESIGN	DS Library Design provides a full suite of similarity and diversity clustering methods specifically tailored for chemical library design. Use Pareto Optimization methods to optimize multiple properties within a chemical library design. All protocols within this package are designed to select the most effective chemical libraries, and members within those libraries, for specific research projects.
DS MCSS	Multiple Copy Simultaneous Search (MCSS[20,21,22]) is a fragment docking methodology that can be used to characterize and analyze binding sites. Multiple fragment copies are randomly distributed in a binding site sphere and CHARMm minimizations are performed to find the most favorable fragment positions. The placed fragments are sorted by the MCSS_Score. ***MCSS was originally developed by Prof. Martin Karplus and his lab at Harvard University.***
DS LUDI	Rapidly identify drug-like scaffolds with DS Ludi, a de novo drug discovery application that uses interaction sites in the receptor binding pocket to search fragment libraries and identify and rank molecules. DS Ludi's robust set of design tools allows you to simulate screening before performing experimental assays, to explore libraries of commercially-available ligand scaffolds, and to modify existing ligands by scoring candidate derivatives in the receptor binding site. DS Ludi contains a library of drug-like fragments, but also gives the ability to add custom fragments.
DS De Novo Evolution	Generate complete, drug-like molecules with DS De Novo Evolution by linking and growing fragments onto a scaffold. Choose from three modes that are optimized for either speed or accuracy: In Quick mode, a single best scoring inhibitor is suggested after each generation ranked by any one of the DS Ludi (pre-requisite) or DS LigandScore (optional) scores. In Full Evolution mode, survivors are selected from generations of inhibitors. In Combinatorial mode, all combinations of derivatives of the scaffold are enumerated.
DS De Novo Ligand Builder	DS De Novo Ligand Builder is a unique fragment based design tool because it uses pharmacophores to guide the placement of fragments. This results in hits that not only complement the protein active site, but that also complement each other to create realistic new drug leads. This powerful tool can rapidly produce lists of completely novel compounds that all contain the features thought to be critical for binding to a specific drug target.

QSAR AND ADMET PRODUCTS

Product	Description
DS ADMET	Get an early assessment of your compounds by calculating the predicted absorption, distribution, metabolism, excretion and toxicity (ADMET) properties for collections of molecules such as synthesis candidates, vendor libraries, and screening collections. Use the calculated results to eliminate compounds with unfavorable ADMET characteristics and evaluate proposed structural refinements, designed to improve ADMET properties, prior to synthesis. Optimizing these properties during early drug discovery efforts is critical for reducing problems in later development phase. Included are models for human intestinal absorption, aqueous solubility, blood brain barrier penetration, plasma protein binding, cytochrome P450 2D6 inhibition, and hepatotoxicity. Filter a set of small molecules and select only those molecules that meet the rules specified by the set of selected SMARTS® rules.

QSAR AND ADMET PRODUCTS (continued)

Product	Description
DS TOPKAT	Evaluate your compounds' performance in experimental assays and animal models. Compute and validate assessments of the toxic and environmental effects of chemicals solely from their molecular structure. TOPKAT (TOxicity Prediction by Komputer Assisted Technology) employs robust and cross-validated Quantitative Structure Toxicity Relationship (QSTR) models for assessing various measures of toxicity and utilizing the patented Optimal Predictive Space validation method to assist in interpreting the results. Examples of Topkat endpoints include: Ames mutagenicity, Rat Oral LD50, Chronic LOAEL, Skin irritation, Ocular Irritancy, Fathead Minnow LD50, and a range of NTP and FDA Carcinogenicity test predictions.
DS QSAR BUNDLE	DS QSAR provides easy access to the hundreds of molecular descriptors, proven in biological systems to correlate with activity. Easily apply modeling techniques such as Bayesian models, multiple linear regression, Partial Least Squares (PLS), Genetic Functional Analysis (GFA), and more.
DS QSAR PLUS BUNDLE	DS QSAR Plus is an extension of the DS QSAR product. It includes Genetic Function Approximation (GFA) regression models, an advanced neural network component and VAMP descriptors, a semi-empirical quantum mechanical method for rapidly calculating accurate electronic properties for thousands of candidate compounds.
DS DMOL3DESCRIPTORS COMPONENT	The density-functional theory (DFT) program DMol3 can use used for calculating electronic properties of compounds at a very high level of accuracy.
DS VAMPDESCRIPTORS COMPONENT	VAMP descriptors, a semi-empirical quantum mechanical method for rapidly calculating accurate electronic properties for thousands of candidate compounds.

REFERENCES:

1. Brooks B. R., Brooks III C. L., Mackerell A. D., Nilsson L., Petrella R. J., Roux B., Won Y., Archontis G., Bartels C., Boresch S. , Caflisch A., Caves L., Cui Q., Dinner A. R., Feig M., Fischer S., Gao J., Hodoscek M., Im W., Kuczera K., Lazaridis T., Ma J., Ovchinnikov V., Paci E., Pastor R. W., Post C. B., Pu J. Z., Schaefer M., Tidor B., Venable R. M., Woodcock H. L., Wu X., Yang W., York D. M. and Karplus M. CHARMM: The Biomolecular simulation Program, *J. Comp. Chem.* **2009**, 30, 1545-1615.

2. Brooks B. R., Bruccoleri R. E., Olafson B. D., States D. J., Swaminathan S., and Karplus M. CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations, *J. Comp. Chem.* **1983**, 4, 187-217.

3. W.Rocchia, E.Alexov, and B.Honig. Extending the Applicability of the Nonlinear Poisson-Boltzmann Equation: Multiple Dielectric Constants and Multivalent Ions. *J. Phys. Chem. B*, **2001**, 105, 6507-6514.

4. Honig B., Nicholls A. Classical Electrostatics in Biology and Chemistry. *Science*, **1995**, 268(5214), 1144-1149.

5. Eswar N., Marti-Renom M.A., Webb B., Madhusudhan M.S., Eramian D., Shen M., Pieper U., Sali A. Comparative Protein Structure Modeling With MODELLER. *Current Protocols in Bioinformatics, John Wiley & Sons, Inc.*, **2006**, Supplement 15, 5.6.1-5.6.30.

6. Renom M.A., Stuart A., Fiser A., Sánchez R., Melo F., Sali A. Comparative protein structure modeling of genes and genomes. A*nnu. Rev. Biophys. Biomol. Struct.*, **2000**, 29, 291-325.

7. Sali A. and Blundell T.L. Comparative protein modelling by satisfaction of spatial restraints. *J. Mol. Biol.*, **1993**, 234, 779-815.

8. Fiser A., Do R.K., Sali A. Modeling of loops in protein structures, *Protein Science* **2000**, 9, 1753-1773.

9. Pierce B., Weng Z. A Combination of Rescoring and Refinement Significantly Improves Protein Docking Performance. *Proteins*, **2008**, 72(1), 270-279.

10. Chen R., Weng Z. ZDOCK: An Initial-stage Protein-Docking Algorithm. *Proteins* **2003**, 52, 80-87.

11. Pierce B, Weng Z. ZRANK: Reranking Protein Docking Predictions with an Optimized Energy Function. *Proteins*, **2007**, 67(4), 1078-1086.

12. Li L, Chen R (joint first authors), Weng Z RDOCK: Refinement of Rigid-body Protein Docking Predictions. *Proteins*, **2003**, 53, 693-707.

13. Chennamsetty N., Voynov V., Kayser V., Helk B. and Trout B. L. Prediction of aggregation prone regions of therapeutic proteins. *J. Phys. Chem. B*, **2010**, 114(19), 6614-6624

14. Chennamsetty N., Voyonov V., Kayser V., Helk B. and Trout B. L. Design of Therapeutic proteins with enhanced stability. *Proc. Nat. Acad. Sci.*, **2010**, 106(29), 11937-11942

15. Chennamsetty N, Helk B., Trout B. L, Voyonov V., Kayser V. PCT/US2009/047954. Filed 19th June, 2009.

16. Chennamsetty N., Voynov V., Kayser K., Helk B. and Trout B.L., *Proteins* **2011**, 79, 888-897.

17. Wu, G.; Robertson, D. H.; Brooks, C. L. III; Vieth, M. Detailed Analysis of Grid-Based Molecular Docking: A Case Study of CDOCKER - A CHARMm-Based MD Docking Algorithm. *J. Comp. Chem.*, **2003**, 24, 1549.

18. Erickson J.A., Jalaie M., Robertson D.H., Lewis R.A., Vieth M., Lessons in Molecular Recognition: The Effects of Ligand and Protein Flexibility on Molecular Docking Accuracy," J *Med Chem.* **2004**, 47(1), 45-55.

19. Koska J., Spassov V.Z, Maynard A.J., Yan L., Austin N., Flook P.K., Venkatachalam C. M. Fully Automated Molecular Mechanics Based Induced Fit Protein–Ligand Docking Method, *J. Chem. Inf. Model.*, **2008**, 48(10), 1965–1973

20. Haider M.K., Bertrand H.-O. and Hubbard R.E. Predicting Fragment Binding Poses Using a Combined MCSS MM-GBSA Approach. *J. Chem. Inf. Model.*, **2011**, 51(5), 1092–1105.

21. Caflisch A., Miranker A. and Karplus M. Multiple copy simultaneous search and construction of ligands in binding sites: application to inhibitors of HIV-1 aspartic proteinase. *J. Med. Chem.*, **1993**, 36 (15), 2142–2167.

22. Miranker A. and Karplus M. Functionality maps of binding sites: a multiple copy simultaneous search method. *Proteins, Structure, Function and Genetics*, **1991**, 11, 29-34.