CERTARA


# Model-based Drug Discovery Solutions from Certara

## Scientists now have a choice of powerful solutions from the leader in model-based drug discovery and development – Certara

### Multi-criteria drug design

A successful drug candidate will need to overcome a variety of hurdles, including adequate potency and selectivity, as well as acceptable absorption, distribution, metabolism and excretion (ADME), physical, and safety properties. Software solutions from Certara allow researchers to create predictive models for ALL of the parameters relevant to successful clinical outcome, and to understand and balance the competing quantitative structure-activity relationships (QSAR) for the multiple criteria a successful drug candidate must satisfy.

### Safety and off-target pharmacology

Industry reports indicate that nearly half of drug candidates fail because of inadequate safety. This represents a staggering loss of investment and missed opportunity. Software solutions from Certara have introduced predictive methods to identify safety risks earlier, and improve the likelihood of success in pre-clinical safety studies.

### Lead optimization

A key challenge faced by discovery scientists during lead optimization (LO) is selecting which compounds to make from a large number of potential synthesis candidates. In LO, a difference of a factor of 50 in the potency of a drug candidate can make the difference between a successful candidate and an uninteresting analog. The challenge is made more difficult because the analogs are often quite similar, differing by just one or two R-groups. Certara continues its history of thought leadership in the area of QSAR, which allows researchers to go beyond categorizing structures as active or inactive, to make accurate predictions about the level of biological activity or potency for a set of close analogs, which is vital to effectively prioritize ideas in LO.

Certara scientists believe predictive science can't just be an academic exercise, and we are focused on delivering the science and software tools that will have a direct impact on your drug discovery challenges and allow your discoveries to be translated into success in the clinic.

### Powerful Solutions From Certara

- SYBYL-X Suite, molecular modeling from sequence through lead optimization
- Muse Invent, identification and optimization of synthesizable lead candidates
- Surflex Suite, powerful predictive models that combine ligand, receptor, and pharmacological information
- Tripos Chemistry Extensions for KNIME®, nodes make cheminformatics capabilities available to the KNIME platform

## Multi-criteria drug design

Certara solutions enable researchers to understand and balance the competing SARs for each of the multiple criteria a successful drug candidate must meet. With the analysis tools in the new Molecular Data Explorer (MDE)—in Certara's flagship product—SYBYL-X, researchers obtain insights into their project data in minutes, for example:

- You can quickly compute cLogP for a set of compounds of interest, plot a histogram of cLogP and a histogram of activity in your cellular assay, and then, by simply selecting the structures with cLogP greater than 3, see how the structures with high predicted logP are distributed in terms of their cellular activity.
- Using a structure similarity map, you can get a visual structural clustering that shows activity/selectivity islands and cliffs at a glance.
- The MDE allows scientists to merge and combine chemical structure data and biological data from multiple sources so that all of the data can be analyzed together, and to explore the relationships between and among the multiple computed or measured properties.

Researchers can prioritize and balance the many factors required by a successful drug candidate using multi-criteria scoring tools available in the Tripos Chemistry Extensions for KNIME and in Muse Invent with TriposScore.

With these technologies, researchers can specify what values of a property are desirable (eg, ideal candidates for my project have a logP between 0 and 3) or undesirable (penalize all compounds with greater than 2 Lipinski violations), and, based on the importance you give to each factor, ideas or entire databases can be ranked using a score that combines all of the factors under consideration, enabling rapid exploration of the impact of changes that may be made to decision criteria.

Ideally, researchers would like tools that can suggest novel chemical ideas for side chains, scaffolds, or entire structures that meet multiple design criteria. You want to identify the scaffolds and R-groups that will simultaneously satisfy the potency, selectivity, physical properties, ADME properties, and safety profile you are seeking.

Certara's Muse Invent is a molecular design workflow that allows discovery scientists to:

- Perform lead- and scaffold-hopping
- Invent new R-groups around a fixed scaffold
- Generate ideas that meet multiple design criteria
- Easily integrate in-house or third-party scoring methods for use as design criteria
- Identify drug candidates that are not only synthesizable but also include the necessary synthesis pathway

Additionally, predictive models that cover all of the parameters relevant to successful clinical outcome are needed in order to design drugs that balance multiple criteria efficiently, and recent advances in SYBYL-X's 3D QSAR capabilities make modeling multiple biological endpoints quick and easy.

With SYBYL-X's latest QSAR method, Topomer CoMFA, researchers can create 3D QSAR models in minutes instead of weeks, and can automatically generate hundreds or even thousands of predictive QSAR models for chemogenomic studies by mining large databases of chemical and biological data.

With the new MDE and Topomer CoMFA 3D QSAR technology in SYBYL-X, Muse Invent molecular invention software, and multi-criteria scoring tools in Tripos Chemistry Extensions for KNIME, researchers can effectively understand and balance the competing SARs for each of the multiple criteria a successful drug candidate must meet.

## Safety and off-target prediction

Nearly half of drug candidates fail because of inadequate safety in pre-clinical testing, representing an expensive loss of investment and lost opportunity. Predictive methods that allow researchers to identify safety and/or off-target pharmacology much earlier in the drug discovery and development cycle are now available from Certara, and allow better decision-making so that:

- Chemistry efforts can be focused on the areas with the best chance of success in pre-clinical and clinical safety
- Biological/safety evaluation explores the areas of greatest risk
- New therapeutic applications can be found for a failed development candidate in order to rescue lost investment

For example, Certara's Topomer Search technology in SYBYL-X was used by scientists at a major pharmaceutical company to successfully predict hERG liability, a key anti-target that can lead to a potentially fatal disorder called long QT syndrome. They developed a predictive model they called TopoHERG based on topomer similarity.

Additionally, Topomer CoMFA's QSAR methods have been successfully applied to model cytochrome P450 activity and successfully guide LO teams to compounds with improved metabolic profiles.

A third example, Surflex-Sim's 3D molecular similarity has been shown to reveal non-trivial off-target biological relationships that would not be found on the basis of simplistic 2D chemical descriptions.

Predictive QSAR models for hundreds of biological targets have been developed using Topomer CoMFA methods to mine, in an automated fashion, the large public repositories of chemical and biological data that are now available. These models provide both accurate biological predictions and a chemical rationale for understanding the SAR at each receptor.

Certara provides predictive solutions that allow researchers to identify safety and/or off-target pharmacology much earlier in the drug discovery and development cycle, empowering better decision-making.

## Lead optimization

Researchers are increasingly recognizing that QSAR and 3D QSAR capabilities allow them to go beyond categorizing structures as active or inactive, allowing them to accurately predict the level of biological activity or potency needed to prioritize ideas in LO.

Accurate 3D QSAR models allow researchers to prioritize their ideas and select those most likely to advance project objectives.

Certara inherited a rich legacy of QSAR pioneering "firsts" when it acquired Tripos, particularly 3D QSAR, and Certara continues to build on that tradition with scientific innovation and solutions for LO.

CoMFA, the first 3D QSAR method, is now an industry standard with literally thousands of literature publications demonstrating CoMFA's utility for molecular discovery.

HQSAR followed, and is a novel 2D QSAR method based on molecular holograms.

Most recently, Topomer CoMFA revolutionized 3D QSAR all over again. Because pose generation is automated with Topomer CoMFA, researchers can:

- Easily generate models for multiple activities
- Identify novel ideas for R-groups that are most likely to lead to improvements in activity using virtual screening based on predictions from 3D QSAR models
- Generate 100's to 1000's of predictive QSAR models for chemogenomic studies automatically by mining large databases of chemical and biological data

Additionally, Certara has invested heavily in making QSAR science accessible to more discovery scientists. The recently introduced workflow-oriented QSAR Project Manager streamlines the organization of QSAR datasets, QSAR models, and QSAR predictions.

With the QSAR project manager, scientists can work more efficiently and effectively, and it is much easier for a non-expert to generate QSAR results.

Certara is also making QSAR science more accessible, for example via a PYTHON toolkit, to allow researchers to build their own customized workflows and deploy QSAR predictions out to the wider discovery team.

## A Natural Evolution

Pharma and biotech organizations can no longer afford the high failure rate of drug candidates, nor tolerate the bottlenecks in their workflows and systems. Resources continue to shrink, while timelines get stretched. As the pressure increases to more rapidly and efficiently produce results in drug discovery, scientists are logically turning to model-based drug discovery and development processes and solutions. They are looking for those tools that will allow agile, but reliable maneuvering through the maze of complex steps necessary to produce success.

Certara knows your success is about having the right tools at the right time in the process, and applying them wisely to translate your discoveries into clinical results.

## About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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