

# SCULPT 3.0

## Brings 3D Visualization to the Lab Bench

**W**ith the acquisition of Interactive Simulations, Inc., last April, MDL added to its arsenal of discovery informatics tools a powerful analysis package for chemists. SCULPT brings interactive 3D visualization and manipulation to the lab bench, enabling scientists to conduct on-the-fly 3D studies. What structural features make two different molecules activate the same receptor? What conformations are possible for a library core structure? With SCULPT, scientists can get the answers they need quickly, without relying on complicated molecular modeling packages.

At the American Chemical Society meeting in New Orleans, LA, in August, MDL announced the first significant enhancement release of SCULPT since acquiring the product. SCULPT 3.0 provides several important, customer-requested updates to the software, according to Mark Surles, MDL's director of decision support.

"To build SCULPT 3.0, we listened closely to what chemists told us about their work," Surles said. "In response, we added an array of new features to SCULPT and integrated the software more tightly with other MDL tools. The result is an analysis package that helps scientists communicate, as well as make, decisions."

An interactive, 3D structural analysis tool for the scientist's desktop, SCULPT has always offered unprecedented capabilities. Access to 3D conformations, combined with the ability to align compounds and compare their similarities and differences, can help scientists

- Discover how compound properties affect binding
- Avoid synthesizing compounds with steric or electrostatic criteria that do not match active compounds

- Choose compounds that sample the shape and location of hydrogen bonds and functional groups

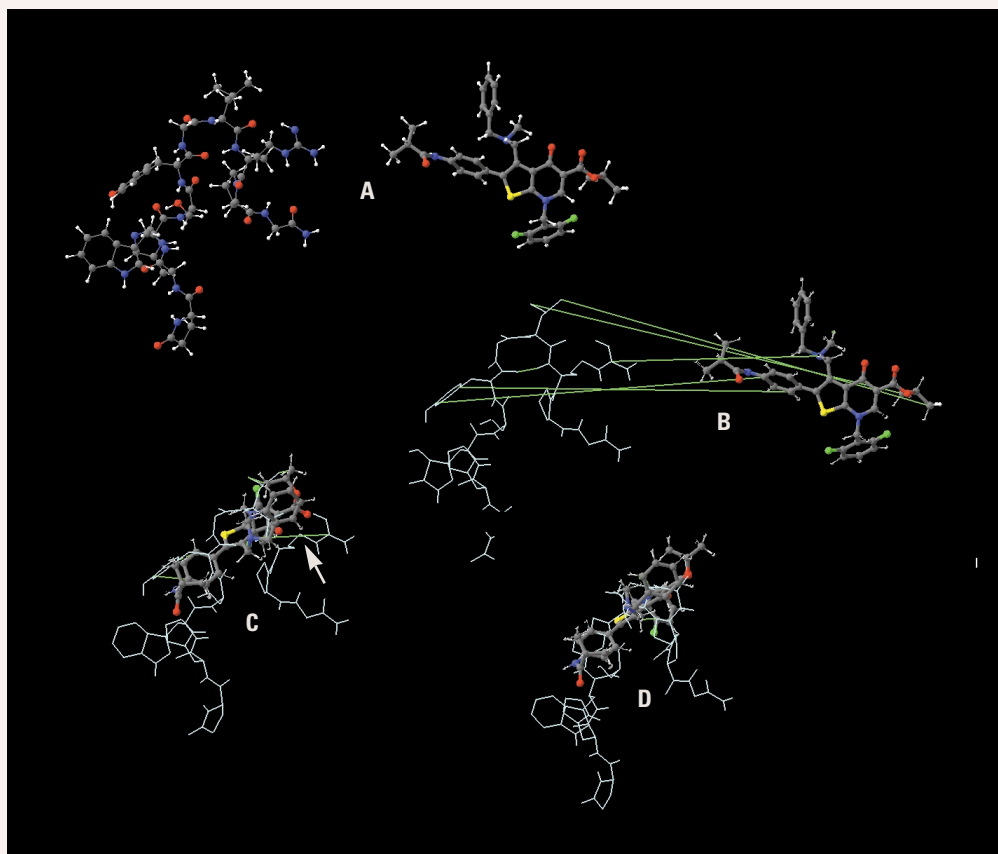
SCULPT 3.0, however, manages to improve on "unprecedented." In addition to adding new 3D tools, enhancements in the latest version of SCULPT make all of the software's visualization and alignment tasks easier and more intuitive. And the software also includes many

new features that help scientists better communicate their results to colleagues.

For instance, SCULPT 3.0 includes additions that make analyzing entire hitlists of compounds as easy as clicking a button. Scientists performing a search using ISIS simply click a button to transfer their search results to SCULPT. SCULPT 3.0 converts the compounds to 3D and

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## Using SCULPT to Gain Competitive Insights



# SCULPT

## Possibilities (and Impossibilities)

# Uncovers

**N**eurocrine Biosciences (San Diego, CA), like so many pharmaceutical and biotechnology companies, has had to adapt its informatics infrastructure to meet the demands presented by combinatorial chemistry and high-throughput screening. New databases and software programs are now available to support chemists at the bench. And, to assist with refining library core structures and combinatorial library design, Neurocrine has put more emphasis on computational

Neurocrine's scientists can use SCULPT to get ideas—quickly. A competitor's publication (A) describes the small molecule antagonist at right as mimicking the peptide hormone at left. To investigate these claims, Neurocrine scientists use SCULPT to flexibly fit the peptide hormone to the antagonist. They begin by building the small molecule in ISIS/Draw and pasting it into SCULPT. They then use SCULPT to tether the features hypothesized to correspond in the two molecules, freezing the peptide in a previously known, favorable conformation (B). Using minimization, they align the two molecules, but find that one pair of features cannot be reconciled (C, indicated by the arrow). The scientists then thaw the peptide conformation, allowing both the peptide and small molecule to find a commonly accessible conformation overlaying the hypothesized common features (D), which can be used to suggest additional functional groups that may improve the small molecule's affinity. Total time for a first glance at a competitor's 3D thinking? Less than five minutes.

**“SCULPT helps scientists see that something that looks good on paper is impossible in 3D space. They can use the software to look for possibilities and to quickly rule out impossibilities.”**

*Scott Struthers, Senior Scientist and Project Leader, Neurocrine Biosciences*

chemistry. Yet, as in most organizations, Neurocrine still faces the challenge of tightly integrating its computational activities with the workflow and goals of its project teams.

According to Scott Struthers, a senior scientist and project leader at Neurocrine, the ties between synthetic chemistry and computational chemistry today are stronger than ever. Yet the tools available to synthetic chemists can be woefully inadequate. “Too often, it seems that synthetic chemists fall back on physical molecular modeling kits to appreciate 3D,” Struthers said. “But just looking at 2D structures or physical models can give scientists a lot of misconceptions about what works. Organizations need software that can bridge the gap between synthesis and modeling so that all the members of a project team can start thinking in three dimensions from the very beginning.”

SCULPT serves as this bridge, offering scientists a way to conduct real-time, interactive investigations in three dimensions. Since Neurocrine licensed SCULPT in 1998, its chemists have been able to take a whole new look at the compounds and libraries being designed in the company's quest for new ways to treat neuropsychiatric, neuroinflammatory and neurodegenerative, and neuroendocrine diseases and disorders.

“Before we licensed SCULPT, there just

wasn't a convenient way for our medicinal chemists to look much beyond a 2D structure,” Struthers said. “With SCULPT, our scientists can test—on the fly—their own ideas about what conformations a molecule might have.”

According to Struthers, the researcher at the bench is willing to leave the complex modeling and diversity analysis to the professional computational chemist in the project team. But even if they wanted to do some of these calculations themselves, two things stand in their way: hardware and software. “Molecular modeling packages often require a chemist to sit down at a UNIX box, and most scientists aren't interested in fooling around with UNIX-based software when they are used to working on a PC,” Struthers noted.

In addition, sophisticated molecular modeling packages do more than synthetic chemists need. “Synthetic chemists are most interested in seeing what their compound or design idea looks like in 3D and comparing that with hypothesized bioactive conformations or pharmacophores,” Struthers said. “Their questions are straightforward: ‘Am I on the right track with this library core structure?’ ‘Will this functional group go into the same orientation as the side chain on the active compound?’ ‘How

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# MDL Software Simplifies Pharmacophore Development

Synthetic chemists have traditionally viewed pharmacophore development and optimization as part of the computational chemistry domain. But a presentation at last August's meeting of the American Chemical Society in New Orleans, LA, revealed that high-throughput chemistry is turning the exploration of pharmacophores into an essential tool in library design.

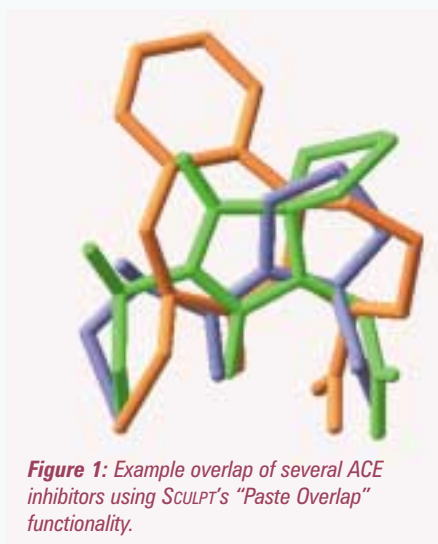
"[P]harmacophores increasingly assume the role of filters for real and virtual libraries of structures," state MDL researchers Dr. Douglas R. Henry, Dr. Ali G. Özkabak, and Dr. Mitchell A. Miller, in collaboration with Dr. Osman F. Güner of Molecular Simulations, Inc. "It is likely [pharmacophores] will increasingly be used as filters for alternative drug actions, side effects, and pharmacokinetic and metabolic property predictions."

Henry and his colleagues propose a simplified method for the development and optimization of 3D property-based pharmacophores, one that can be performed without specialized molecular modeling software. Their technique relies on two MDL tools—SCULPT and Cheshire—to identify and characterize potential pharmacophore candidates and uses a custom ISIS/Host program to optimize the final pharmacophore.

This article summarizes the approach. Further details can be found in a forthcoming book edited by Güner, to be published by International University Line (<http://www.iul-press.com>). For more information on the chapter, titled "Development and Optimization of Property-based Pharmacophores," or the book, contact the publisher.

## An Approach for Bench Chemists

According to the authors, the nature of pharmacophore development has changed as new tools have been introduced to support scientists. "With the introduction



*Figure 1: Example overlap of several ACE inhibitors using SCULPT's "Paste Overlap" functionality.*

of flexible 3D searching and large structural databases, pharmacophore development becomes, in modern terminology, a problem in structural data mining," they write. Automated algorithms abound, as do an array of scientific information management tools.

To illustrate how the average bench researcher might engage in pharmacophore development, the authors combined several commonly available tools with which most scientists would already be familiar. Their technique encompasses four steps:

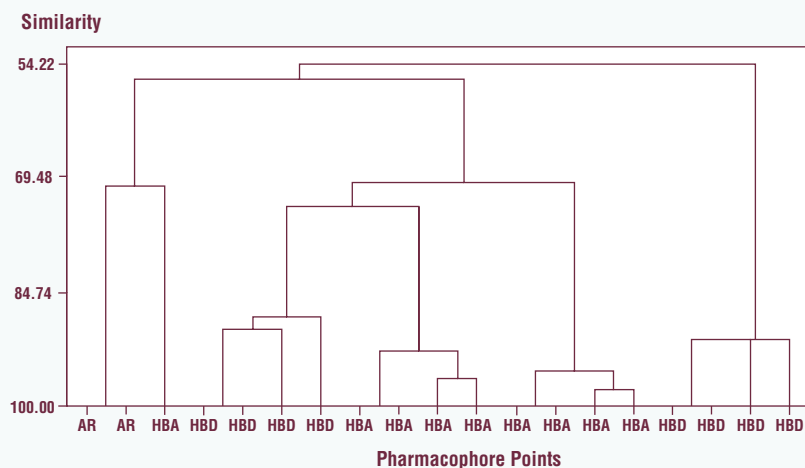
1. Flexible superposition of active structures onto a rigid or docked analog using SCULPT
2. Identification of relevant functional and physicochemical property groups using the chemical perception and manipulation language Cheshire for ISIS
3. Hierarchical clustering of the identified groups to visually guide the selection of an initial pharmacophore
4. Optimization of the pharmacophore using a custom ISIS/Host application program

## Superpositioning with SCULPT

Henry and his co-authors note that because relatively few docked ligands have been characterized in public databases of crystal structures, such as the Protein Data Bank, superposition and comparison of known active analogs are the best first steps in pharmacophore development. Alignment algorithms can provide strong insights into the steric and electrostatic properties important to binding.

There are two general approaches to superpositioning. Atom- and bond-matching methods identify similarities among compounds, often using maximal common substructure (MCSS) comparisons. MCSS is most successful among well-characterized, drug-sized molecules with a common structural framework. The other approach uses steric and electrostatic field-driven optimizations to determine the potential alignment of structures. The most well-known field method is Smith and Kearsley's SEAL technique, which is designed to simulate the binding of two small structures to an active site even when the details of the receptor site are unknown.

The authors selected SCULPT to handle superpositioning because of the program's combination of flexibility, power, and usability. Because the program implements both MCSS and SEAL methodologies automatically and in combination with simplified force-field molecular relaxation, scientists can take a real-time look at how a flexible, mobile structure relates to a template structure (see Figure 1). Other interactions, such as van der Waals and Coulombic interactions and constrained energy minimization, are also performed rapidly by SCULPT, giving scientists real-time updates of atom coordinates. As a result, scientists can quickly obtain a set of superpositioned active structures for further evaluation.



**Figure 2:** Hierarchical clustering of putative pharmacophore points for a set of superimposed ACE inhibitors. Points are for aromatic ring centroids (AR), H-bond donors (HBD), and H-bond acceptors (HBA).

### Characterizing Receptor Site Interactivity

The next step in pharmacophore development is identifying the atoms and functional groups that could potentially interact with complementary atoms and groups in the receptor site. Henry and his co-authors note that, computationally, all pharmacophores used in 3D searching are topological—most software programs store and search structures not as properties, but as connection tables. Chemists, however, prefer to describe functional groups by their properties—a hydrogen bond donor, for instance, instead of its topological equivalent N-H, O-H, or S-H.

With its JavaScript-like command and control syntax, associative arrays, and transparent access to all the atom, bond, fragment, ring, and collection

information associated with a molecule, Cheshire for ISIS can give scientists enormous insight into the properties possessed by a set of actives. In this particular paper, the authors developed a Cheshire script to count rotatable bonds and identify aromatic ring centroids and H-bond donors in the superimposed structures from SCULPT. Cheshire produced a table listing the location and type of each possible pharmacophore point in the ensemble. The authors note that, with a little more scripting, Cheshire perception could have been combined with property calculation. In this case, the result would have been a combined set of possible pharmacophore points and properties that would have provided more in-depth information for developing the initial query.

### Initial Pharmacophore Generation

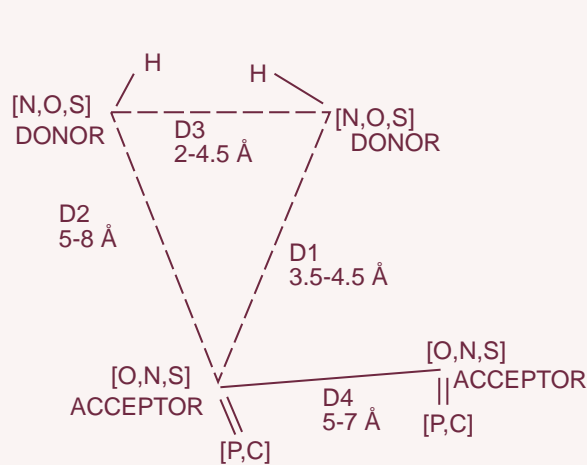
Armed with the table of pharmacophore points from Cheshire for ISIS, Henry and his colleagues were ready to let their initial pharmacophore take shape. The authors write that most scientists prefer to be guided by intuition and experience at this stage; yet, in this age where high throughput is almost mandatory, automated techniques can be quite appealing. The technique proposed in this paper offers a way to combine automation and intuition.

The authors first hierarchically clustered the pharmacophore points using single-linkage or Ward's linkage algorithms. The results are represented as a dendrogram, which scientists can visually trim to include as many and whichever points appear to be meaningful for the pharmacophore. The dendrogram shown in Figure 2, for instance, shows five well-separated clusters from the pharmacophore points generated by the Cheshire for ISIS scripts. Visual examination allows scientists to winnow the list to include those functional properties most worthy of further optimization.

### Pharmacophore Optimization

Traditional optimization techniques require molecular modeling and X-ray crystallography. But Henry and his co-authors propose mining a 3D structural database as a less expensive, faster way of producing a more selective pharmacophore that will generate higher search

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Parameter	Initial Value (mean)	Optimized Value (mean)
<b>Optimizing function 1</b>		
D1 (Å)	3.5-4.5 (4.04)	1.8-4.8 (3.30)
D2 (Å)	5.0-8.0 (6.94)	5.9-7.9 (6.90)
D3 (Å)	2.0-4.5 (2.96)	2.6-5.9 (4.25)
D4 (Å)	5.0-7.0 (6.09)	3.5-7.6 (5.55)
Function value	0.57	0.63
Iterations	53	
Yield (active, MDDR)	404	422
<b>Optimizing function 2</b>		
D1 (Å)	3.5-4.5 (4.04)	2.0-4.2 (3.10)
D2 (Å)	5.0-8.0 (6.94)	5.1-9.0 (7.05)
D3 (Å)	2.0-4.5 (2.96)	3.1-6.4 (4.75)
D4 (Å)	5.0-7.0 (6.09)	2.7-6.1 (4.40)
Function value	0.68	0.79
Iterations	36	
Yield (active, MDDR)	404	425

**Figure 3:** The table shows optimization results for the ACE inhibitor pharmacophore indicated. While optimization in general increased both the yield and the specificity of the pharmacophores, Function 2 converged more rapidly and performed slightly better than Function 1.





SCULPT 3.0  
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aligns them automatically so that their structures can be readily compared. This tight integration between SCULPT and other MDL software makes it easier for scientists to explore hypotheses during the course of their research.

SCULPT 3.0 users will also benefit from being able to

- **Automatically convert 2D structures to 3D models.** SCULPT 3.0 automatically generates low-energy, 3D conformations for structures pasted into SCULPT from ISIS/Draw, ISIS/Base, or Chemscape Chime. The conversions can also be applied to entire lists of molecules saved as SDfiles.
- **Automatically align compounds to each other or to bound ligands.** Compound superpositioning and comparison reveal how compounds may interact with receptor sites. SCULPT 3.0 uses two different alignment algorithms: a maximal common

substructure (MCSS) methodology, which identifies structural similarities between compounds, and the SEAL approach, which uses steric and electrostatic field-driven optimizations to determine the potential alignment of structures.

- **View high-quality 3D models and surfaces.** Significantly improved graphics in SCULPT 3.0 provide production-quality images and new visualization features. Scientists can quickly determine the orientation of and distance between functional groups, the size and volume of compounds or important Rgroups, and the position and potential influence of hydrogen bond donors and acceptors on the conformation. SCULPT also generates solvent-accessible surfaces around one or more compounds, colored by the charge of the contributing atoms. Other available SCULPT 3.0 visualizations include protein ribbon representations, side-chain characteristics, and ball-and-stick models.

- **Share results with colleagues throughout their organization.** In addition to integrating better with ISIS, SCULPT also connects to enterprise reporting and communication systems. OLE embedding enables SCULPT images to be stored in Microsoft Word, email documents, and intranet Web sites as live 3D objects. Scientists on the receiving end of a report or email update can rotate molecules, query basic structural properties, and toggle the visualizations without having to learn or even launch SCULPT. These features keep project teams connected, enabling scientists to pool their combined knowledge to determine the next step to take in a research plan.

To learn more about how SCULPT 3.0 can help your scientists make better decisions at the bench, visit MDL's Web site at <http://www.mdli.com/sculpt>, contact your MDL sales representative, or the MDL office nearest you. ❖

SCULPT at Neurocrine  
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might these diverse screening hits bind to the same receptor?"

"SCULPT helps scientists see that something that looks good on paper is impossible in 3D space," Struthers continued. "They can use the software to look for possibilities and to quickly rule out impossibilities."

Scientists at Neurocrine have been working with SCULPT for over a year, using it for superpositioning and comparing screening hits and active compounds (see "Using SCULPT to Gain

Competitive Insights," page 4). Chemists designing new molecules and libraries also consult SCULPT to sort through their ideas to determine which make the most sense to pursue. Even Struthers, a computational chemist by training, frequently turns to SCULPT instead of a UNIX-based molecular modeling tool. "SCULPT gives me answers quickly when I just need to check something out," he said.

With the release of SCULPT 3.0, Struthers is particularly interested in making SCULPT models and research more widely available on Neurocrine's intranet. The tighter integration between SCULPT and Chemscape Chime Pro is

enabling Neurocrine to create interactive Web pages containing SCULPT data.

"The Web gives us a way to share information that has previously been inaccessible—unless you are looking over someone's shoulder at a computer screen," Struthers explained. "Making SCULPT data available throughout Neurocrine will help project teams communicate in three dimensions. It should be particularly useful to the researchers designing compounds, who should be thinking about the conformational flexibility of compounds earlier in their investigations." ❖

Pharmacophore Development  
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yields. Miller wrote an ISIS/Host application to perform repeated searches over a 3D database, each time modifying a set of constraint parameters in the pharmacophore to produce higher yielding and/or more selective search results.

Figure 3 (see page 7) shows the training and prediction results that the authors obtained for optimizing an ACE inhibitor pharmacophore against a set of 200 known inhibitors in MDL's MDDR database. The initial pharmacophore retrieved 404 of the 471 possible ACE inhibitors, a

good showing, particularly when compared to the results obtained using a published ACE inhibitor, which retrieved just 356 structures. The resulting optimized pharmacophores showed tightening of some ranges and some shifts of the mean values. Comparing the optimization functions shows the second function, developed by Güner and presented at the 1998 Charleston Conference, converged more rapidly and yielded a pharmacophore with slightly better prediction performance. Finally, in each of the optimizations with this data set, both the yield and the specificity increased as a result of optimization.

## Conclusions

The authors' analyses, excerpted here, were intended to be illustrative of a technique. The results themselves were secondary. Yet this simple approach demonstrates that pharmacophore development can be done speedily with the assistance of industry-standard, readily available tools. The authors hope that this type of database mining will provide scientists with more flexibility during the early stages of drug development. ❖

# SCULPTing Hits into 3D Queries

The tight integration between SCULPT and other MDL software, such as ISIS/Draw, lets scientists add more power to their searches. For instance, SCULPT can be used to turn a set of active 2D compounds into a 3D conformationally flexible substructure (CFS) search query, which can retrieve a more structurally relevant set of hits from a database search.

Figure 1 shows a group of compounds that displayed activity in a particular screen. Unfortunately, the scientists do not have a 3D model of the target site. And while there seems to be some correlation among the 2D structures, the scientists are not sure why there is a 30 percent variation in the activity data.

To investigate which features of these structures influence activity, the scientists select “Chemistry → Transfer to SCULPT.” The compounds are seamlessly transferred to SCULPT, converted into 3D models, and automatically aligned to each other (see Figure 2). Several structural features are present in similar orientations among the molecules, including a six-membered aromatic ring, a nearby H-bond acceptor and sulfur atom, and a hydrophobic methyl substituent. The absence of and position of the methyl substituent in Actives-3 and Actives-5, respectively, may explain these compounds’ decreased activity.

Using these observations as a guide, the scientists measure the distance and angle parameters between the functional parts of the molecules, either directly in SCULPT or by transferring the structures back to ISIS/Draw (see Figure 3). Comparing the results and selecting “Chemistry → Create 3D” produces a 3D CFS query that averages the values for each compound (see Figure 4). This query specifies an aromatic ring, a simple H-bond acceptor, a five-membered sulfur heterocycle, a methyl group, and an exclusion sphere with distance and angle parameters reflecting the measurements from the five original molecules. Executing the query against MDDR-3D 99.2 (105,372 compounds) using default CFS parameters retrieves 10 hits—a much more refined list than the 5,863 hits retrieved from a 2D substructure search using the fragments upon which the 3D query was based. ❖

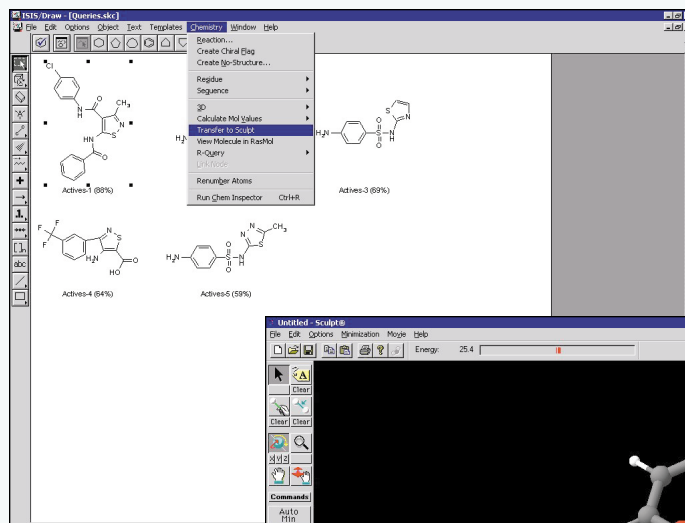


Figure 1

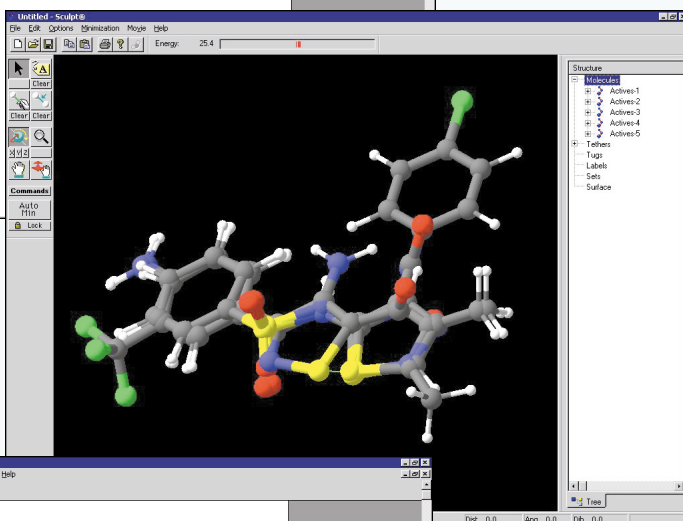


Figure 2

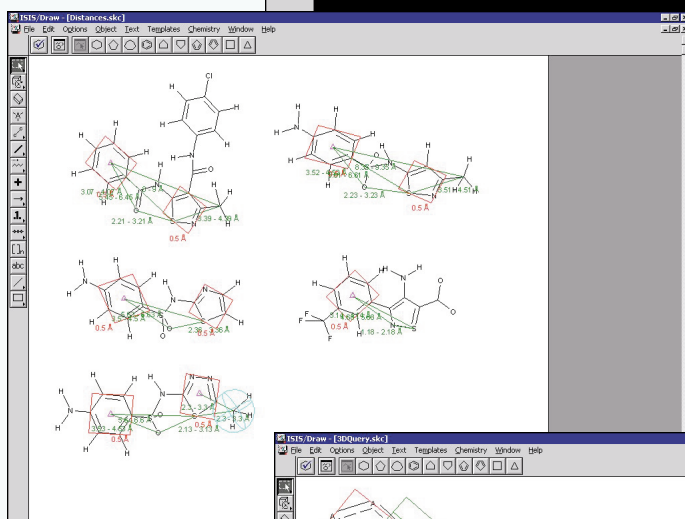


Figure 3

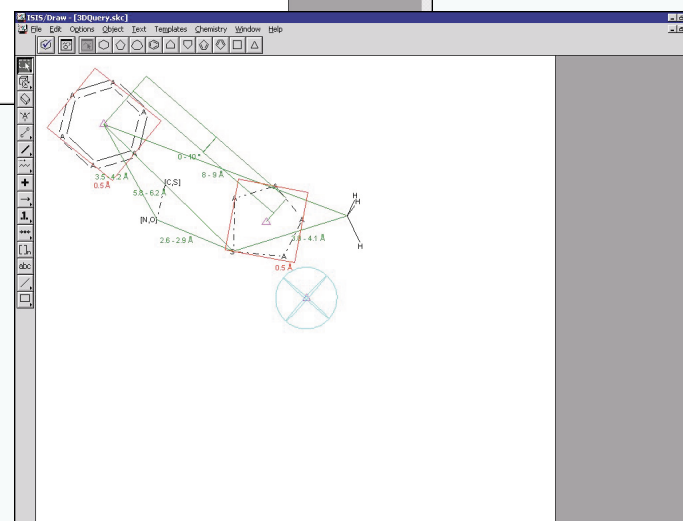


Figure 4