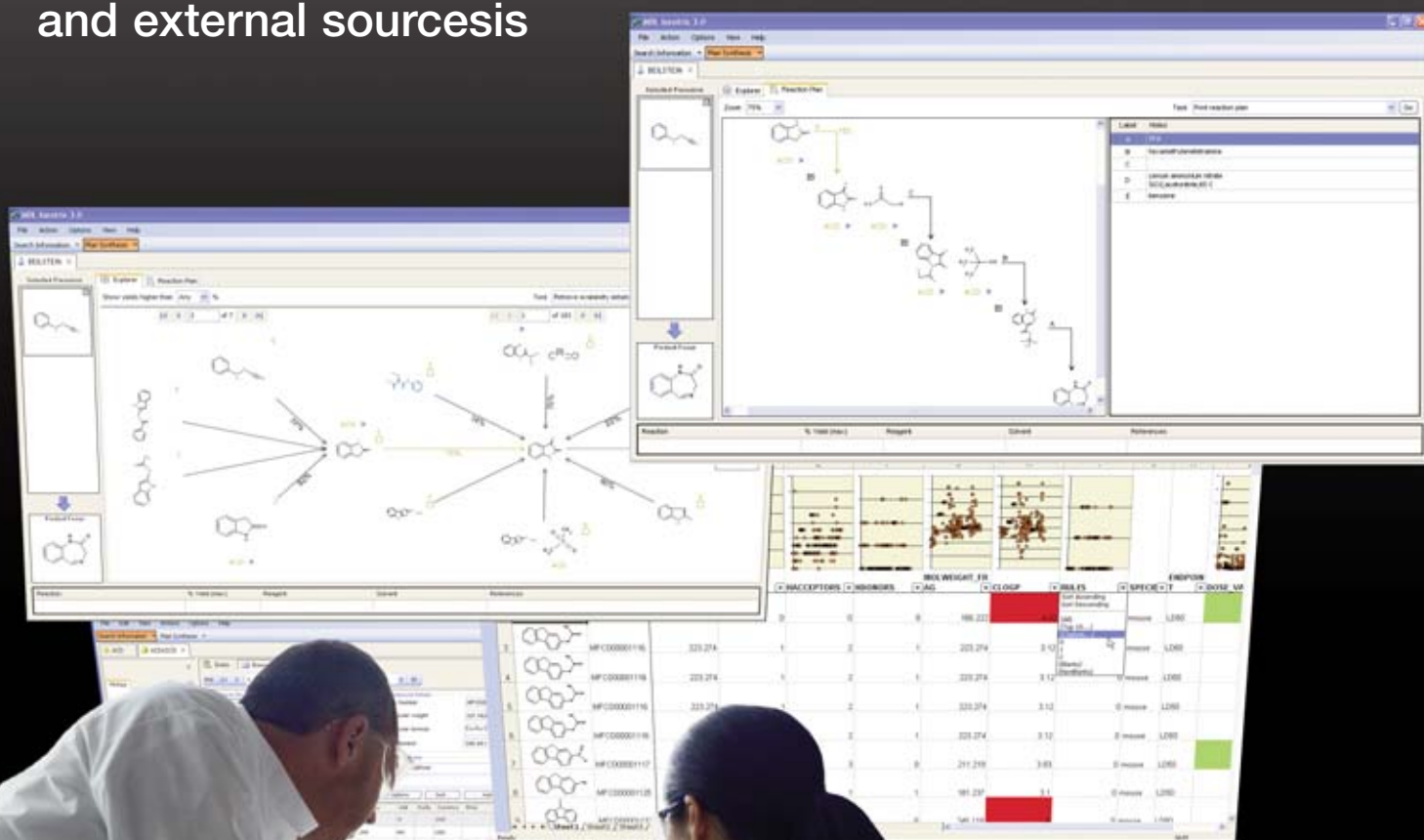


MOLECULAR CONNECTION

2007 • Vol 25 No 3

Isentris 3.0

Dynamically delivering relevant content from internal and external sources



MDL Isentris in action

- Rgroup decomposition using Isentris for Excel
- Building a simple query-browse application with MDL Isentris controls



MDL[®] Assay Explorer[®] at Daiichi Pharmaceutical

Providing fast, flexible access to experimental data

MOLECULAR CONNECTION

2007 • Vol 25 No 3



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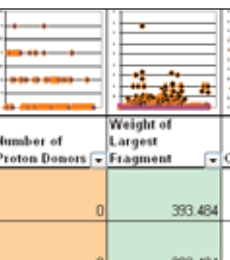
Celebrating 25 years of publication in 2007

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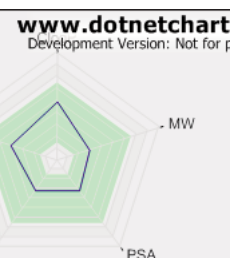
Accelerating research with MDL® Draw's powerful scientific calculator add-ins

18 Corporate Connections

Partnership with MathSpec supports R&D workflows by accelerating identification of structures in mass spectral data using MDL® ACD



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Access Molecular Connection online at www.mdl.com. *Be sure to bookmark us!*

Search the way you want. **Find** relevant data faster. **Power** your decisions with industry-leading chemistry tools.

The new Isentris[®] 3.0

As a researcher, one of your greatest challenges is managing, accessing and fully exploiting massive amounts of diverse, complex information. This daily data blizzard includes chemistry and biology information from in-house sources and commercial databases, citations from journals, papers and Internet resources, lab notebook entries and results from your favorite calculators and predictive tools, to name just a few items.

To make sound decisions based on all this valuable information, you need an informatics system that helps you access data systematically—one that illuminates your findings by helping you understand the relationships between data sets. Most importantly,

(continued on page 4)

(continued from page 3)

you need a system that helps you determine what data is critical for decision making in prioritizing and optimizing lead compounds.

The MDL® ISENTRIS® 3.0 informatics system, scheduled for release this August, helps you stay ahead of the competition by accessing commercial and in-house data and searching them simultaneously. For example, by automatically providing proprietary and commercial sourcing information when you review a reaction, ISENTRIS gives you all the information you need when you need it, enabling you to make informed decisions with confidence and quickly move to the next step.

“With ISENTRIS, you can quickly assess information from a variety of commercial sources, including CrossFire Beilstein,” says Dr. Dominic John, ISENTRIS Group Manager, Elsevier MDL. “Then you can add your proprietary data to the mix and easily search, browse, organize and convey this comprehensive content in the context of your workflow using flexible combined query, browse and report forms that you can fine-tune to meet your needs. ISENTRIS also offers unparalleled rapid development, high performance and scalability to meet the needs of your organization.”

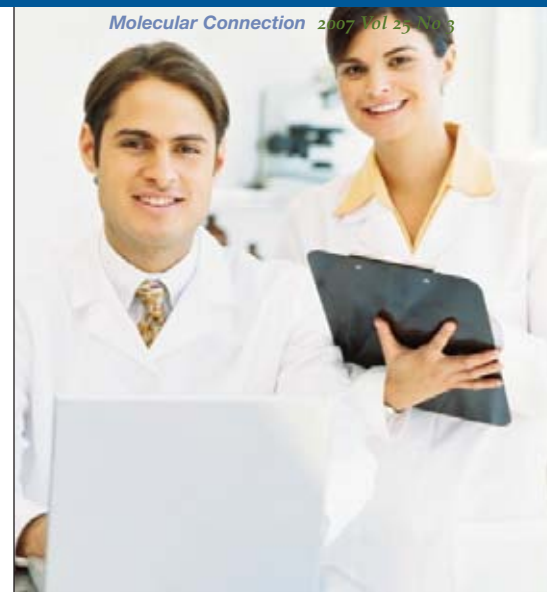
The MDL® ISENTRIS® 3.0 informatics system helps you stay ahead of the competition by accessing commercial and in-house data and searching them simultaneously.

To see the system in action right now, take the MDL ISENTRIS tour. [Link]

How is ISENTRIS different?

More than 75 of the world's leading pharmaceutical, biotechnology and chemical companies have adopted MDL ISENTRIS because the system speeds research, cuts costs and boosts productivity. To appreciate the everyday benefits of ISENTRIS, however, you need look no further than the laboratory workbench.

With ISENTRIS, you no longer have to dig



through huge volumes of irrelevant data. Instead, immediately target your valuable internal data and augment your findings with relevant data from external sources.

You can turn your data upside down to see it in a different context and explore interesting relationships. For example, while browsing a set of reactions you come across an interesting citation and wish to see all the reactions associated with the citation. With ISENTRIS, you can easily view all the reactions to assess the quality and type of information in the citation. This provides a broader perspective on your data and makes for better informed decisions.

You can customize your data displays, so that they are meaningful and useful. Dynamic, personalized data views—based on your researcher profile or the question you are asking—automatically present information in the context of your workflow, helping you extract maximum value from the data at hand (Figure 1).

ISENTRIS lets you work in ways that make sense to you—and it remembers what you've done. A history tree captures the sequence of queries and list manipulations used to select important data, so you can rerun workflows and share them with colleagues. As you move about the information landscape, ISENTRIS automatically and intelligently retains your data manipulations, making time-consuming, repetitive queries a thing of the past.

You can immediately search and browse reaction information in CrossFire Beilstein and MDL® Patent Chemistry Database. These rich sources give you access to over 14 million reactions for synthesis planning. ISENTRIS easily performs hundreds of simultaneous searches and

Out-of-the-box tools and services supporting R&D organizations

MDL ISENTRIS offers comprehensive tools and services supporting scientists, developers and system administrators in R&D organizations.

Integrated solutions for scientists

- Forms-based searching and browsing of chemical and biological data
- Advanced chemical drawing, presentation and query tools
- Cherry picking of data, list manipulation and decision tracking (history tree)
- Advanced visualization with Spotfire DecisionSite
- Powerful and easy reporting through HTML, Adobe PDF and Microsoft Excel/ Word/PowerPoint
- Support for SAR analysis to prioritize and optimize lead compounds
- Unique Reaction Planner for identifying known synthetic pathways

Flexibility for developers

- Faster application development with fully documented APIs
- Standard development technologies (.NET and Java)
- Support for Web and thick client applications
- Web services
- Chemical business rules and calculations

Ease-of-use for system administrators

- Fast data access
- Superior WAN performance
- Quick, easy design of data views

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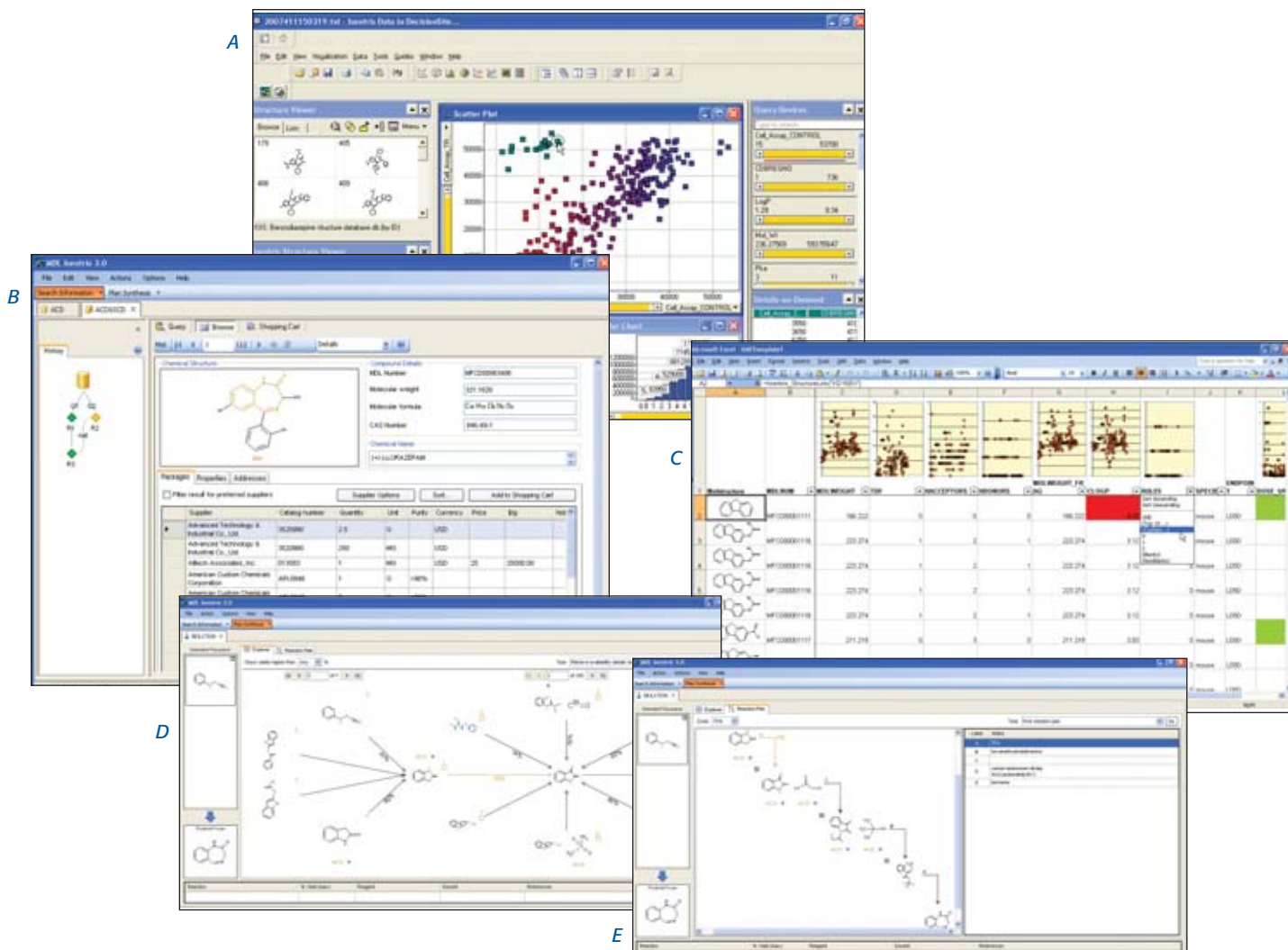


Figure 1: ISENTRIS accelerates research with powerful, integrated, out-of-the-box capabilities. You can utilize Spotfire visualizations (A) and customized views of project data (B). You can easily convert data to SAR tables (C) and rapidly generate synthesis pathways using the Reaction Planner (D and E).

(continued from page 3)

instantly brings back results from multiple sources (e.g., known toxicity, biological activity, property data, synthetic pathways, availability of starting materials, etc.).

You can send your results to Spotfire DecisionSite, use Spotfire's extensive visualization tools to interpret the data and return the data to ISENTRIS for continued searching and decision making.

With a minimal numbers of clicks, create a list of references to acquire, compounds to purchase, spreadsheets to analyze or reports to share with colleagues. With a single click, report your findings in PDF, HTML, Word and PPT formats with no administrator support required.

ISENTRIS is different because it makes it very easy to access the information you need from internal and external sources within the context of your workflow.

Instead of making you search for data, ISENTRIS pushes relevant information to you while also providing access to the DiscoveryGate content platform and to integrated workflow applications like MDL® Draw, MDL® Registration, MDL® Logistics, MDL® Notebook and ISENTRIS for Excel.

In addition, organizations can take advantage of flexible .NET controls for application development and the unsurpassed chemistry sophistication exemplified by the powerful MDL Direct data cartridge, which combines full reaction searching and proven performance on

databases with over five million reactions and at least 20 million structures.

"The vision and strategy underlying ISENTRIS has grown out of many customer meetings," says Dr. Trevor Heritage, Senior VP and Chief Scientific Officer of Elsevier MDL. "By listening closely to customers, we have gained an intimate understanding of the difficulties involved in accessing, processing, managing and analyzing data. The solution that has emerged is MDL ISENTRIS, the most powerful system for knowledge registration, information delivery and laboratory workflow support available today. ISENTRIS not only provides focused content; it also provides the means to manage and fully exploit the content using powerful, integrated tools for data analysis and collaboration...and ISENTRIS is backed by Elsevier MDL, a company with nearly 30 years of experience delivering

*The bottom line is—the days
of many clicks and
multiple, tedious, parallel
searches are over.*

(continued on page 6)

(continued from page 5)

scalable discovery informatics solutions and unrivaled customer care.”

Synthesis planning and decision support

Isestris 3.0 overcomes your challenges with data access, especially in the areas of synthesis planning and decision support, enabling you to get the most out of data and to work more effectively and collaboratively with colleagues.

MDL Isestris provides advanced forms-based information access, flexible tabular displays and a powerful search/browse engine. “One way to think of it is as a kind of work bench where you can organize all the data and functionality you need in the ways that work best for you,” says Dr. Dominic John. “In Isestris, you can easily navigate across data, tasks and applications. The system provides useful summary views, but you can also easily drill into the details to make quick decisions. A unique ‘tell me what I don’t know’ service automatically informs you about relevant information from multiple sources without your having to ask for it. The bottom line is—the days of many clicks and multiple, tedious, parallel searches are over.”

Isestris 3.0 launches your favorite tools for processing, enriching and visualizing data. Integration of applications such as Microsoft Excel spreadsheets, Spotfire DecisionSite and ACD/Labs calculators ensures that you always have the best tools at hand to make informed decisions. (See this issue’s associated article on the integration of ACD/Labs’ powerful

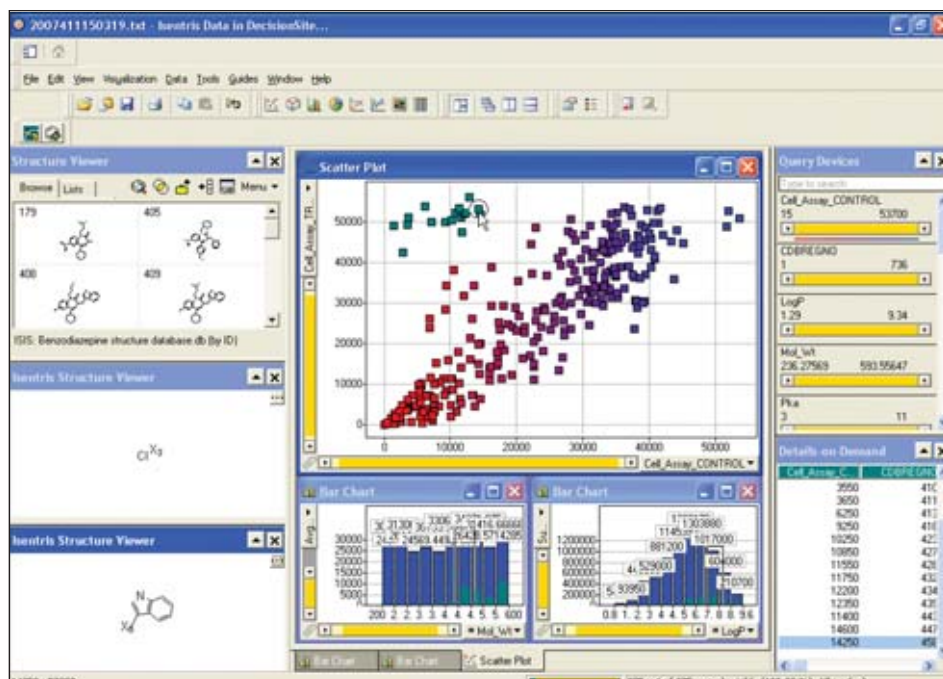


Figure 2: Integration between Isestris and Spotfire DecisionSite offers powerful data visualization capabilities, accelerating the filtering of lead compounds.

scientific calculators with MDL® Draw.)

Isestris forms for searching and browsing scientific data also function as convenient reporting templates, enabling you to quickly and easily disseminate your findings to colleagues. (See this issue’s associated article entitled “Taking the drudgery out of scientific reporting.”)

Faster synthesis planning, reduced costs

Whether you’re searching for starting materials or intermediates, designing

solution-phase or solid-phase combinatorial libraries or planning novel syntheses, Isestris supports your synthesis workflow by providing comprehensive reaction data and a unique Reaction Planner that together improve the speed, efficiency and cost-effectiveness of synthesis planning.

To find suitable reaction transformations to create novel compounds, you can search with a single query over both commercial and in-house reaction data, including more than 17 million reactions in one of the largest compilations of reaction databases in the world (CrossFire Beilstein, MDL Patent Chemistry Database and the MDL® synthetic methodology databases). Inclusion of reaction data from patents helps you to avoid synthesis routes that might infringe on another’s intellectual property. The Isestris Reaction Planner, which finds known synthetic pathways to given, known compounds, is a ‘must-have’ tool for synthetic chemists. With it, you can construct an efficient, cost-effective synthesis plan in just minutes. Starting with a simple structure search, the system automatically finds, collates and links appropriate reaction steps from commercial sources and your own in-house reaction databases.

A direct link to compound availability and pricing enables you to see what starting materials are available and their associated



Isestris pushes relevant information to you while also providing access to the DiscoveryGate content platform and to integrated workflow applications like MDL® Draw, MDL® Registration, MDL® Logistics, MDL® Notebook and Isestris for Excel.

(continued on page 7)

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costs. If a particular starting material is not available, the Reaction Planner back-tracks and looks for reactions that lead to it. In this way, the system quickly builds up a practicable synthetic route—and you avoid numerous time- and resource-consuming manual searches exploring different routes to assemble the data required to make a decision.

Finally, you can easily export a reaction plan and create a report describing the plan along with the compounds to procure and the citations to review. Fast, easy reporting facilitates project team collaboration and decision making.

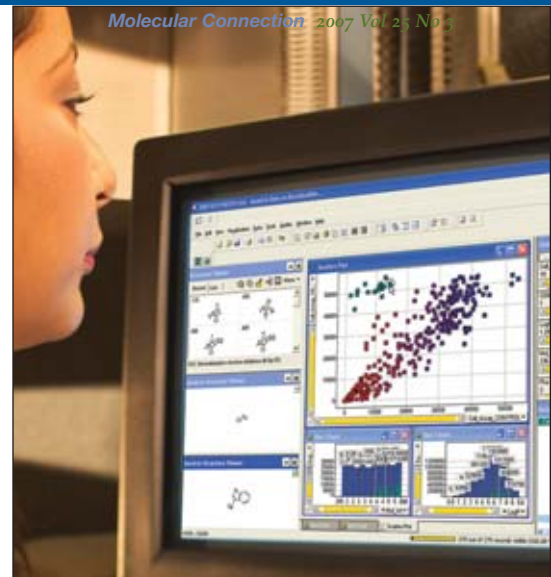
Integrating best-of-breed services and tools

You can think about the ISENTRIS system as a set of services, some provided by Elsevier MDL, others provided by third parties or by customers. This services component of ISENTRIS offers many valuable opportunities for application developers and the research organizations they support. As Elsevier MDL builds its own applications, like MDL Logistics, MDL Registration, MDL Notebook, etc., we are exposing these functionalities as services that can be

leveraged by other MDL applications—and potentially by your own applications.

These services support virtually every activity within an R&D organization. There are services for integrating, pivoting, summarizing and transforming data, for aggregating and de-duplicating results, for collating citations, for managing enumeration, for registering compounds, for sourcing and purchasing reagents. For example, the shopping cart functionality of MDL Logistics seamlessly integrates with third-party purchasing systems like SAP and Ariba, enabling you to

A 'tell me what I don't know' service automatically informs you about information from multiple sources without your having to ask for it.



submit materials to a corporate purchasing system for immediate acquisition.

Fully supported and documented APIs at all levels of the ISENTRIS system—on the client, middle tier and database back-end—facilitate the ready extension and integration of custom and third-party functionality. This makes it much easier for application developers to provide best-of-breed tools for research scientists and system administrators alike.

The ISENTRIS client features a .NET presentation layer that is highly customizable using standard development tools and offers a high degree of flexibility in building scientific applications. As the .NET environment supports both thick and thin client capabilities including installed clients on the desktop and dynamically updateable clients, developers can easily and quickly create recomposable user interfaces that meet the needs of scientists.

With ISENTRIS 3.0, the ISENTRIS system moves to a popular application server on the middle tier (Apache Tomcat) with SSL and Linux support. Tomcat is freely available for download as part of the Mozilla/Apache suite of open source licensed applications, APIs and services. The primary benefit of the Tomcat servlet container is that it enables R&D organizations to quickly deploy Web-rich applications without having to purchase additional components.

Step up with confidence

You may be considering moving to MDL ISENTRIS from MDL ISIS, from another vendor's platform or from an in-house developed system. Whatever the case, you can step up to ISENTRIS with confidence,

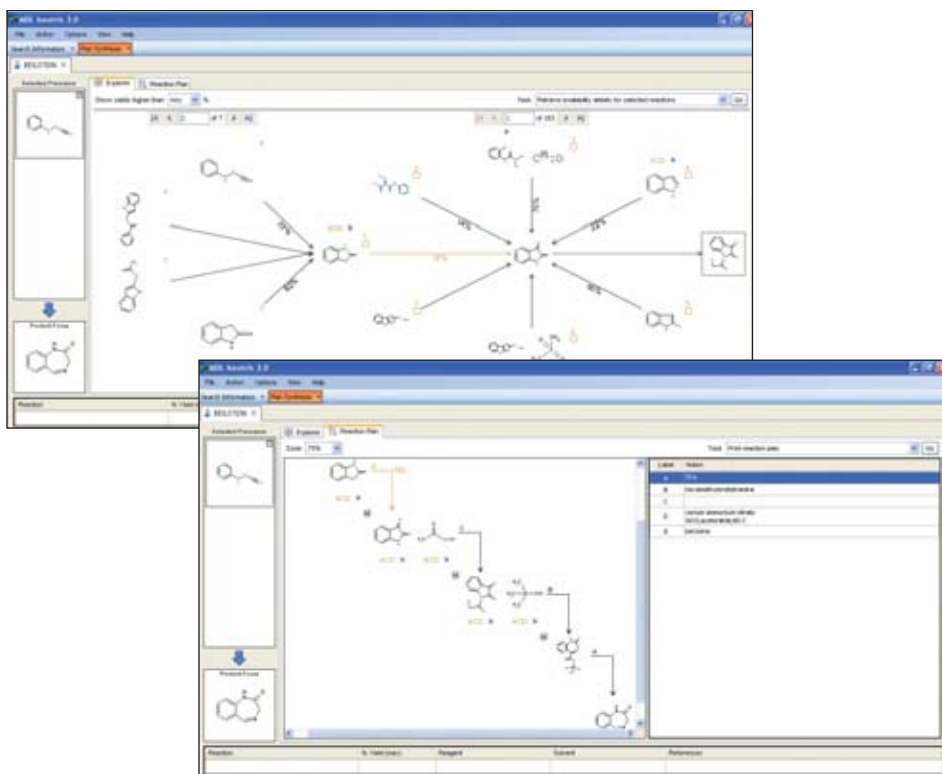
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Figure 3: Dynamically access and share information from multiple data sources in a single integrated view. For example, the Reaction Planner makes it possible to explore the precursor steps from available reactions, as shown above with CrossFire Beilstein data.

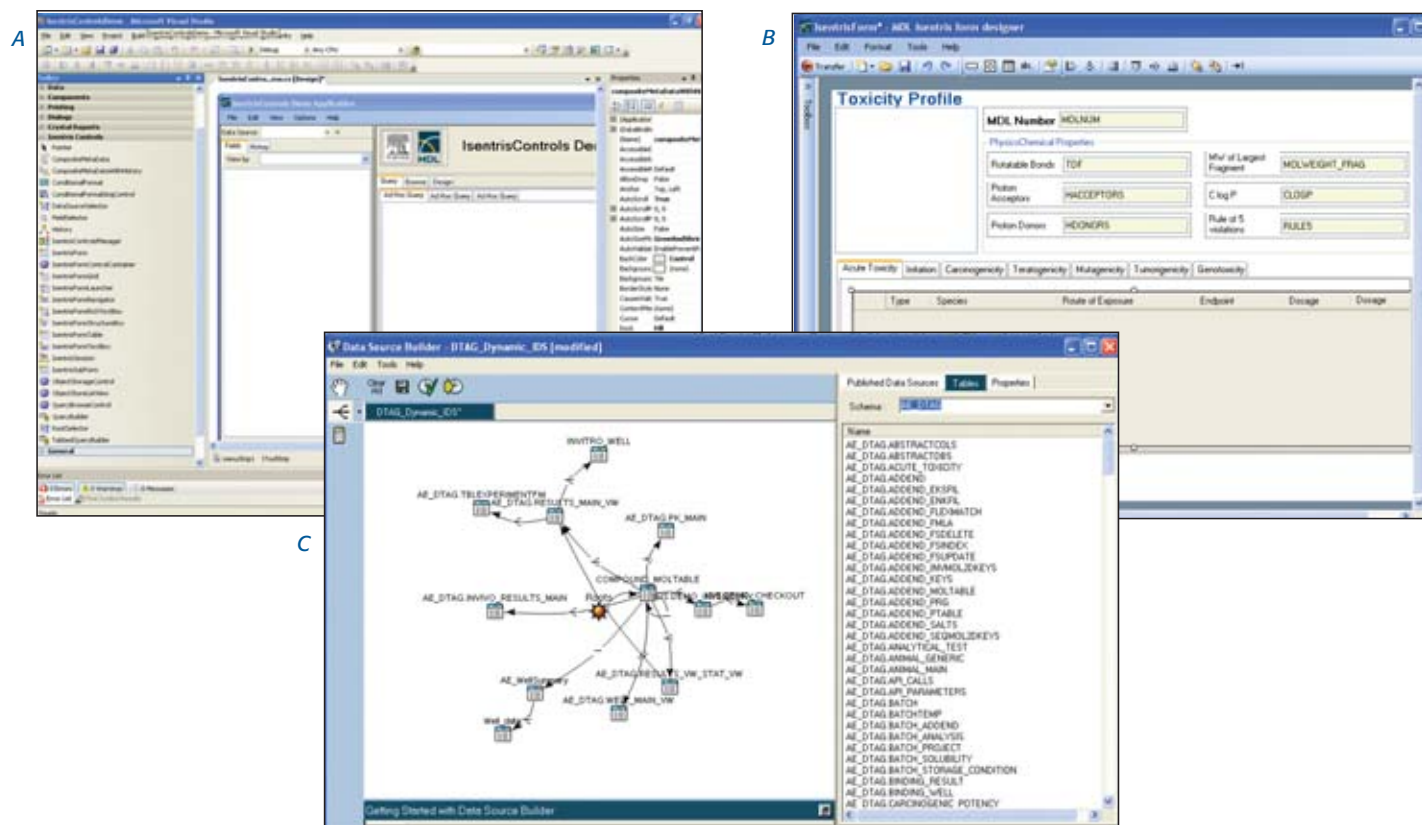


Figure 4: Isetris provides flexible configuration set-up forms (A), the ability to configure data sources (B) and extensive application development capabilities (C).

(continued from page 7)

and without interrupting your operations.

Begin by working with Elsevier MDL to demonstrate the value of Isetris in your organization. Consider the Isetris Starter Kits (or develop a custom transition plan) with the assistance of Elsevier MDL consultants and deploy Isetris in stages using whatever flexible approach is most appropriate for your business needs.

See the article on putting MDL Isetris into practice in the previous issue of *Molecular Connection* (Volume 25, Number 2).

Migrating to Isetris lets you leverage your investment in Elsevier MDL's industry-leading cheminformatics technology and **does not require rebuilding your informatics infrastructure**. As ISIS and Isetris share key design and data representation features, you can even run the two systems concurrently and take a step-by-step approach to migrating your chemical structure repositories and workflow applications to Isetris.

Your existing ISIS files (lists, molfiles, SDFiles, spreadsheets, chemical sketches)

are all forward-compatible with Isetris, and Elsevier MDL Consulting can assist in transitioning your ISIS Hviews to Isetris Integrating Data Sources.

With Isetris 3.0, you have a powerful array of proven, out-of-the-box informatics solutions at your fingertips. You avoid the many difficulties and limitations inherent in hosting duplicate or parallel databases. You can be up and running quickly thanks to straightforward migration protocols, compatible file formats and short learning curves. In the end, your critical informatics infrastructure will be securely installed on a solid foundation provided by Elsevier MDL, the pioneering leader in discovery informatics.

Delivering all your scientific information

The Isetris 3.0 release represents a significant milestone in the evolution and maturation of Isetris capabilities.

- The ability to access both in-house and commercial data through the Isetris client ensures that essential information is included in the decision-making process.

- Self-service, query-by-form functionality in the client speeds research by enabling you to access and manipulate content yourself, without having to request assistance from system developers or administrators.
- The availability service automatically flags data related to specific workflows, pointing you to critical information that you might otherwise overlook.
- Beilstein reaction data in the Reaction Planner accelerates synthesis planning.
- Integration with Spotfire DecisionSite lets you interact with your data in a rich and visually stimulating graphical environment.

MDL Isetris 3.0 makes information and applications more accessible to researchers. The system integrates content and analytical tools in a user-friendly framework that promotes collaboration, accelerates discovery and is easy for customer organizations to leverage and extend.

Discover Isetris for yourself. Contact an Elsevier MDL Account Manager for more information or take the Isetris tour. [link]

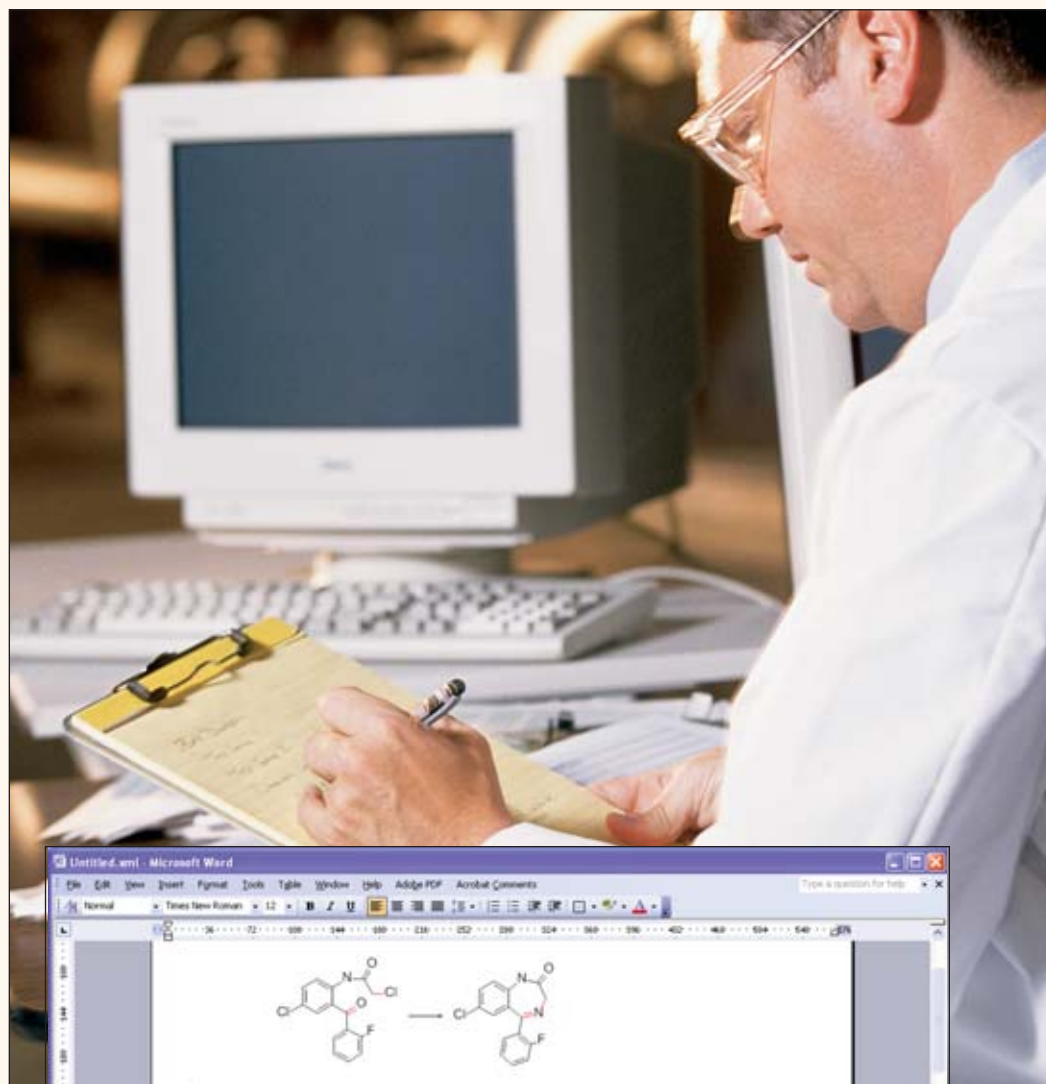
¹ The MDL ISIS Hview (heterogeneous view) presents data in tree-structured views that are useful for searching content. However, the need to maintain hundreds of isolated Hviews in a system built on proprietary coding increases the complexity and cost of data storage. The MDL Isetris Integrating Data Source dynamically represents multiple derived hierarchies providing real-time updated views of data as well as powerful data pivoting and other list management capabilities that offer significant advantages over Hview technology.

Taking the drudgery out of scientific reporting

Reporting scientific information is a necessary but often laborious and time-consuming task requiring repetitive cutting, pasting, formatting and annotating of data. And the effort is cumulative, as similar reports are often required every week or month.

Commercially available reporting tools help scientists create reports, but they suffer from inherent limitations. In most cases, the tools cannot interpret and display scientific data formats such as chemical structures. Scientific data are highly structured, so data experts are needed to use the tools to create report templates. The high overhead in maintaining these templates, and the underlying query and access systems, puts the luxury of personalized reporting templates beyond the reach of most scientists. The MDL® Iseptris® system changes this by transforming and simplifying the way scientists create reports.

(continued on page 10)



MDL Iseptris 2.0 - [ALL REACTIONS]

File View Options Database Help

TDQGVY ALL REACTIONS

Query Browse Selected References

Reactions: 14 / 8

Summary References Scheme Conditions Reagents Solid Support Protecting Group

Variations

MDL Number	% Yield	Year	Reference	Path	Step	Reagents	Conditions
RX00005820	53	2006	RODRIGUEZ, B.; SALL, E. V.; SINGHATHI, B. V.; SINGH, S. C. <i>Org. Macromol. Chem.</i> 2006, 413, 417-421	A	1 OF 3	EtOH	REFLUX, (50 °C)
				B	1 OF 3	HCl-CH ₂ (CH ₂) ₂ -CH ₂ -Cl	
				C	1 OF 3	NHCl	
				D	1 OF 3		
				E	1 OF 3		

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Summary Variations

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				C	1 OF 3	NHCl	
				D	1 OF 3		
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Title: Synthesis of Some New Substituted Triazol[4,3-b]1,2,4-triazole Derivatives as Potent Anticancer Agents. Location: Dep. Postgrad. Stud. Res. Chem., Mangalore Univ., Mangalagangotri, Mangalore 574 199, India

112 At 14.2pt Ln 1 Col 1 English (U.S.)

Figure 1: The background image shows reaction data displayed in an Iseptris form. The foreground image shows the report created in Microsoft Word. Data which may be hidden in the form are automatically formatted for inclusion in the report.

Isestris takes the drudgery out of reporting... there's no longer the excuse that reporting is too much effort..

(continued from page 9)

In Isestris, forms are used to search and browse scientific data and as report templates. You can easily modify the default query and browse forms to display additional database fields simply by dragging, dropping and arranging fields of interest in detailed forms or tables. The resulting reports instantly reflect your changes, offering true ad-hoc WYSIWYG reporting. You can then save these preferences for future use and/or share them with colleagues.

Isestris intelligently formats data represented in forms for reporting. Reports created from forms, which contain tables with rows or fields that must be scrolled to be displayed, are automatically reformatted to display all of the data in the report format selected (Figure 1). You can save reports created in Isestris in a variety of formats including Microsoft® Word/PowerPoint®/ Excel®, PDF and HTML, or you can send reports directly to the printer.

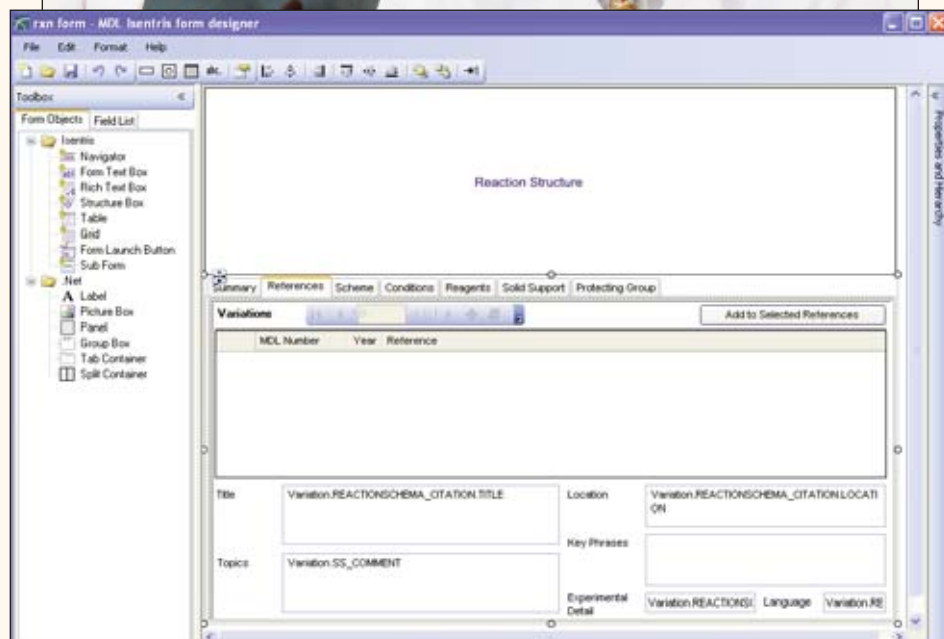


Figure 2: The reaction form displayed in Figure 1 is easily modified and saved for future use using the form designer functionality of Isestris.

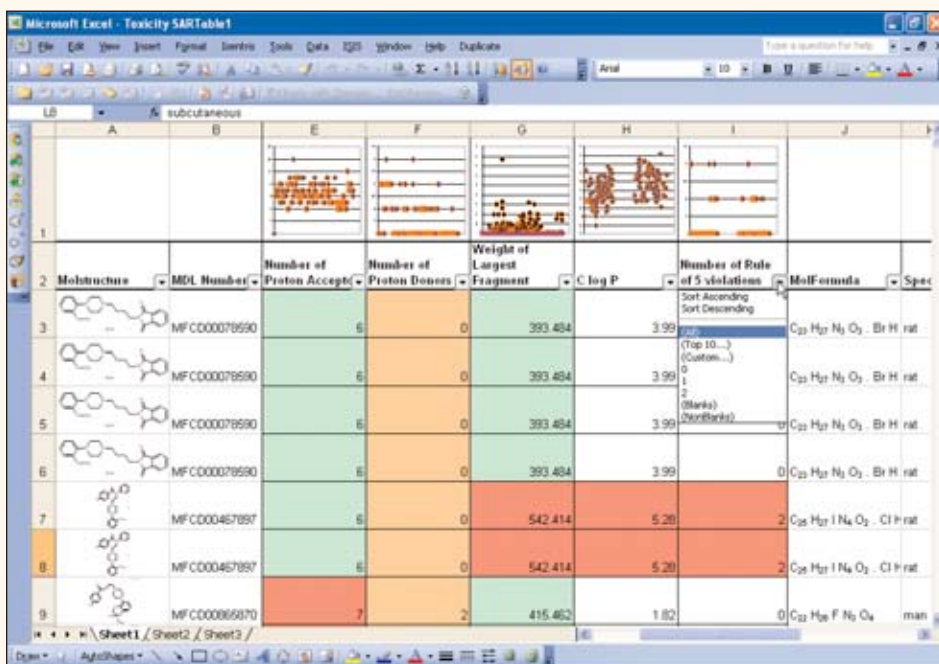


Figure 3: This report illustrates what you can achieve in seconds when reporting data from Isestris using an Excel template and Isestris for Excel functionality. This rich SAR table instantly provides automatic filtering and dynamic graphs showing the distribution of physicochemical and biological properties (Lipinski rule of five) with conditional formatting applied automatically.

“Scientists may want to create their own forms from scratch, or they may need to modify an existing Isestris form. The form designer functionality in Isestris makes both of these tasks easy,” says Dr. Dominic John, Senior Product Manager at Elsevier MDL.

In addition to providing highly structured document reporting, Isestris also supports reporting to Microsoft Excel spreadsheets. Isestris for Excel enables you to auto-format data into reports using Excel templates that offer exactly the view, calculations and visualizations you need every time, in seconds (Figure 3).

“Isestris takes the drudgery out of reporting. Researchers can quickly and easily create the reports they need and share them with colleagues in a timely manner. With MDL Isestris, there’s no longer the excuse that reporting is too much effort,” concludes John.

For more information about the powerful Isestris system, contact your Elsevier MDL account manager or visit www.mdl.com. Register for a live Web seminar. www.mdl.com/webinar ■



Using DiscoveryGate[®] in medicinal chemistry and cancer research

by Dr. Guido Kurz, CNIO Centro Nacional de Investigaciones Oncologicas (Spanish National Cancer Research Center), Madrid, Spain

Researchers can eliminate undesirable leads early in the lead generation process by quickly accessing information on pharmacological effects, side effects and drug-drug interactions for compounds or compound classes of interest, as well as their corresponding metabolites.

The DiscoveryGate online platform supports this timely drug assessment by providing researchers with quick access to a wealth of information, all from within the same system, from data sources which are otherwise dispersed.

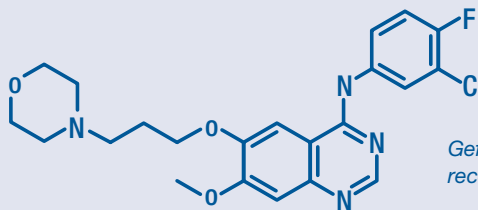
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*The CNIO
has adopted
DiscoveryGate
because it offers
both chemists and
biologists access
to a wide range
of information
at the interface
between the
two disciplines.*

Case Study

Let us assume that we are interested in checking information known about the reference compound gefitinib, specifically the existence of clinical and pre-clinical data, synthetic protocols and commercial vendors.



Gefitinib (Iressa®) is a known EGFR inhibitor recently approved in lung cancer therapy.

Let us further assume that we also work on Epidermal Growth Factor Receptor (EGFR) inhibitors and want to check their adverse clinical effects. Like Iressa, our compound of interest contains a solubilizing morpholine and we want information on its mechanism of action. We need to either buy or synthesize Iressa to use it as a reference standard in our preclinical tumor models.

1. Search the PharmaPendium™ database for adverse effects and drug safety information (Figure 1). PharmaPendium provides a wealth of clinical and pre-clinical information on Iressa including:

- FDA Approval Package:
- Medical/clinical review with description of clinical trials, key efficacy findings, metabolite profile in humans (with structures), full PK parameters, toxicity findings (>200 pages)
- Pharmacological review (preclinical activity, PK and toxicity in different species (>120 pages)
- Chemistry
- Label
- *Mosby's Drug Consult™* (Drug Monographs)
 - FDA Approval Package with information spanning physico-chemical properties, formulation data, drug-drug interactions, preclinical and clinical data.
 - *Meyler's Side Effects of Drugs*

Drug-related adverse event ^a	Number (%) of Patients	
	250 mg/day (264/352)	500 mg/day (264/352)
Diarrhea	49 (18)	79 (30)
Rash	44 (16)	49 (19)
Anorexia	21 (8)	37 (14)
Dry skin	13 (5)	30 (12)
Nausea	13 (5)	29 (11)
Weighting	12 (5)	18 (7)
Pruritus	8 (3)	18 (7)
Ascites	7 (3)	13 (5)
Asthenia	6 (2)	13 (5)

Figure 1: Adverse effects of Iressa from the Label in the FDA Approval Package (search parameter highlighted in results)

(continued on page 13)

(continued from page 12)



Centro Nacional de Investigaciones Oncológicas (CNIO)

Located in Madrid, the Centro Nacional de Investigaciones Oncológicas (CNIO) was founded in 1998 as Spain's National Cancer Research Center. With approximately 400 scientists engaged in basic and applied research, such as molecular diagnostics and drug discovery, the mission of the CNIO is to:

- Carry out research driving towards the discovery of new and effective diagnostics for cancer patients
- Bring scientific breakthrough to the clinic to ensure advancement is translated into a reality for patients within the National Health System
- Transfer CNIO-developed technology to innovative companies
- Create a new and efficient management system, to break away from the traditional Spanish model

The CNIO is one of the few European Cancer Centers to allocate resources to both basic and applied research in an integrated fashion, thus supporting the interaction of basic research programs with those of molecular diagnostics and drug discovery.

For more information: www.cnio.es

Conduct a **Drug search** for Iressa to display Adverse Effects/Toxicity results (Figures 2 and 3).

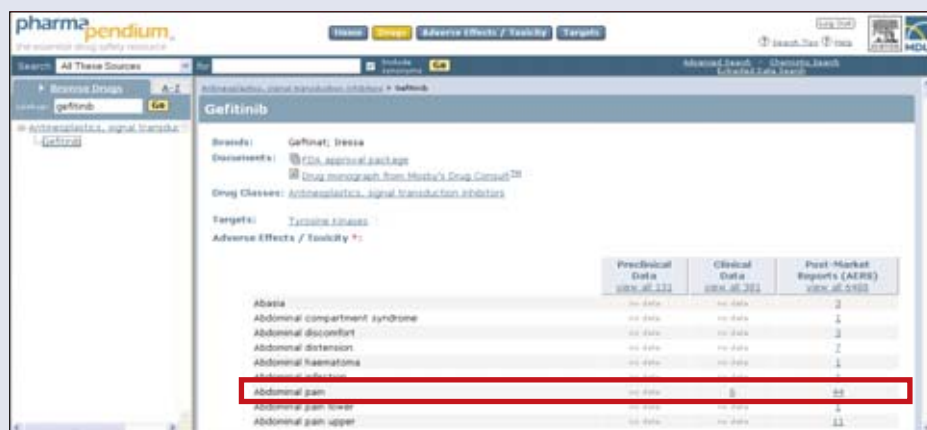


Figure 2: Clicking on the hyperlink under Clinical Data for Abdominal pain displays the clinical data for Iressa

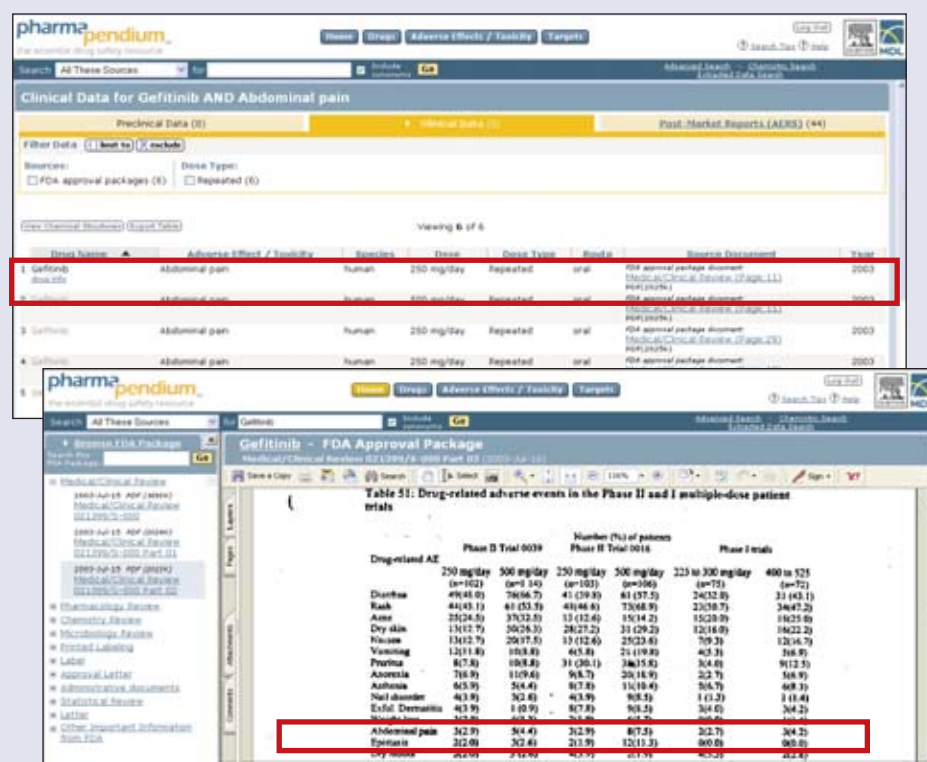


Figure 3: Adverse effects of Iressa in primary FDA report provided by PharmaPendium.

2. Search for Iressa in xPharm®, a database of pharmacological information that maps the interactions between agents, principles, targets and disorders for drugs (Figure 4).



Figure 4: xPharm search results for Iressa showing related records (color coded): two orange codes for Agents (the Iressa concise drug report plus a monograph on tyrosine kinase inhibitors) and one purple color code indicating a Disorder.

(continued on page 14)

(continued from page 13)

DiscoveryGate provides database content that spans the drug discovery spectrum, from target validation to clinical data.

Click on the **Gefitinib** record to review the concise drug report. In xPharm, all references are color coded and records are cross referenced (Figure 5).

Pharmacokinetics

When ¹⁴C-labeled gefitinib was administered orally to albino and pigmented rats, radioactivity was widely and rapidly distributed, with the highest levels being found in [liver](#), [spleen](#), [lung](#) and gastrointestinal tract, whereas low levels were found in brain. Levels of radioactivity persisted in melanin-containing tissues (pigmented eye and skin). When administered either orally or i.v., excretion of radioactivity of ¹⁴C-labeled gefitinib by either rat, dog or human occurred predominantly via the bile into feces, with <7% of the dose being eliminated in urine [\(Kobayashi et al 2004\)](#).

Rat

	Value	Units	Prep. and Route of Adm.	Reference	Comments
Absorption					
Availability					
Distribution					
Volume of Distribution	9-10	L/kg	i.v.	(Kobayashi et al 2004)	
Plasma Protein Binding	87.5 ± 0.5	%	i.v.	(Kobayashi et al 2004)	Male (binding independent of dose)
Plasma Protein Binding	8.2 ± 1.4	%	i.v.	(Kobayashi et al 2004)	Female (binding independent of dose)
Metabolism					
Plasma Half-Life	2	hrs	i.v.	(Kobayashi et al 2004)	
Bio half-life	72	hrs	orally	(Kobayashi et al 2004)	85% of the administered radioactivity is recovered.
Clearance	70	%	i.v.	(Kobayashi et al 2004)	within 24 hours.
Routes of Elimination	Feces.				

Putency

	Value	Units	Organ/Tissue	Prep. and Route of Adm.	Cell Line/Type	Effects	Exp. End Point	Reference	Comments
Female athymic mice (BALB/c, nu/nu)									
DOSE 150	mg/kg			orally				(Kobayashi et al 2004)	Mean tumor volume in the gefitinib-treated group was significantly smaller than that in the vehicle-treated group by Day 31.
EC50 10±2	µmol/L		Malignant rhabdoid		HBT cell line	Growth inhibition		(Kobayashi et al 2004)	Gefitinib at 150 mg/kg had a cytostatic effect on established HBT xenografts.

Other Information

Web Sites:

FDA information on gefitinib: <http://www.fda.gov/cder/foia/ba/2003/0217996.pdf>

Gefitinib information from MedlinePlus: <http://www.nlm.nih.gov/medlineplus/medlineplus/article.jsp?id=i39543>

Further Reading:

Isobe, Herbert, Onn, Current management of advanced non-small cell lung cancer: targeted therapy, *Semin. Oncol.*, 32(3) (2005) 315-328.

Reck, Gatzemeier, Gefitinib ("Iressa"): a new therapy for advanced non-small-cell lung cancer, *Respir. Med.*, 99(3) (2005) 299-307.

Bibliographic References

Journal Citations:

Fao, W., Miller, V., Zakowski, M., Doherty, J., Politi, K., Sarkaria, I., Singh, B., Heelan, R., Rusch, V., Fulton, L., Mards, E., Kupfer, D., Wilson, R., Kris, M., and Varmus, H., EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1100470/>

McKillop, D., Hutchison, M., Partridge, E.A., Bushby, N., Cooper, C.M., Clarkson-Jones, J.A., Herron, W., and Swaisland, H.C., Metabolic disposition of gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in rat, dog and man. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1100470/>

Taguchi, F., Koh, Y., Koizumi, F., Tamura, T., Saji, N., and Nishio, K., Anticancer effects of ZD6474, a VEGF receptor tyrosine kinase inhibitor, in gefitinib ("Iressa")-sensitive and resistant xenograft models. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1100470/>

Kuwahara, Y., Hoshi, H., Ozono, S., Kita, M., Ishiura, T., Kuroda, H., and Sugimoto, T., Antitumor activity of gefitinib in malignant rhabdoid tumor cells in vitro and in vivo. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1100470/>

Citing this Article

Cite this article using http://www.xpharm.com/citation?article_id=132036

Figure 5: Pharmacology data (PK and PD) on Iressa in xPharm. Scrolling to the end of the record displays useful links to the primary literature, reviews and related Websites.

Click on the **Tyrosine Kinase Inhibitors** record to review target class and competitor compound information (Figure 6)

DiscoveryGate | xPharm®

Home | Contacts | Search | Alerts | Targets | Disorders | Principles

Tyrosine Kinase Inhibitors

Click [here](#) to cite this article.

Introduction

The tyrosine kinase inhibitors are a family of small molecules or peptides with the ability to inhibit either cytosolic or receptor tyrosine kinases. Inhibition by this class of agents is through direct competition for ATP binding to the [kinase domain](#) ([imatinib](#), [dasatinib](#), [sunitinib](#), [vandetanib](#), [sorafenib](#), [nintedanib](#), [amivantamab](#), [osimertinib](#), [olaparib](#), [pazopanib](#), [vandetanib](#), [sunitinib](#), [regorafenib](#), [nintedanib](#), [amivantamab](#)), allosteric inhibition of the tyrosine kinase (avastin), inhibition of ligand binding to receptor tyrosine kinases (e.g., [cetuximab](#)), inhibition of tyrosine kinase interaction with other proteins (e.g., UCE1A, [lapatinib](#), [cyclophosphamide](#)) or destabilization of the tyrosine kinase (e.g., [vandetanib](#) and [sunitinib](#)). The majority of tyrosine kinase inhibitors are currently not in clinical use. The notable exceptions ([imatinib](#), [dasatinib](#), [sunitinib](#), [vandetanib](#), [regorafenib](#), [nintedanib](#)) show promise as "targeted" therapeutics in the treatment of cancers in which specific tyrosine kinases have been implicated.

Human Pharmacokinetics

[imatinib](#), [sunitinib](#), and [dasatinib](#) are available orally. [cetuximab](#) is available as an intravenous injection.

Targets-Pharmacodynamics

[imatinib](#) predominantly targets [c-kit tyrosine kinase](#) and its oncogenic fusion form Bcr-Abl. Imatinib also targets the tyrosine kinase c-kit and the platelet derived growth factor (PDGF) receptor tyrosine kinase. [sunitinib](#), [dasatinib](#), and [vandetanib](#) each predominantly target the epidermal growth factor (EGF) receptor tyrosine kinase. Limitations in the effectiveness of gefitinib have been demonstrated to result from polymorphisms in the EGF receptor sequence [\(Zhai et al 2005\)](#).

Target Name(s):

- Abl tyrosine kinase
- Bcr-Abl tyrosine kinase
- c-kit tyrosine kinase
- PDGF receptor tyrosine kinase
- EGF receptor tyrosine kinase

Therapeutics

Figure 6: Compare Iressa with its closest competitor Tarceva

(continued on page 15)



(continued from page 14)

3. Search in MDL® Drug Data Report (produced by Elsevier MDL and Prous Science) for drug data information on Iressa (Figure 7).

DiscoveryGate® | MDL® Database Browser

queries results reports

MDL® Drug Data Report

MDL® Drug Data Report

Available Data

Substance (9) Mols (1)

Biologs (1) Identifications (1)

Literature and Patents (1)

Substance (9)

External Registration Number: 23388

Prous Entry Number: 23388

Evident Number:

CAS Registry Number:

Derivative:

Chemical Name:

• 4-(3-CHLORO-4-FLUOROPHENYLAMINO)-7-METHOXY-6-(3-MORPHOLINYLPROPYL)QUINAZOLINE

Generic Name: GEFITINIB + PRODRUG

Formula: C22H24ClF4N4O3

Molecular Weight: 488.5076

Development Phase: Launched

Year: 2002

Figure 7: Pharmacological activity information displayed for the Iressa record in the MDL® Drug Data Report database. 'Also found in' links at the top of each DiscoveryGate record offer immediate connections to relevant information on the same compound in other data sources.

Click on the **Metabolite** link to display the Iressa record in the MDL® Metabolite Database and return to the FDA Approval Package in the PharmaPendium database (Figure 8).

DiscoveryGate® | MDL® Database Browser

queries results reports

MDL® Metabolite Database

Available Data

View results as Transformation:

Transformation Results — Transformation

MEX number: PINT00076071

Path: MT011370-A, MT011370-B, MT011370-C, MT011370-D, MT011370-E

Step: 1 of 2, 1 of 2, 1 of 2

Scheme: MT011370

Chemical Name and Synonyms:

- Gefitinib
- 4-(3-Chloro-4-Fluorophenylamino)-7-methoxy-6-(3-morpholinylpropyl)quinazolin-2(1H)-one
- IRISA
- ZD1839

pharma pendium

Gefitinib - FDA Approval Package

Fig. 4 Structures of ZD1839 and its metabolites [Applicant's Figure]

ZD1839

M2189

M2188

Figure 8: The results in MDL Metabolite show oxidation of the morpholine moiety in 9 of 13 cases with data on species and enzymes including references. In the PharmaPendium data, five metabolites are identified in human plasma (CYP3A4). O-desmethyl gefitinib has the same exposure and EGFR-TK activity, but only 1/14 of its potency in a cell-based assay. With an elimination half-life of 48 hours, this compound is stable and metabolism of morpholine is not an issue.

(continued on page 16)

(continued from page 15)

In summary, within a few minutes we reviewed clinical, metabolite, toxicological, patent and adverse side effects data on Iressa. Additionally, we accessed the primary literature and quickly determined whether it is safe and cost-effective to buy or synthesize the reference compound.

The DiscoveryGate platform offers compiled information from various areas of the drug development process and also provides access to the primary literature and reports. The CNIO has adopted DiscoveryGate because it offers both chemists and biologists access to a wide range of information at the interface between the two disciplines. The platform also provides database content that spans the drug discovery spectrum, from target validation to clinical data. ■

4. To find purchasing information for the reference compound, click on the **ACD** link to retrieve related records in the MDL® Available Chemicals Directory database, the world's largest collection of chemical supplier catalogs (Figure 9).

DiscoveryGate® | MDL® Database Browser

Record # 1 Total Records: 1

MDL® Available Chemicals Directory

Available Data

Click on a link to add the information to this page

Set current view as default

Substances (75) Suppliers (71)

Clones (171) Notes (71)

Substance [View](#)

ACD Registry Number	184475
Availability	Large and small quantities
MDL Number	MPC004327632
CAS Registry Number	184475-25-2
Chemical Name and Synonyms	

Figure 9: MDL ACD displays pricing, packaging and supplier contact details for the Iressa compound.

5. We can also synthesize Iressa using information provided in multiple data sources containing synthesis information, including the Beilstein Database and ChemInform Reaction Library. Click on **Patent Chemistry** to review synthesis information for patented molecules including retro-synthetic schemes (Figure 10).

DiscoveryGate® | MDL® Database Browser

Patent Chemistry Database

Synthetic Scheme for Substance 3822517

Reaction Scheme

Substance 182712

Substance 3822517

Reaction 5321361

Reaction 1844764

Reaction 516053

Reaction 5321361

Substance 148889

Substance 3822516

Reaction 1850034

Reaction 9823731

Links to Reaction 5321361

Links to Reaction 5321361

Figure 10: The MDL® Patent Chemistry Database includes information on three synthetic routes from the patent literature, including two patents from AstraZeneca and one from Natco Pharma.

The records in the MDL Patent Chemistry Database contain detailed synthetic protocol information for the synthesis of Iressa (Figure 11).

DiscoveryGate® | MDL® Database Browser

Patent Chemistry Reaction 5321362

Reaction Identification

Reaction ID	5321362
Reactant	3822517
Reactant	4-chloro-7-methoxy-1-methyl-1H-imidazo[5,1-b]pyridine
Reactant	118712
Reactant	para-fluoro-methyl
Product	1822138
Product	4-(2-chloro-6-fluorophenylamino)-2-(2-methoxy-4-(piperidin-4-yl)propyl)-7-methoxy-1-methyl-1H-imidazo[5,1-b]pyridine
Reaction Specification	5321362
Reaction Entry Date	2004/03/26
Reaction Update Date	2004/03/26

Reaction Details

Reaction Details record 1 of 1

Citation

- 252613

Type of Material

- Preparation

Example Name

2

Example Title

Example 2: Preparation of 4-(2-chloro-6-fluorophenylamino)-2-(2-methoxy-4-(piperidin-4-yl)propyl)-7-methoxy-1-methyl-1H-imidazo[5,1-b]pyridine

Example Text

The resultant dried slurry was cooled to about 0 deg C and reagent (2) (10g) was added within the temperature of the reaction mixture was maintained between 0 deg AND 5 deg C. The reaction mass was warmed to about 20 deg C and held at that temperature for about 1 hour. A solution of 3-chloro-4-fluorobenzonitrile (180 mg) in reagent (2) (200 mg) was added and the resultant reaction mixture was stirred and warmed to about 24 deg C and held at that temperature for about 1 hour. The mixture was stirred and cooled to about 20 deg C and reagent (3) (20 mg) and water (1.000 mg) were added in turn. A mixture of aqueous sodium carbonate (147 mg) and water (40 mg) was added portionwise to the stirred reaction mixture. The resultant mixture was warmed to about 24 deg C and the two liquid phases were allowed to separate. The lower aqueous layer was run off. The remaining organic phase was initially cooled to about 30 deg C, warmed to about 20 deg C and finally cooled to about 20 deg C at a rate of about 0.5 deg C per hour. The resultant solid was collected by filtration, washed in turn with isopropanol and ether and dried with warm nitrogen gas (20 deg C). There was thus obtained 4-(2-chloro-6-fluorophenylamino)-2-(2-methoxy-4-(piperidin-4-yl)propyl)-7-methoxy-1-methyl-1H-imidazo[5,1-b]pyridine (224 mg, m.p. about 194 deg C) (218 mg C).

Page 11-12

Product

1822138

Product

4-(2-chloro-6-fluorophenylamino)-2-(2-methoxy-4-(piperidin-4-yl)propyl)-7-methoxy-1-methyl-1H-imidazo[5,1-b]pyridine

Stage Number

1

Reactant

3822517

Reactant

4-chloro-7-methoxy-1-methyl-1H-imidazo[5,1-b]pyridine

Substent FDB

118712

Substent

Sulfone

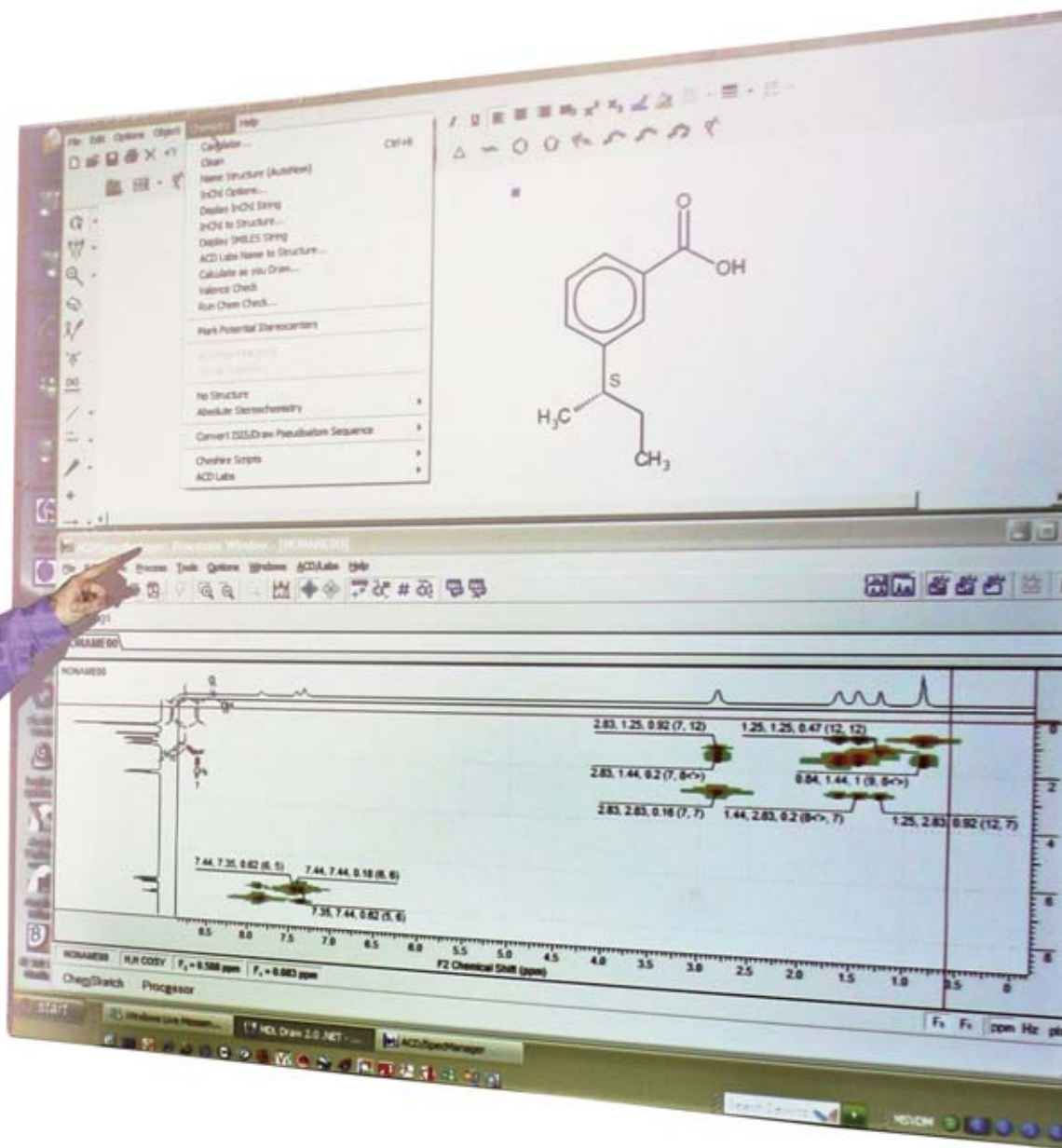
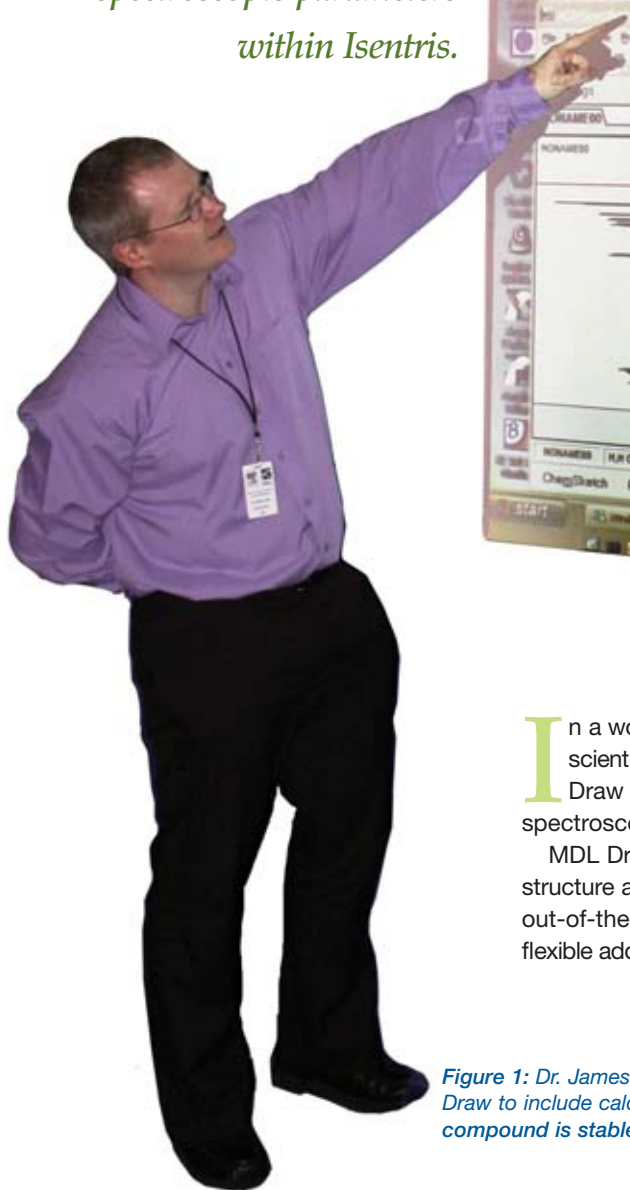
Quantity in Substent Mixture

17801

Figure 11: Detailed synthetic protocol information for the synthesis of Iressa

MDL[®] Draw calculator add-ins improve workflow efficiency

Elsevier MDL and ACD/Labs are working together to build a series of MDL Draw add-ins that will enable scientists to calculate molecular properties and assess spectroscopic parameters within Isentris.



In a world where research groups can routinely synthesize thousands of compounds a day, scientists shouldn't have to waste time tracking down a ¹³C NMR shift or a pKa value. MDL[®] Draw calculator add-ins enable scientists to determine molecular properties and assess spectroscopic parameters without having to leave the MDL[®] Isentris[®] environment.

MDL Draw's innovative, easy-to-use drawing capabilities, including quick and accurate structure and query drawing, improve scientists' efficiency. "MDL Draw does not try to provide out-of-the-box support for every scientific workflow a customer might have. Instead, its flexible add-in capability enables customers to build in those custom and third-party workflows

(continued on page 18)

Figure 1: Dr. James Jack demonstrating the extensions he and fellow consultants have developed enabling MDL Draw to include calculators from ACD/Labs, an MDL[®] Isentris[®] Alliance partnership half-life of 48 hours, this compound is stable and metabolism of morpholine is not an issue.

(continued from page 17)

that are unique to an organization,” says Dr. James Jack, Senior Consultant at Elsevier MDL. “Once added, they become part of your personalized set of tools and menus in MDL Draw. For example, you can add scientific calculators, predictors, enumerators, chemistry business rule checks and vocabulary for your stereochemistry rules.”

At the 2007 European Users' Group Meeting in Strasbourg, France, Dr. Jack demonstrated proof-of-concept prototype extensions for adding calculator functionality to MDL Draw.

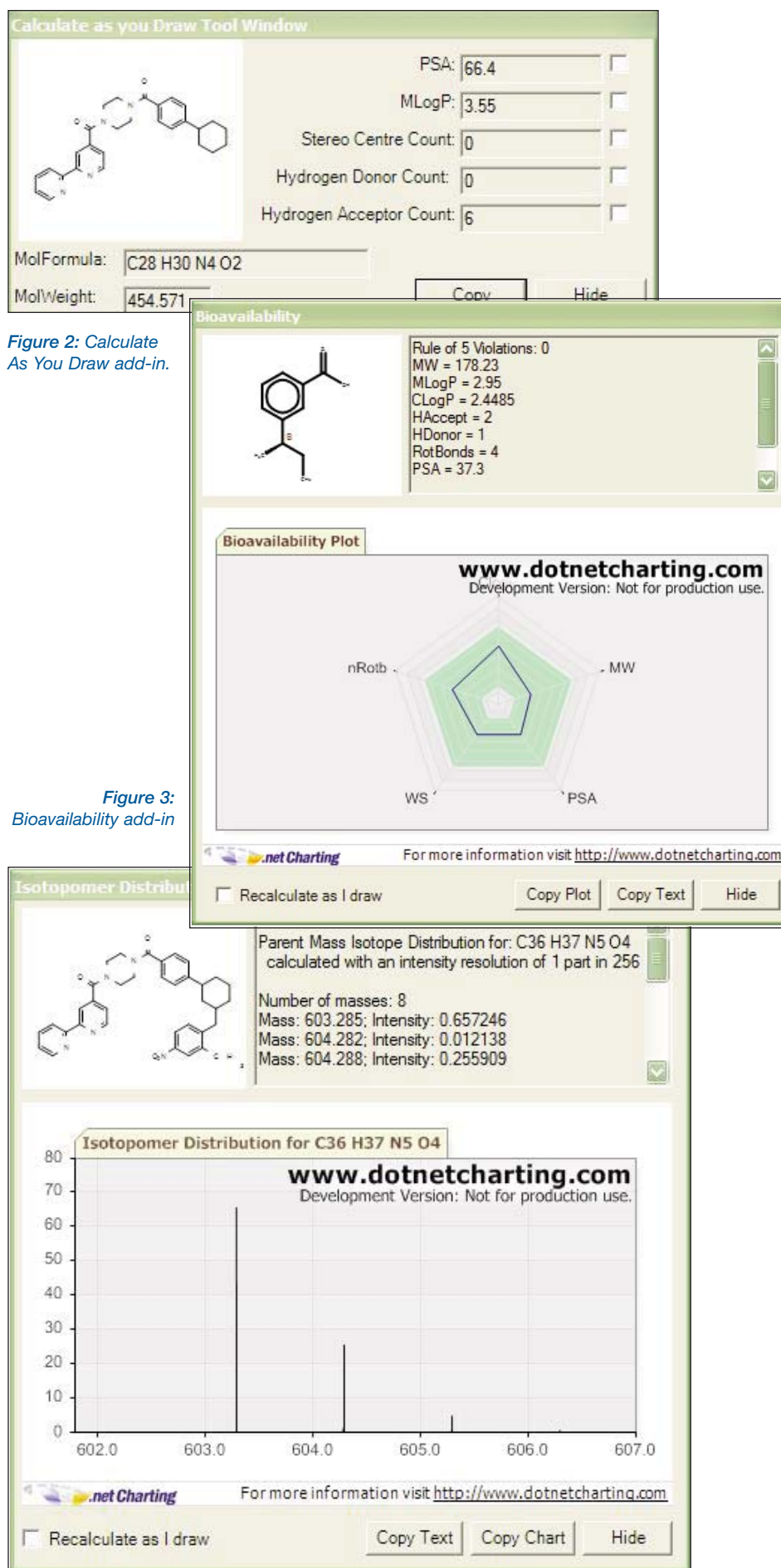
“MDL Draw is a very powerful chemical drawing application with a well-defined .NET API which allows Draw to be extended in ways that could be only dreamt of in MDL® ISIS,” says Jack. “Moreover these extensions can be produced quickly and easily using industry-standard programming languages.”

Access powerful calculators from within MDL Draw

The prototypes developed cover simple structure-to-InChI, InChI-to-structure and SMILES-to-structure conversions, as well as, calculated values using MDL® Cheshire and calculators from Advanced Chemistry Development, Inc (ACD/Labs). Examples of other developments include: the Calculate As You Draw add-in, which uses MDL Cheshire scripts to calculate numerous structural properties on-the-fly (Figure 2); the Bioavailability add-in, which calculates a series of properties for the whole canvas or a selection using MDL Cheshire and plots them using a third-party .NET graphing control (Figure 3); and the Isotopomer Distribution add-in, which predicts the molecular ion peaks for the whole canvas or a selection (Figure 4).

Isestris Alliance partnership spurs innovation

Recognizing the need to integrate physical property data into modern discovery information management systems, ACD/Labs partnered with Elsevier MDL in 1996 and is now a member of the MDL® Isestris® Alliance partner program. Elsevier MDL and ACD/Labs are working together to build a series of MDL Draw add-ins that will enable scientists to calculate molecular properties and assess spectroscopic parameters within Isestris. Today, without leaving the Isestris environment, scientists can use software from ACD/Labs to perform



(continued on page 19)

Figure 4: Isotopomer Distribution add-in

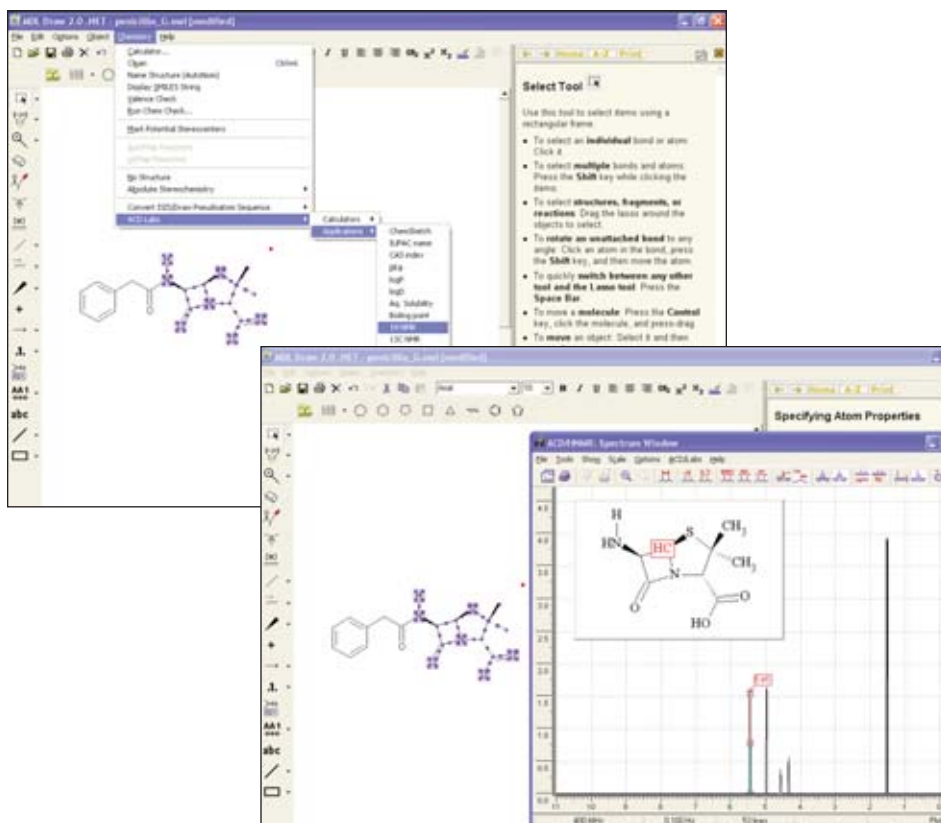


Figure 5: ACD/Labs HNMR and CNMR programs use an internal database of experimentally derived “rules” to predict spectra for new compounds.

“Success depends upon how quickly you develop a lead compound—waiting to make a decision until something is experimentally known may cause you to lose valuable development time.”

Val Kulkov
CEO
Advanced Chemistry Development

(continued from page 18)

calculations and store relevant calculated physical property data automatically (including; ^{13}C NMR shifts, ^1H NMR shifts and coupling constants, pKa, LogP, solubilities, bioconcentration factors, adsorption coefficients, boiling points and systematic chemical names).

“While tools from ACD/Labs are powerful in isolation, the company realized several years ago that its software could be made even more valuable to researchers by integrating it with Elsevier MDL, the standard for communicating chemical information,” explained Val Kulkov, CEO of Advanced Chemistry Development. “Success depends upon how quickly you develop a lead compound—waiting to make a decision until something is experimentally known may cause you to lose valuable development time.”

“ACD/Labs software has some of the most accurate prediction algorithms available. It has made a lot of sense to combine our strengths. Through the Isentris Alliance, Elsevier MDL and ACD/Labs are working towards providing integrated solutions that offer researchers physical property data calculations out-of-the-box with Isentris”, concluded Kulkov.

If you are interested in learning more about these proof-of-concept prototypes, visit www.mdl.com to sign up for a free Webinar—“Add scientific calculators to MDL® Draw.”

Sign-up for a 30-day trial of MDL Draw (no fee, no obligation to buy, subject to acceptance of the applicable MDL Draw Evaluation license).

www.mdl.com/prom

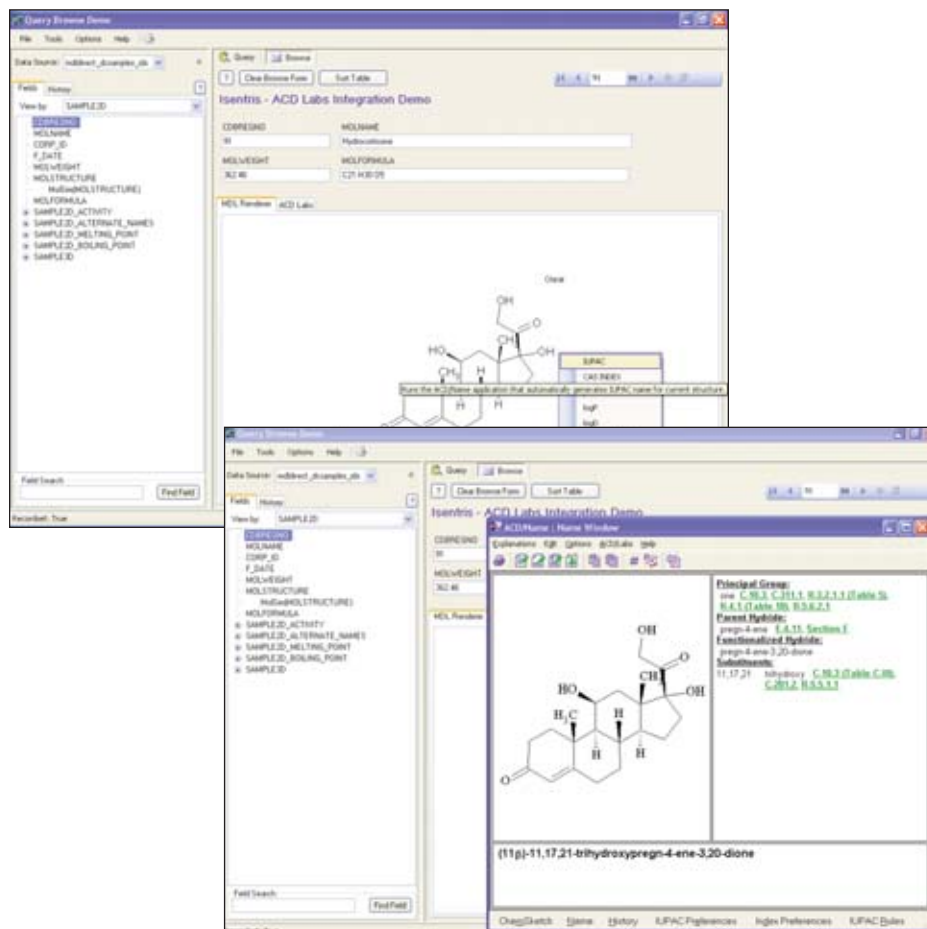


Figure 6: ACD/Labs offers ACD/Name, a popular software algorithm that generates accurate systematic names for almost any organic structure in accordance with IUPAC rules.

Elsevier MDL and MathSpec

*Partnership enables faster identification
of chemical structures from mass
spectral data using MDL[®] ACD*

Modern liquid chromatography/mass spectrometry (LCMS) instruments make it relatively easy to obtain accurate-mass fragmentation data. When this development is combined with the ready availability of large molecular structure databases and today's faster computers, the stage is set for transforming the "art" of interpreting mass spectral data into a systematic computational process.

Elsevier MDL is partnering with MathSpec, Inc. to enable researchers using MathSpec's Rational Numbers™ FragSearch program to elucidate chemical structures from mass spectral data using MDL[®] Available Chemicals Directory (MDL ACD), the industry-standard chemical sourcing database. This will improve R&D productivity by enabling scientists to quickly identify small organic compounds from accurate-mass fragmentation data, reducing the need for traditional mass spectral libraries.

"This partnership supports research workflows by accelerating the identification of structures from LCMS data," says Dr. Trevor Heritage, Senior VP and Chief Scientific Officer of Elsevier MDL. "The use of MDL ACD with MathSpec's powerful search tool also confirms ACD's position as the premier database of commercially available chemical structures."

"Completely complementary to traditional interpretation and spectral library searching, *Rational Numbers* FragSearch is designed to assist scientists in identifying small organic compounds from accurate-mass fragmentation data (MS/MS or CID-MS)," says Dr. Daniel Sweeney, President of MathSpec. "The objective is to draw a rough picture of molecules that could yield a particular set of numbers, and then to search through an index of the MDL ACD database to find matching compounds. These compounds can then be viewed and conveniently ordered from suppliers," said Sweeney.

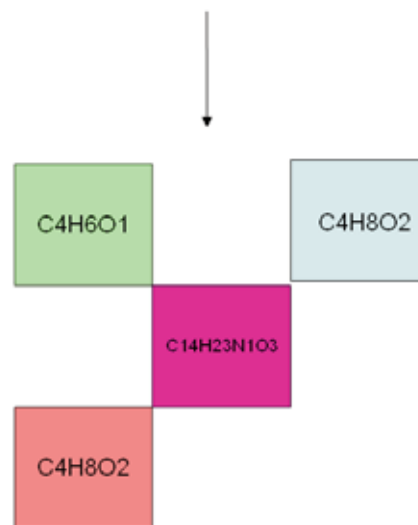
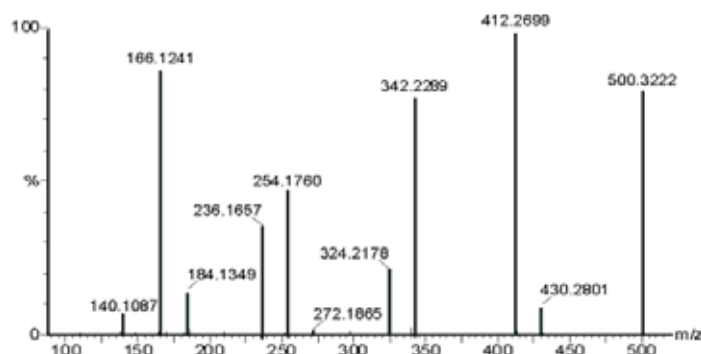


Figure 1: A modular structure is similar to the chemical structure. Searching is accomplished by comparing the heavy atom distributions of modular structures generated from accurate-mass fragmentation data to the heavy atom distributions of molecular structures found in MDL ACD.

(continued on page 21)

Searching is accomplished by comparing the heavy atom distributions of modular structures generated from accurate-mass fragmentation data to the heavy atom distributions of molecular structures found in MDL ACD.

(continued from page 20)

“The list of MDL Numbers generated by the Rational Numbers program can be imported into the DiscoveryGate® online content platform or MDL® ISENTRIS®. Not only can the scientist then locate the compounds of interest for purchase in MDL ACD, but the ‘Also found in’ links in DiscoveryGate and the Availability Service of ISENTRIS offer immediate connections to other relevant information on the same compound in other data sources,” says Carmen Nitsche, “Using Elsevier MDL’s content distribution channels, we and our content partners can deliver critical chemistry and bioactivity content to researchers during the various stages of discovery research.” ■

Figure 2: Dr. Daniel Sweeney, President of MathSpec and Carmen Nitsche, Director Business Development, Elsevier MDL at the recent ACS National Meeting & Exposition in Chicago



Library Searching - Without Libraries

Rational Numbers is a software tool for identifying small molecules from accurate-mass fragmentation data:

- * If the compound of interest is known, Rational Numbers can assign fragment ions in its spectrum.
- * If the compound is unknown but previously reported, the program can search accurate-mass fragmentation data directly against molecular structure databases; traditional mass spectral libraries are no longer needed.
- * If the compound is novel, Rational Numbers can compute and generate modular structures which closely approximate the molecular structure

(partition). The software does not use fragmentation rules; instead it uses a novel computational approach. Modern computers and accurate-mass fragmentation data have made this new orthogonal approach possible.

Rational Numbers software can also be used to assign fragments to a known or proposed compound.

The program can transform monochrome structures created in MDL® ISIS/Draw and other structure editors into color-coded molecular structures with the colors corresponding exactly to the cells of the modular structure. This makes the fragmentation very easy to visualize. A

change in the mass of an individual colored cell should increase or decrease only the color-coded fragments containing that cell. In this way, it is very easy to pinpoint the location of structural modifications in the molecule.

Try Rational Numbers FragSearch today!
For more information and to sign-up for a free trial go to—www.mathspec.com

Sign-up for a 30-day trial of DiscoveryGate (no fee, no obligation to buy, subject to acceptance of the applicable DiscoveryGate evaluation license) www.discoverygate.com

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- MDL[®] Assay Explorer[®]
- MDL[®] Plate Manager
- DiscoveryGate[®]

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MDL Isentris—*Integrating data and workflows*

