Molecular Connection 2007 Vol 25 No 3

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.

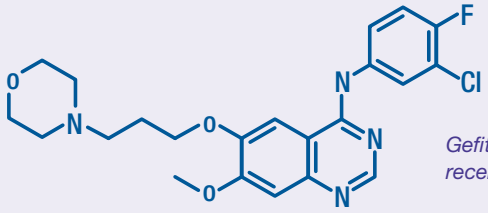
(continued on page 12)

(continued from page 11)

The CNIO has adopted DiscoveryGate because it offers 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 for 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)
  - Information spanning clinical pharmacology data, pharmacokinetic data, mechanism of action, distribution/metabolism/excretion, drug-drug interactions, etc.
- *Meyler's Side Effects of Drugs*

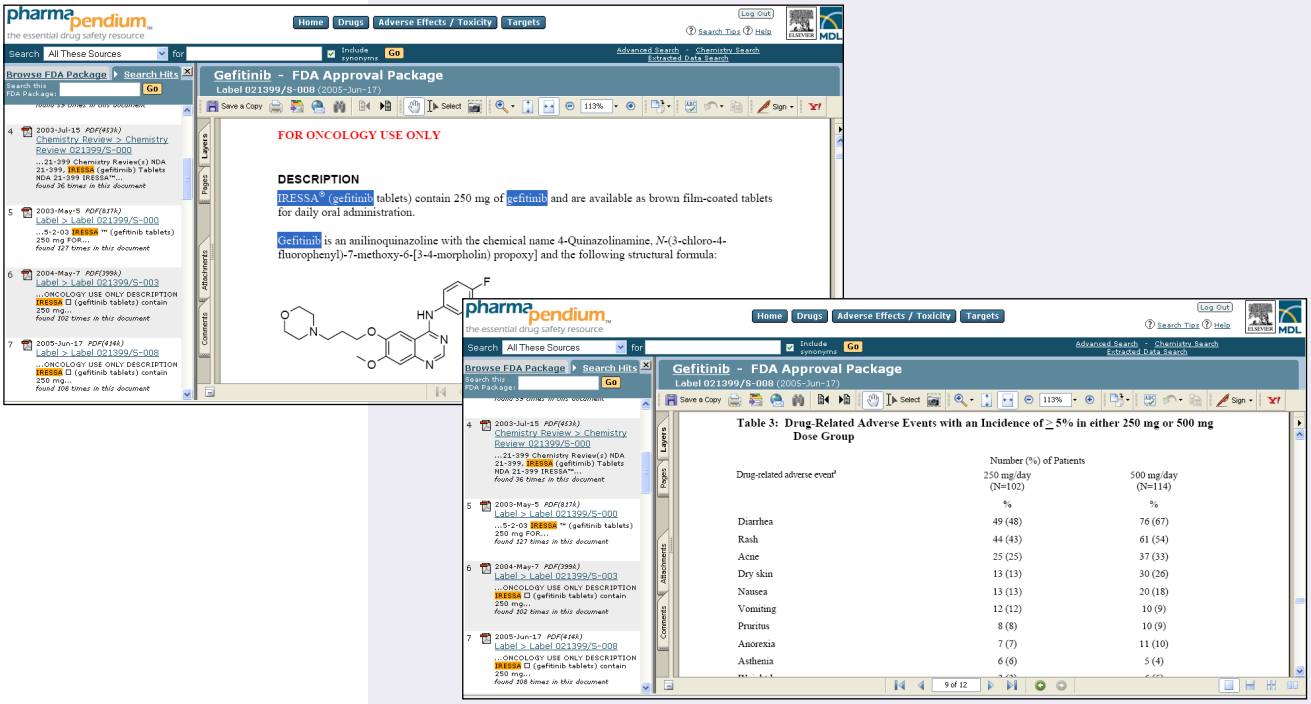


Figure 1: Adverse effects of Iressa from the Label in the FDA Approval Package (search parameter highlighted in results)

(continued on page 13)

(continued from page 12)

Centro Nacional de Investigaciones Oncologicas (CNIO)

Located in Madrid, the Centro Nacional de Investigaciones Oncologicas (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).

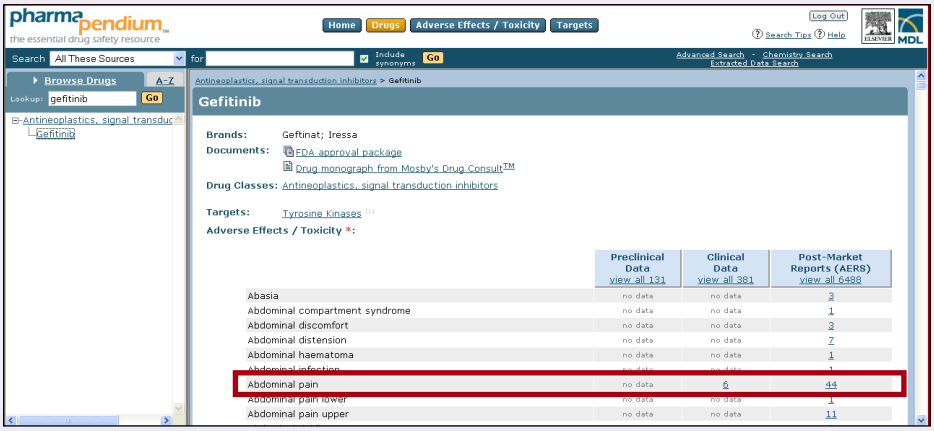


Figure 2: Clicking on the hyperlink under Clinical Data for Abdominal pain displays the clinical data for Iressa

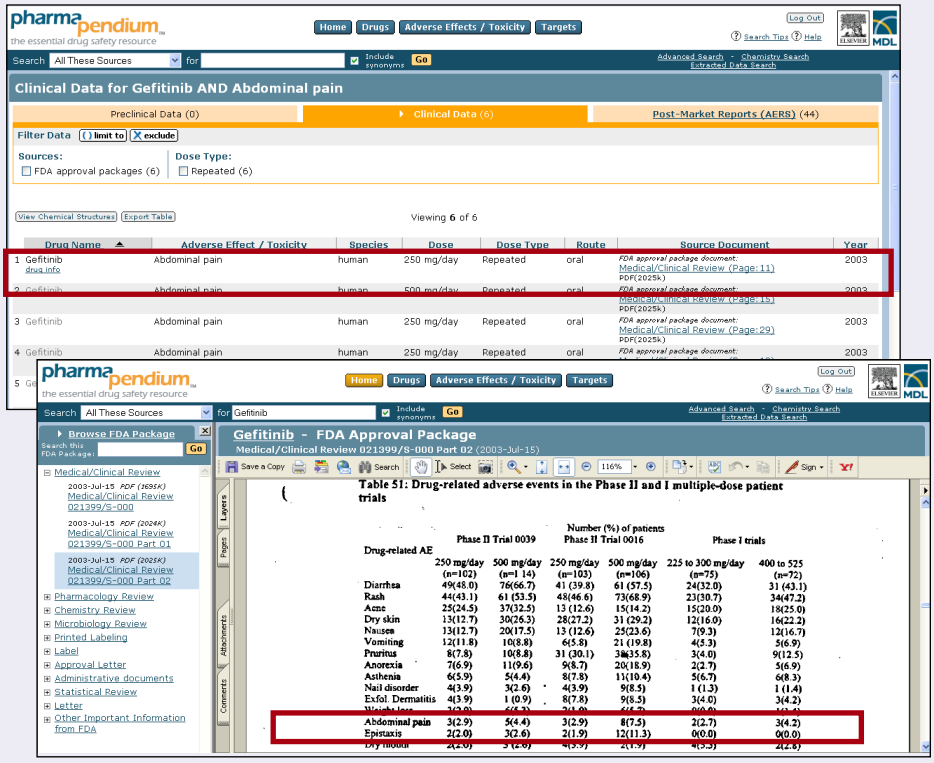


Figure 3: Adverse effects of Iressa in primary FDA report provided by PharmaPendium.

2. Search for Iressa in xPharm®, a database of pharmacological information that maps the interactions among 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 ^{14}C-labeled getinib was administered orally to albino and pigmented rats, radioactivity was widely and rapidly distributed, with the highest levels being found in liver, kidney, 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 ^{14}C-labeled getinib by either rat, dog or human occurred predominantly via the bile into feces, with <7% of the dose being eliminated in urine McKillop et al (2004).

Rat

	Value	Units	Prep. and Route of Admin.	Reference	Comments
Absorption					
Bioavailability					
Distribution					
Volume of Distribution	9–10		l/kg	McKillop et al (2004)	
Plasma Protein Binding	87.5 ± 0.5	%	i.v.	McKillop et al (2004)	Male (binding independent of dose)
Plasma Protein Binding	8.2 ± 1.4	%	i.v.	McKillop et al (2004)	Female (binding independent of dose)
Metabolism					
Plasma Half-Life	2	hrs	i.v.	McKillop et al (2004)	
Bio Half-Life	72	hrs	orally	McKillop et al (2004)	65% of the administered radioactivity is recovered.
Clearance	70	%	i.v.	McKillop et al (2004)	Within 24 hours.
Routes of Elimination	Feces.				

Potency

	Value	Units	Organ/Tissue	Prep. and Route of Admin.	Cell Line/Type	Effects	Exp. End Point	Reference	Comments
Female athymic mice (BALB/c, nu/nu)									
DOSE 150		mg/kg		orally				Kuwahara 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 10–12		µmol/l	Malignant rhabdoid tumor		MRT cell lines	Growth inhibition		Kuwahara et al (2004)	Gefitinib at 150 mg/kg had a cytostatic effect on established MRT xenografts.

Other Information

Web Sites:

FDA information on gefitinib: http://www.fda.gov/cder/foi/label/2003/021399lbl.pdf

Gefitinib information from MedicineNet: http://www.medicinenet.com/gefitinib/article.htm

Further Reading:

Isobe, Herbst, 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) 298-307.

Bibliographic References

Journal Citations:

Pao, W., Miller, V., Zakowski, M., Doherty, J., Politi, K., Sarkaria, I., Singh, B., Heelan, R., Rusch, V., Fulton, L., Mardis, 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. *Proc. Natl. Acad. Sci. USA, 2004, 101, 13306-13311*

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. *Xenobiotica, 2004, 34(10), 917-934*

Taguchi, F., Koh, Y., Koizumi, F., Tamura, T., Saijo, N., and Nishio, K., Anticancer effects of ZD6474, a VEGF receptor tyrosine kinase inhibitor, in gefitinib ("Iressa")-sensitive and resistant xenograft models. *Cancer Sci., 2004, 95(12), 984-989*

Kuwahara, Y., Hosoi, H., Osone, S., Kita, M., Iehara, T., Kuroda, H., and Sugimoto, T., Antitumor activity of gefitinib in malignant rhabdoid tumor cells in vitro and in vivo. *Clin. Cancer Res., 2004, 10(17), 5940-5948*

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 | Contents | Search | Agents | Targets | Disorders | Principles

Quick Search within All xPharm Go Search Tips | About | Logout

Tyrosine Kinase Inhibitors

Mary J. Cismowski

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 tyrosine kinase (genistein, lavendustin C, PP1-AG1872, PP2-AG1879, SU6656, CGP77675, PD166285, imatinib, erlotinib, gefitinib), allosteric inhibition of the tyrosine kinase (lavendustin A), inhibition of ligand binding to receptor tyrosine kinases (e.g., cetuximab), inhibition of tyrosine kinase interaction with other proteins (e.g., UCS15A, pp60-v-Src inhibitor peptide) or destabilization of the tyrosine kinase (e.g., herbimycin A and radicicol). The majority of tyrosine kinase inhibitors are currently not in clinical use. The notable exceptions (imatinib, cetuximab, erlotinib, gefitinib) show promise as "targeted" therapeutics in the treatment of cancers in which specific tyrosine kinases have been implicated.

Human Pharmacokinetics

Imatinib, erlotinib, and gefitinib are available orally. Cetuximab is available as an intravenous injection.

Targets-Pharmacodynamics

Imatinib predominantly targets Abl 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. Erlotinib, gefitinib, and cetuximab 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 Paez et al (2004).

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).

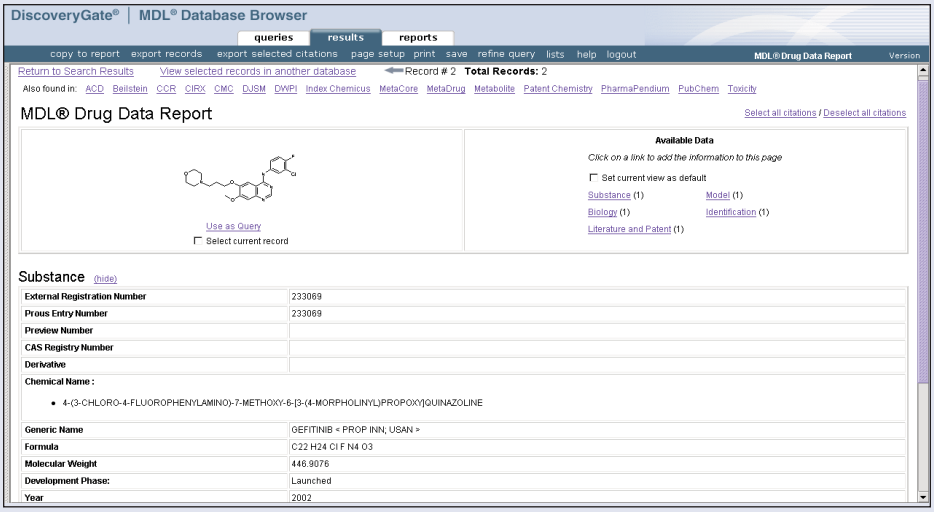


Figure 7: Pharmacological activity information displayed for the Iressa record in the MDL® Drug Data Report database. 'Also found in' links at the top of each DiscoveryGate record offer immediate connections to relevant information on the same compound in other data sources.

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).

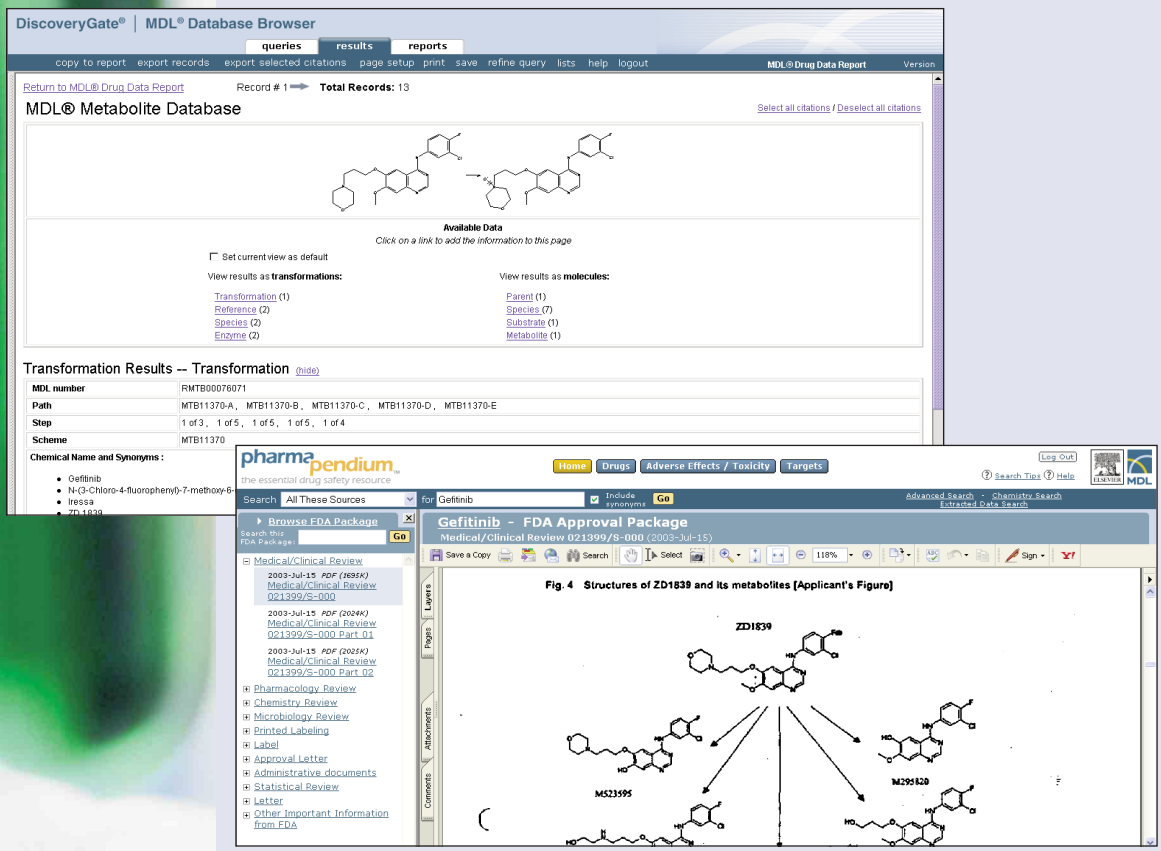


Figure 8: The results in MDL Metabolite show oxidation of the morpholine moiety in 9 of 13 cases with data on species and enzymes including references. In the PharmaPendium data, five metabolites are identified in human plasma (CYP3A4). O-desmethyl gefitinib has the same exposure and EGFR-TK activity, but only 1/14 of its potency in a cell-based assay. With an elimination half-life of

(continued on page 16)

(continued from page 15)

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).

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).

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

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.■

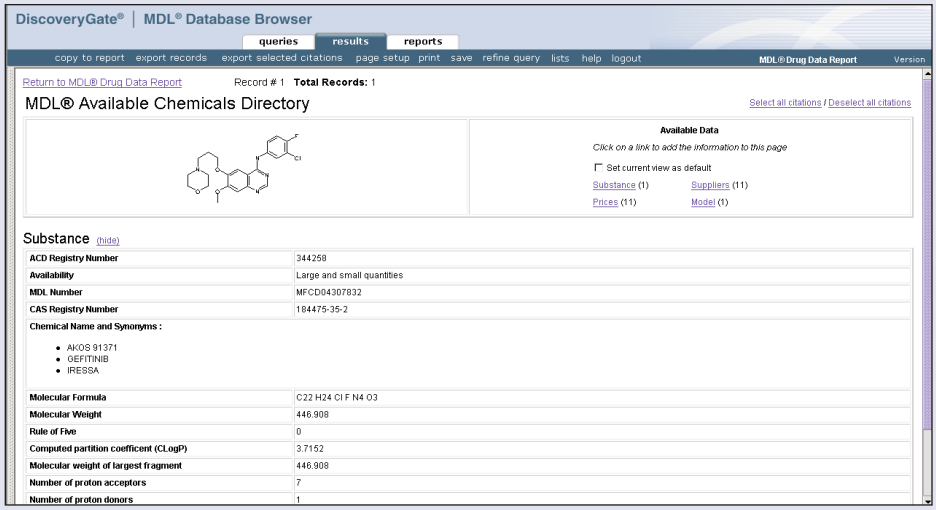


Figure 9: MDL ACD displays pricing, packaging and supplier contact details for the Iressa compound.

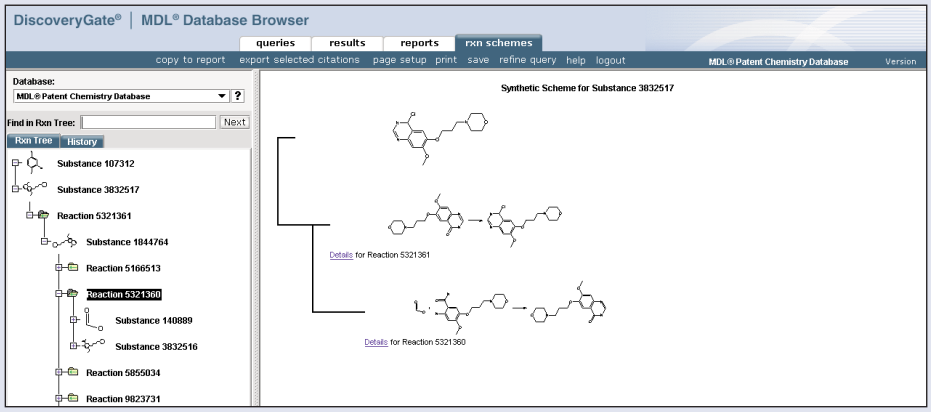


Figure 10: The MDL® Patent Chemistry Database includes information on three synthetic routes from the patent literature, including two patents from AstraZeneca and one from Natco Pharma.

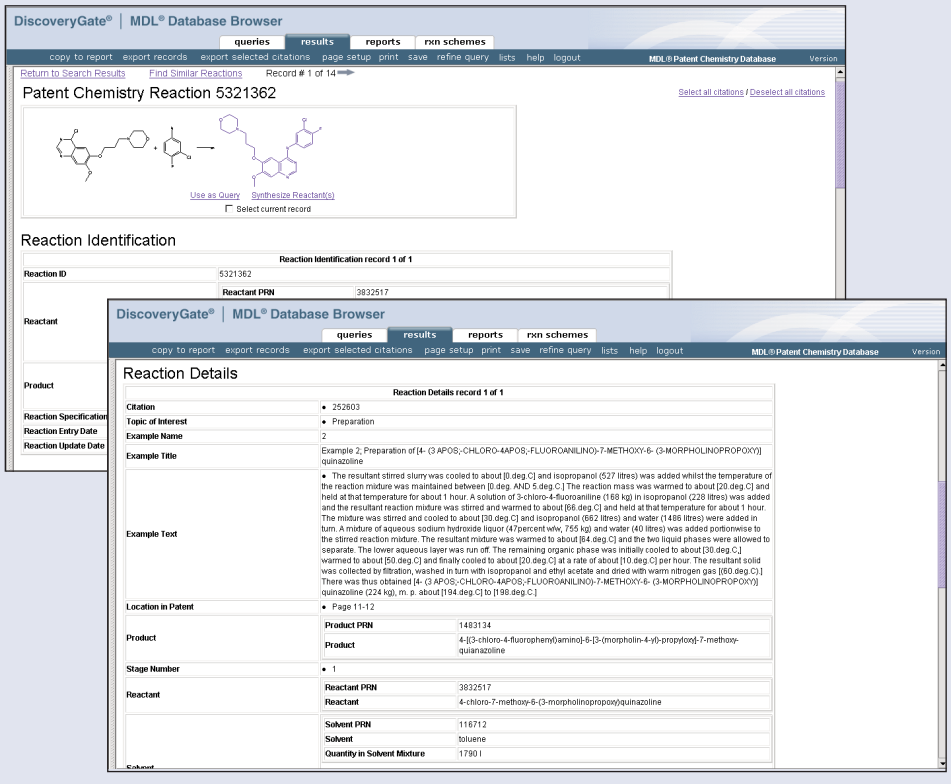


Figure 11: Detailed synthetic protocol information for the synthesis of Iressa