



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.

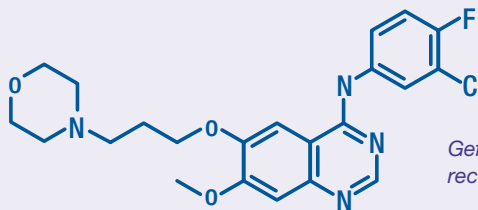
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*The CNIO
has adopted
DiscoveryGate
because it offers
chemists and
biologists access
to a wide range
of information
at the interface
between the
two disciplines.*

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*

Drug-related adverse event ^a	Number (%) of Patients 250 mg/day (N=102)	500 mg/day (N=114)
	%	%
Diarrhea	49 (48)	76 (67)
Rash	44 (43)	61 (54)
Acne	25 (25)	37 (33)
Dry skin	13 (13)	30 (26)
Nausea	13 (13)	20 (18)
Vomiting	12 (12)	10 (9)
Pruritus	8 (8)	10 (9)
Anorexia	7 (7)	11 (10)
Asthenia	6 (6)	5 (4)

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

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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).

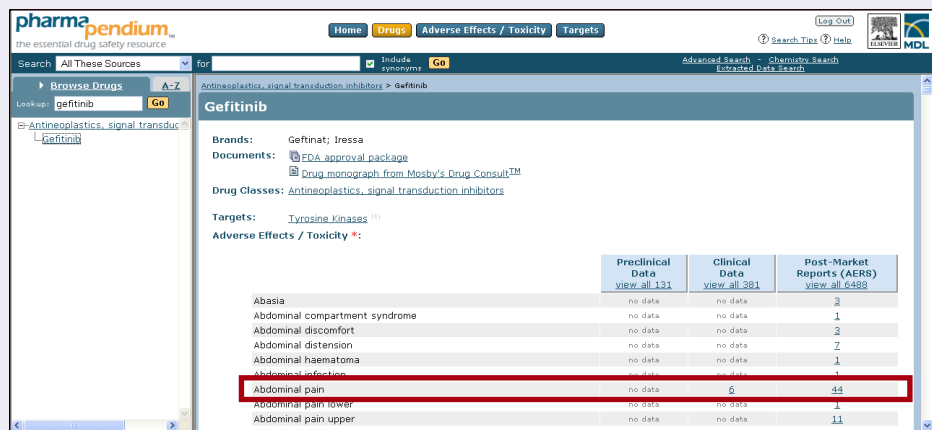


Figure 2: Clicking on the hyperlink under Clinical Data for Abdominal pain displays the clinical data for Iressa

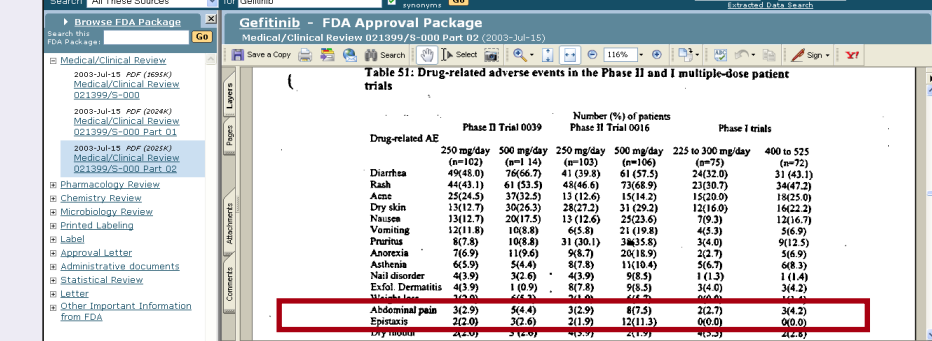
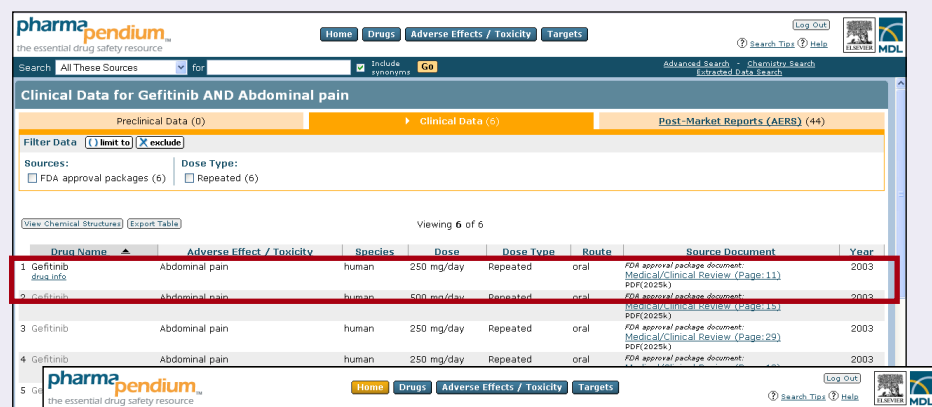


Figure 3: Adverse effects of Iressa in primary FDA report provided by PharmaPendium.

2. Search for Iressa in xPharm®, a database of pharmacological information that maps the interactions 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.

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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](#), [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 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 [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				Kawahara 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		Kawahara 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/2003/021399bl.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), 917-932.

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.

Kawahara, Y., Hosoi, H., Ozone, 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).

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Tyrosine Kinase Inhibitors

[Mary J. Cismowski](#)

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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](#) ([imatinib](#), [gefitinib](#), [erlotinib](#), [sunitinib](#), [lapatinib](#), [dasatinib](#), [vandetanib](#), [amafanib](#), [nintedanib](#), [osimertinib](#)), 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](#), [p50-y-Src inhibitor peptide](#)) or destabilization of the tyrosine kinase (e.g., [herbimycin A](#) and [calicostin](#)). 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 [Abi 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 [sunitinib](#) 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 [Pae2 et al \(2004\)](#).

Target Name(s):

[Abi 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

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

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queries results reports

copy to report export records export selected citations page setup print save refine query lists help logout MDL® Drug Data Report Version

Return to Search Results View selected records in another database Record # 2 Total Records: 2

Also found in: [ACD](#) [Beilstein](#) [CCR](#) [CIRX](#) [CMC](#) [DJSM](#) [DWPI](#) [Index.Chemicus](#) [MetaCore](#) [MetaCrug](#) [Metabolite](#) [Patent.Chemistry](#) [PharmaPendium](#) [PubChem](#) [Toxicity](#)

MDL® Drug Data Report [Select all citations / Deselect all citations](#)

Available Data
Click on a link to add the information to this page
 Set current view as default
[Substance \(1\)](#) [Model \(1\)](#)
[Biologic \(1\)](#) [Identification \(1\)](#)
[Literature and Patent \(1\)](#)

Substance [\(hide\)](#)

External Registration Number	233069
Prous Entry Number	233069
Preview Number	
CAS Registry Number	
Derivative	
Chemical Name:	
• 4-(3-CHLORO-4-FLUOROPHENYLAMINO)-7-METHOXY-6-[3-(4-MORPHOLINYL)PROPOXY]QUINAZOLINE	
Generic Name	GEFITINIB • PROP INN, USAN •
Formula	C22 H24 Cl F N4 O3
Molecular Weight	448.9076
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).

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Return to MDL® Drug Data Report Record # 1 Total Records: 13

MDL® Metabolite Database [Select all citations / Deselect all citations](#)

Available Data
Click on a link to add the information to this page
 Set current view as default
View results as **transformations**: [Transformation \(1\)](#) [Reference \(2\)](#) [Species \(2\)](#) [Enzyme \(2\)](#)
View results as **molecules**: [Parent \(1\)](#) [Species \(7\)](#) [Substrate \(1\)](#) [Metabolite \(1\)](#)

Transformation Results -- Transformation [\(hide\)](#)

MDL number	RMTB00076071
Path	MTB11370-A, MTB11370-B, MTB11370-C, MTB11370-D, MTB11370-E
Step	1 of 3, 1 of 5, 1 of 5, 1 of 5, 1 of 4
Scheme	MTB11370

Chemical Name and Synonyms:

- Gefitinib
- N-(3-Chloro-4-fluorophenyl)-7-methoxy-6-(3-(4-morpholinyl)propoxy)quinazolin-4-amine
- ZD1839

pharmapendium™
The essential drug safety resource

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Search: All These Sources For Gefitinib Include synonyms Go

Advanced Search Chemical Search Extended Data Search

Browse FDA Package Search this FDA Package

Medical/Clinical Review
2003-Jul-15 PDF (2659K)
Medical/Clinical Review 021399/S-000
2003-Jul-15 PDF (2624K)
Medical/Clinical Review 021399/S-000 Part 01
2003-Jul-15 PDF (2624K)
Medical/Clinical Review 021399/S-000 Part 02

Pharmacology Review
Chemistry Review
Microbiology Review
Printed Labeling
Label
Approval Letter
Administrative documents
Statistical Review
Letter
Other Important Information from FDA

Geftinib - FDA Approval Package
Medical/Clinical Review 021399/S-000 (2003-Jul-15)

Save a Copy Search Select 118%

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

ZD1839
M523595
M295820

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

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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. ■

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Return to MDL® Drug Data Report Record # 1 Total Records: 1

MDL® Available Chemicals Directory

Select all citations / Deselect all citations

Available Data

Click on a link to add the information to this page

Set current view as default

Substance (1) Suppliers (11) Prices (1) Model (1)

Substance (hide)

ACD Registry Number	344258
Availability	Large and small quantities
MDL Number	MFC04307632
CAS Registry Number	184475-35-2
Chemical Name and Synonyms :	
<ul style="list-style-type: none"> AKOS 91371 OEFTINIB IRESSA 	
Molecular Formula	C22 H24 Cl F N4 O3
Molecular Weight	446.908
Rule of Five	0
Computed partition coefficient (CLogP)	3.7152
Molecular weight of largest fragment	446.908
Number of proton acceptors	7
Number of proton donors	1

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

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Database: MDL® Patent Chemistry Database

Find in Rxn Tree: Next

Rxn Tree History

- Substance 107312
- Substance 3832517
 - Reaction 5321361
 - Substance 1844764
 - Reaction 5166513
 - Reaction 5321360
 - Substance 140889
 - Substance 3832516
 - Reaction 5855034
 - Reaction 9823731

Synthetic Scheme for Substance 3832517

Details for Reaction 5321361

Details for Reaction 5321360

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.

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queries results reports rxn schemes

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Return to Search Results Find Similar Reactions Record # 1 of 14

Patent Chemistry Reaction 5321362

Select all citations / Deselect all citations

Use as Query Synthesize Reactant(s)

Select current record

Reaction Identification

Reaction Identification record 1 of 1

Reaction ID: 5321362

Reactant PRN: 3832517

Reactant

Product

Reaction Specification

Reaction Entry Date

Reaction Update Date

Reaction Details

Reaction Details record 1 of 1

Citation: 252603

Topic of Interest: Preparation

Example Name: 2

Example Text

Example 2, Preparation of 4- (3 APOS;CHLORO-4APOS;FLUORONANILINO)-7-METHOXY-6- (3-MORPHOLINOPROPOXY) quinazolinone

The resultant stirred slurry was cooled to about [0 deg C] and isopropanol (57 litres) was added whilst 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-fluorophenylamine (168 kg) in isopropanol (228 litres) was added and the resultant reaction mixture was stirred and warmed to about [66 deg C] and held at that temperature for about 1 hour. The mixture was stirred and cooled to about [30 deg C] and isopropanol (662 litres) and water (148 litres) were added in turn. A mixture of aqueous sodium hydroxide liquor (47 percent w/w, 755 kg) and water (40 litres) was added portionwise to the stirred reaction mixture. The resultant mixture was warmed to about [64 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 [50 deg C] and finally cooled to about [20 deg C] at a rate of about [10 deg C] per hour. The resultant solid was collected by filtration, washed in turn with isopropanol and ethyl acetate and dried with warm nitrogen gas [80 deg C]. There was thus obtained [4- (3 APOS;CHLORO-4APOS;FLUORONANILINO)-7-METHOXY-6- (3-MORPHOLINOPROPOXY) quinazolinone (224 kg), m. p. about [194 deg C] to [198 deg C].

Location in Patent

Page 11-12

Product

Product PRN: 1483134

Product: 4-[[3-chloro-4-fluorophenylamino]-6-β-(morpholin-4-yl-propyl)-7-methoxyquinazolin-2(1H)-one]

Stage Number

1

Reactant

Reactant PRN: 3832517

Reactant: 4-chloro-7-methoxy-6-β-(3-morpholinopropyl)quinazolin-2(1H)-one

Solvent PRN: 116712

Solvent: toluene

Quantity in Solvent Mixture: 1790 l

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