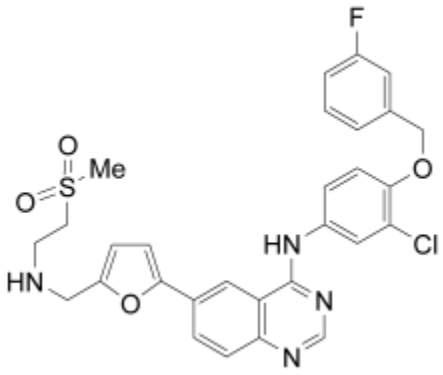
Product **Lapatinib**



Nomenclature	N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl] amino]methyl]-2-furanyl]-4-quinazolinamine
OtherNames	Lapatinib Ditosylate (USAN)
DevelopmentCode	GW-572016 ; GW572016 ; GW-2016 ; GW2016 ; GW-572016F ; GW572016F ; GSK-572016 ; GSK572016 ; 572016
Brand	Tyverb (GSK: EU) Tykerb (GSK: USA)
RN	231277-92-2 ; 388082-78-8
GeneralFormula	C29H26ClFN4O4S
MW	581,1
PriorityDate	1998
LaunchingDate	2007
LastUpdate	2011/01
Patent Info	WO2006026313 (2006) Priority : US20040605404P, 27 Aug. 2004 (Smithkline Beecham Cork) Preparation of IV (6-iodo-4(3H)-quinazolinone): Junhui You, et al., Synthesis and anticoccidial activity of 4-(2-methoxyphenyl)-2-oxobutylquinazolinone derivatives , ARKIVOC 2008 (xvii) 1-11 Preparation of VI (4-chloro-6-iodoquinazoline): Substituted Heteroaromatic Compounds And Their Use In Medicine: WO9609294 (1996) Priority : GB19940018852, 19 Sep. 1994 (Wellcome Found, GB) Preparation of IX (5-formyl-2-furanboronic acid): Method for metal-organic production of organic intermediate products by means of aryl lithium-bases US20060131762 (2006) Priority : DE20021040262, 31 Aug. 2002 (Clariant Corporation) Bicyclic Heteroaromatic Compounds As Protein Tyrosine Kinase Inhibitors: WO9935146 (1999) Priority : GB19980000569, 12 Jan. 1998 (Glaxo Group Ltd., GB) Anilinoquinazolines As Protein Tyrosine Kinase Inhibitors: WO0104111 (2001) Priority : GB19990016213, 9 Jul. 1999 (Glaxo Group Ltd, GB)

Lapatinib Study Supports Cancer Stem Cell Hypothesis, Encourages Industry Research.
Schmidt C.
J Natl Cancer Inst. 2008 May 13;

Tuma RS., Lapatinib moves forward in inflammatory and early HER2-positive breast cancer trials, J Natl Cancer Inst. 2007 Mar 7;99(5):348-9.

McHugh LA. et al., Combined treatment of bladder cancer cell lines with lapatinib and varying chemotherapy regimens--evidence of schedule-dependent synergy, Urology. 2007 Feb;69(2):390-4.

Nahta R. et al., Lapatinib induces apoptosis in trastuzumab-resistant breast cancer cells: effects on insulin-like growth factor I signaling, Mol Cancer Ther. 2007 Feb;6 (2):667-74.

Xia W. et al., Lapatinib antitumor activity is not dependent upon phosphatase and tensin homologue deleted on chromosome 10 in ErbB2-overexpressing breast cancers, Cancer Res. 2007 Feb 1;67(3):1170-5.

Montemurro F. et al., Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity, Expert Opin Biol Ther. 2007 Feb;7(2):257-68.

Geyer CE. et al., Lapatinib plus capecitabine for HER2-positive advanced breast cancer, N Engl J Med. 2006 Dec 28;355(26):2733-43.

Moy B. et al., Lapatinib: current status and future directions in breast cancer, Oncologist. 2006 Nov-Dec;11(10):1047-57. Review.

Kelly H. et al., Delivery of a healthy baby after first-trimester maternal exposure to lapatinib, Clin Breast Cancer. 2006 Oct;7(4):339-41.

Kawada K. et al., Prospective Study of Positron Emission Tomography for Evaluation of the Activity of Lapatinib, a Dual Inhibitor of the ErbB1 and ErbB2 Tyrosine Kinases, in Patients with Advanced Tumors, Jpn J Clin Oncol. 2007 Jan;37(1):44-8.

Johnston SR. et al., Lapatinib: a novel EGFR/HER2 tyrosine kinase inhibitor for cancer, Drugs Today (Barc). 2006 Jul;42(7):441-53. Review.

Lackey KE., Lessons from the drug discovery of lapatinib, a dual ErbB1/2 tyrosine kinase inhibitor, Curr Top Med Chem. 2006;6(5):435-60. Review.

Konecny GE. et al., Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells, Cancer Res. 2006 Feb 1;66(3):1630-9.

Nelson MH. et al., Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors, Ann Pharmacother. 2006 Feb;40(2):261-9.

Bai F. et al., Determination of lapatinib (GW572016) in human plasma by liquid chromatography electrospray tandem mass spectrometry (LC-ESI-MS/MS), J Chromatogr B Analyt Technol Biomed Life Sci. 2006 Feb 2;831(1-2):169-75.

Xia W. et al., Combining lapatinib (GW572016), a small molecule inhibitor of ErbB1 and ErbB2 tyrosine kinases, with therapeutic anti-ErbB2 antibodies enhances apoptosis of ErbB2-overexpressing breast cancer cells, Oncogene. 2005 Sep 15;24 (41):6213-21.

Burris HA 3rd. et al., Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas, J Clin Oncol. 2005 Aug 10;23(23):5305-13.

Chu I. et al., The dual ErbB1/ErbB2 inhibitor, lapatinib (GW572016), cooperates with tamoxifen to inhibit both cell proliferation- and estrogen-dependent gene expression in antiestrogen-resistant breast cancer, Cancer Res. 2005 Jan 1;65(1):18-25.

Wood ER. et al., A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells, Cancer Res. 2004 Sep 15;64(18):6652-9.

L.A. McHugh et al. GW572016, a dual tyrosine kinase inhibitor, blocks activation of ErbB1 and ErbB2 in a bladder cancer cell line.AACR Annual Meeting [March 27-31, Orlando (Florida)], 2004, Abst 4398.

R.L. Tansik et al. Synergistic induction of apoptosis between GW572016 and inhibitors of phosphatidylinositol 3-kinase/AKT pathway. AACR Annual Meeting [March 27-31, Orlando (Florida)], 2004, Abst 4661.

Kim TE. et al., Lapatinib ditosylate GlaxoSmithKline, IDrugs. 2003 Sep;6(9):886-93.

W. Xia et al. Anti-tumor activity of GW572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways., Oncogene (2002), 21(41), 6255-6263.

B.R. Keith et al. Anti-tumor activity of GW2016 in the ErbB-2 positive human breast cancer xenograft, BT474. Proc Amer Assoc Cancer Res 2001, 42: Abst 4308.

K.E. Lackey et al. The discovery of a new anti-cancer agent GW2016: A potent, dual EGFR/ErbB-2 tyrosine kinase inhibitor. Proc Amer Assoc Cancer Res 2001, 42: Abst 4582.

R.J. Mullin et al. Antitumor activity of GW2016 in the EGFR positive human head and neck cancer xenograft, HN5. Proc Amer Assoc Cancer Res 2001, 42: Abst 4579.

D.W. Rusnak et al. The effects of the novel EGFR/ErbB-2 tyrosine kinase inhibitor, Gw2016, on the growth of human normal and transformed cell lines. Proc Amer Assoc Cancer Res 2001, 42: Abst 4309.

W. Xia et al. GW2016, a dual inhibitor of ErbB-2 and EGFR tyrosine kinases: Effects on receptor tyrosine autophosphorylation downstream signalling intermediates, and in vivo anti-tumor activity. Proc Amer Assoc Cancer Res 2001, 42: Abst 3635.

Originator

	GlaxoSmithKline (GSK)
Developer	GlaxoSmithKline (GSK)
Market	Launched
Uses	Antineoplastic
BioClass	Cytotoxic ; Apoptotic ; Antiproliferative
Reactions & Technology	Iodination Chlorination N-Arylation Palladium catalyzed coupling Reductive Amination Diazotation Sandmeyer Reaction O-Alkylation Nitro Reduction Nitration Lithiation Boric acid Synthesis
Comments	Lapatinib is a dual kinase inhibitor indicated for the treatment of breast cancer and several othe solid tumors. June 2010: The UK National Institute for Health and Clinical Excellence (NICE), did not recommend publicly-funded use of Tyverb. This is the final rejection. February 2010: The EMEA European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion for the authorisation of a new therapeutic indication for Tyverb® (lapatinib) in the European Union. Lapatinib, in combination with an aromatase inhibitor (AI), is indicated for the treatment of post-menopausal women with hormone receptor (HR)-positive, HER2 (ErbB2) over-expressing metastatic breast cancer and for whom chemotherapy is currently not intended. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor. January 2010: The US FDA approved Tykerb combination of lapatinib and letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor May 2008: results from recent clinical trials demonstrated that lapatinib decreased tumorigenic breast cancer stem cells in the primary breast cancers among women receiving lapatinib treatment. The prevention of the renewal of tumorigenic stem cells is of major importance because tumorigenic stem cells are resistant to conventional chemotherapy. March 2007: The US FDA has approved Tykerb (TM) (Lapatinib) to be used in combination with Capectabine (Xeloda TM), for patients with advanced, metastatic breast cancer that is HER2 positive (tumors that exhibit HER2 protein). The combination treatment is indicated for women who have received prior therapy with other cancer drugs, including an anthracycline, a taxane, and Trastuzumab (Herceptin TM). Marketing applications for Lapatinib (Tykerb/Tyverb) have been filed in the European Union, Switzerland, Canada, Brazil, Australia, and South Korea. December 2006: Lapatinib is ongoing 56 clinicals trials, from phase I to III, alone or in combination to treat several types of solid tumors. These trials are sponsored by GlaxoSmithKline and major academic institutions, and carried out in the USA as

well as in the whole world.

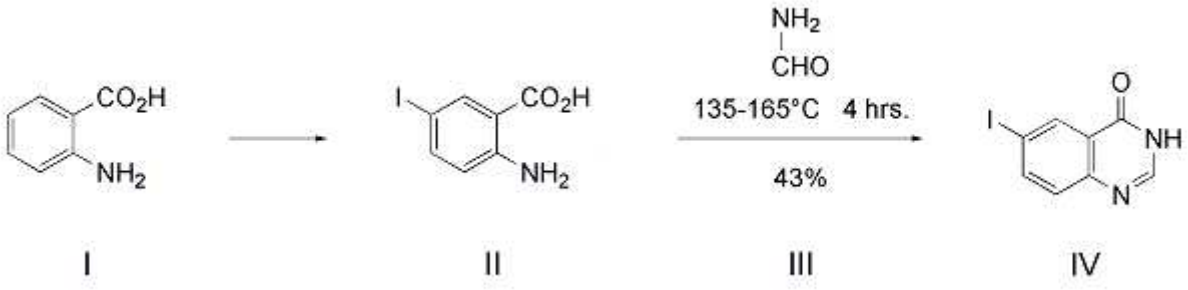
2003: Phase III

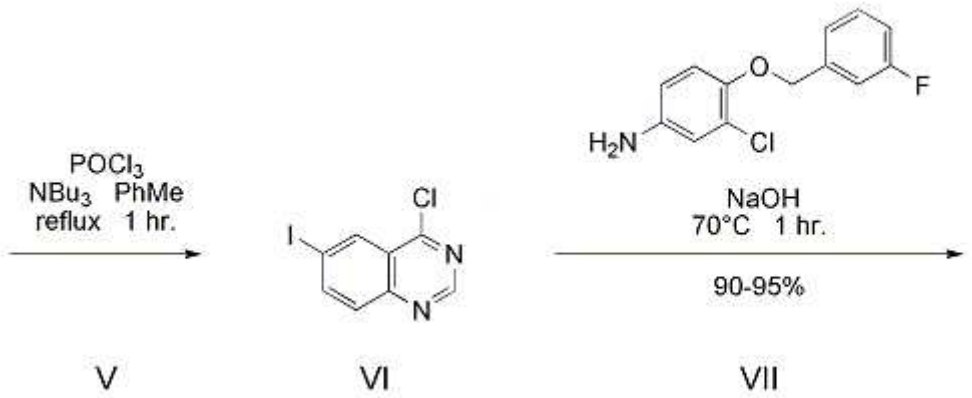
The compound is developed as the ditosylate salt (CAS-RN: 388082-78-8)

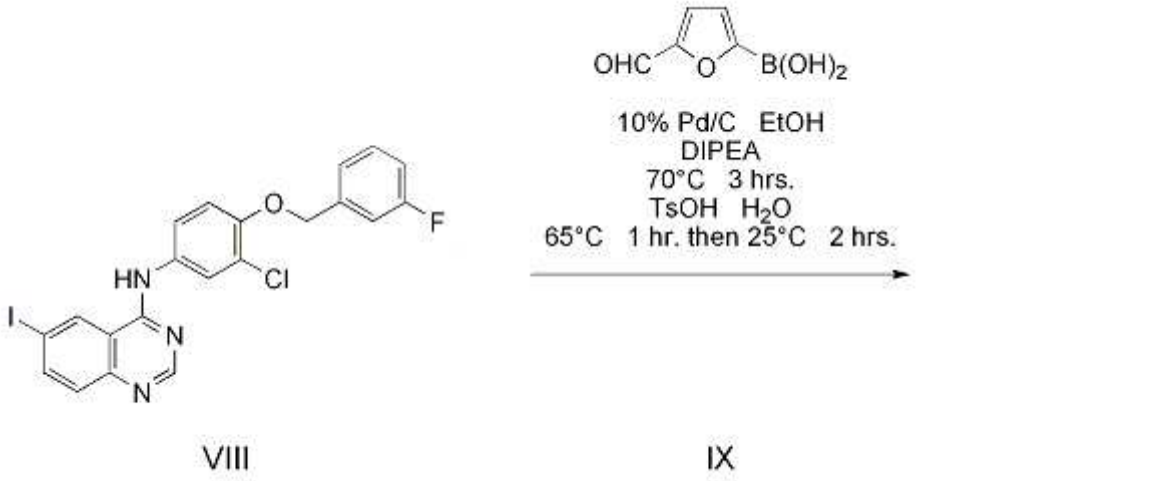
Tykerb (lapatinib ditosylate) is an epidermal growth factor receptor (EGFR) and ErbB-2 (Her2/neu) dual tyrosine kinase inhibitor, under development by GlaxoSmithKline as a treatment for solid tumours such as breast and lung cancer. This novel investigational agent has attracted considerable interest, as it appears to arrest the development of breast cancer in some patients with metastatic, treatment-refractory disease.
Protein tyrosine kinases are enzymes that provide a central switch mechanism in cellular signal transduction pathways. As such they are involved in many cellular processes such as cell proliferation, metabolism, survival and apoptosis. Several protein tyrosine kinases are known to be activated in cancer cells and to drive tumour growth and progression.

Tyverb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

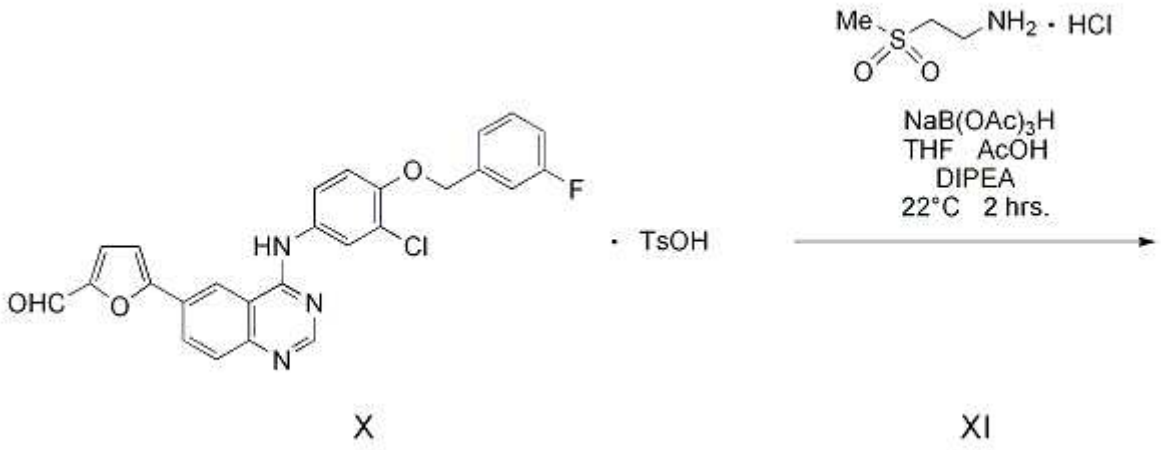
- in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (see section 5.1).
- in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor



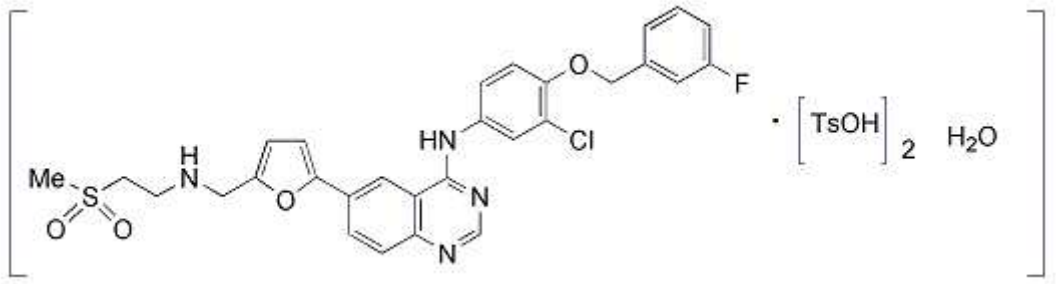


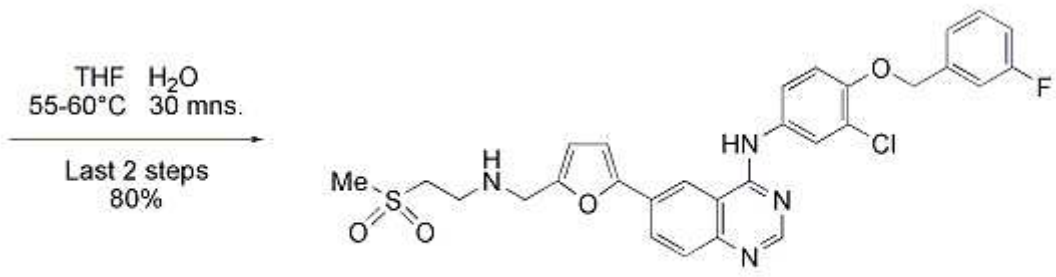


VIII IX



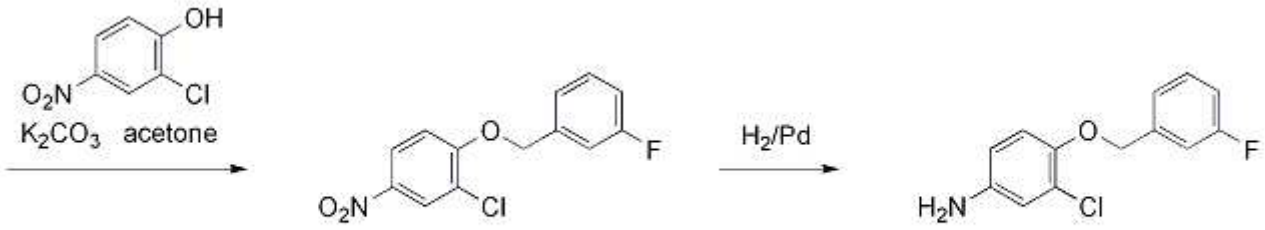
X XI





Lapatinib

Preparation of VII

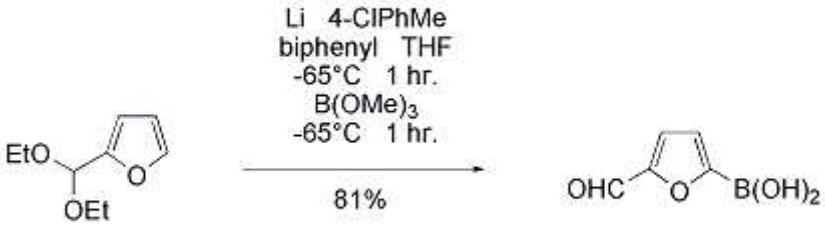


XVI XVII VII

Preparation of XVI

XVIII XVI

Preparation of IX



XIX XX XXI IX

Intermediates List

I	2-aminobenzoic acid
II	2-amino-5-bromobenzoic acid
III	formamide
IV	6-iodo-4(3H)-quinazolinone
V	phosphoryl chloride
VI	4-chloro-6-iodoquinazoline
VII	3-chloro-4-[(3-fluorophenyl)methoxy]benzenamine
VIII	6-iodo-N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-4-quinazolinamine

IX	5-formyl-2-furanboronic acid
X	5-[4-[[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]amino]-6-quinazolinyl]-2-furancarboxaldehyde
XI	2-(methylsulfonyl)ethanamine
XII	3-methylbenzenamine
XIII	3-methylbenzenediazonium fluoride
XIV	1-fluoro-3-methylbenzene
XV	1-(chloromethyl)-3-fluorobenzene
XVI	2-chloro-4-nitrophenol
XVII	2-chloro-1-[(3-fluorophenyl)methoxy]-4-nitrobenzene
XVIII	2-chlorophenol
XIX	2-(diethoxymethyl)furan
XX	lithium
XXI	boric acid trimethyl ester