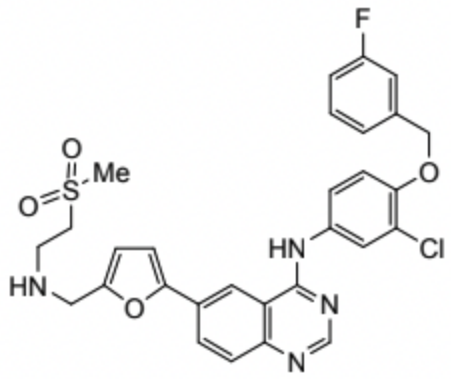
BECKER DATA

Complete Monograph for an Active Ingredient



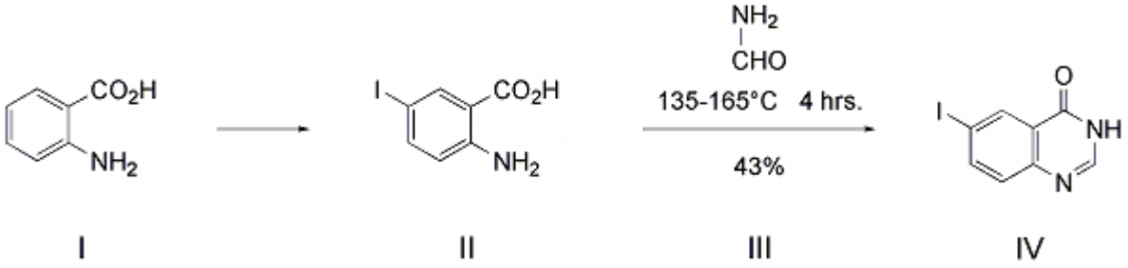
Product	**Lapatinib**
Dev. code	GW-572016 ; GW572016 ; G
Chem. name	N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine
Other Names	Lapatinib Ditosylate (USAN)
Brand	Tyverb (GSK: EU) Tykerb (GSK: USA)
RN	231277-92-2 ; 388082-78-8
Priority Date	1998
Launching Date	2007
MW	581,1
Mp Bp	
General Form.	C29H26ClFN4O4S

Patents	WO2006026313 (2006) Priority : US20040605404P, 27 Aug. 2004 (Smithkline Beecham Cork) BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS: WO9935146A1 (1999) Priority : GB19980000569, 12 Jan. 1998 (Glaxo Group Ltd, GB) Quninazoline and pyridopyrimidine derivatives EP1454907 (2004) Priority : GB19980000569 12 January 1998 (GLAXO GROUP) 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.
Owner	GlaxoSmithKline (GSK)
Market	Launched
Developer	GlaxoSmithKline (GSK)

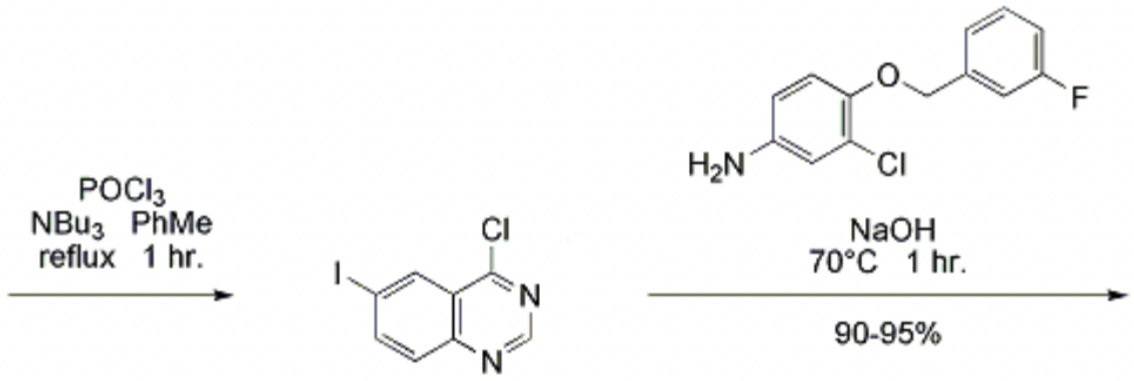
Uses	Antineoplastic
Chem. class	
Bio. class	Cytotoxic ; Apoptotic ; Antiproliferative
Technology	Iodination Chlorination N-Arylation Palladium catalyzed coupling Reductive Amination Diazotation Sandmeyer Reaction O-Alkylation Nitro Reduction Nitration Lithiation Boric acid Synthesis
Comments	Lapatinib is a dual kinase inhibitor indicated for the treatment of breast cancer and several other 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 over expresses 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 in 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
Intermediates	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
Activity	HER-2 (ErbB-2) and epidermal growth factor receptor (EGFR) dual kinase inhibitor

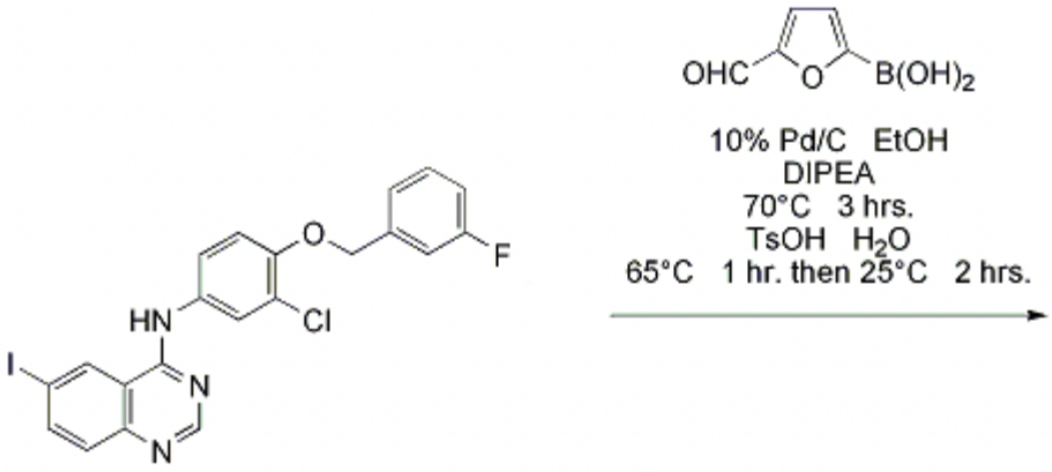
Reaction Sequences



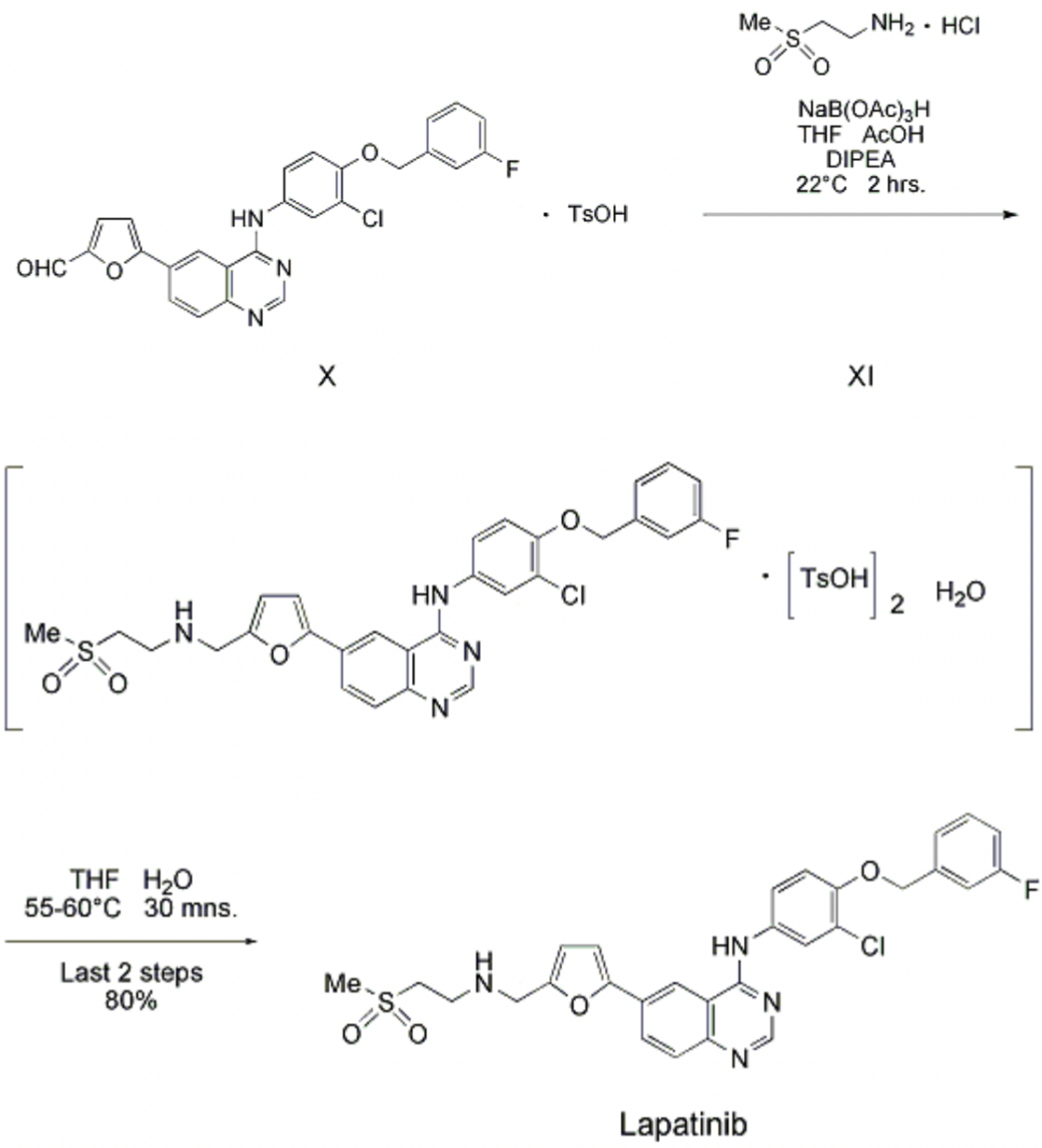
I II III IV



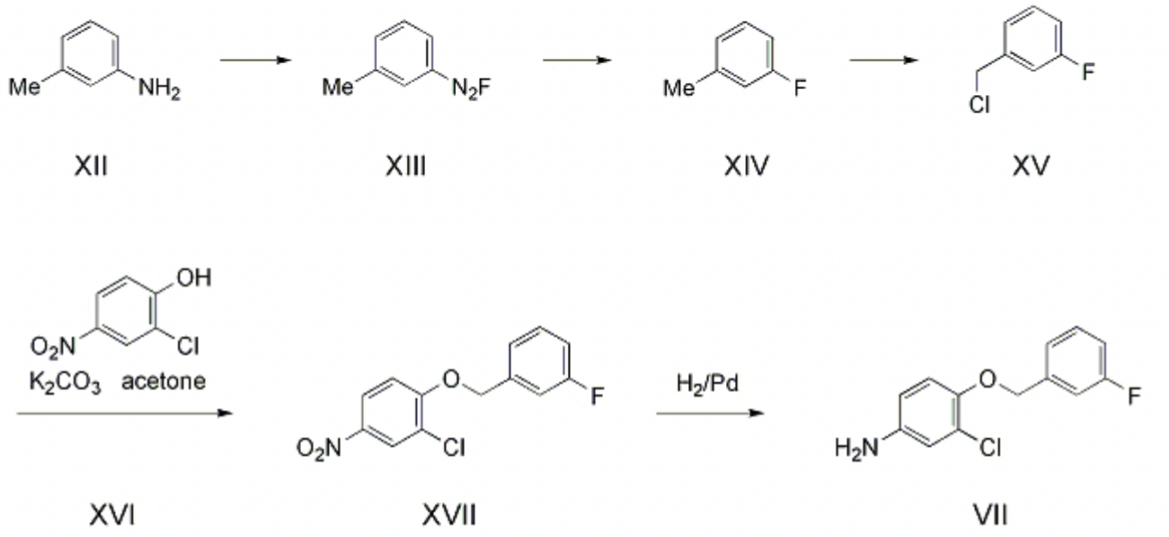
V VI VII



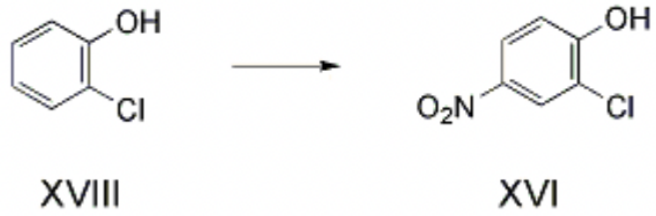
VIII IX


Me
S
O
O
NH2 · HCl
NaB(OAc)3H
THF AcOH
DIPEA
22°C 2 hrs.
OHC
O
HN
Cl
O
F
N
N
· TsOH
X
XI
Me
S
O
O
H
N
O
HN
Cl
O
F
N
N
· [TsOH]2 H2O
THF H2O
55-60°C 30 mns.
Last 2 steps
80%
Lapatinib

Preparation of VII



Preparation of XVI



Preparation of IX