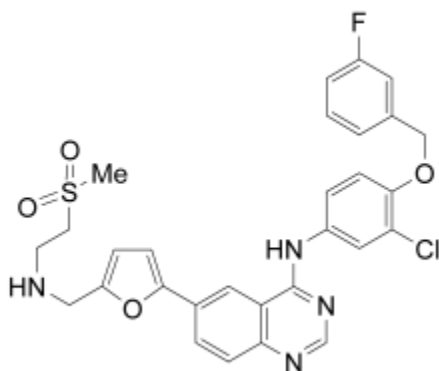


**Product**      **Lapatinib**



*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*      C<sub>29</sub>H<sub>26</sub>ClFN<sub>4</sub>O<sub>4</sub>S

*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):

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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)

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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.

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<i>Developer</i>	GlaxoSmithKline (GSK)
<i>Market</i>	GlaxoSmithKline (GSK)
<i>Uses</i>	Launched
<i>BioClass</i>	Antineoplastic
<i>Reactions &amp; Technology</i>	Cytotoxic ; Apoptotic ; Antiproliferative
<i>Comments</i>	<p>Iodination</p> <p>Chlorination</p> <p>N-Arylation</p> <p>Palladium catalyzed coupling</p> <p>Reductive Amination</p> <p>Diazotation</p> <p>Sandmeyer Reaction</p> <p>O-Alkylation</p> <p>Nitro Reduction</p> <p>Nitration</p> <p>Lithiation</p> <p>Boric acid Synthesis</p> <p>Lapatinib is a dual kinase inhibitor indicated for the treatment of breast cancer and several othe solid tumors.</p> <p>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.</p> <p>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.</p> <p>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</p> <p>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.</p> <p>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).</p> <p>Marketing applications for Lapatinib (Tykerb/Tyverb) have been filed in the European Union, Switzerland, Canada, Brazil, Australia, and South Korea.</p> <p>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</p>

well as in the whole world.

2003: Phase III

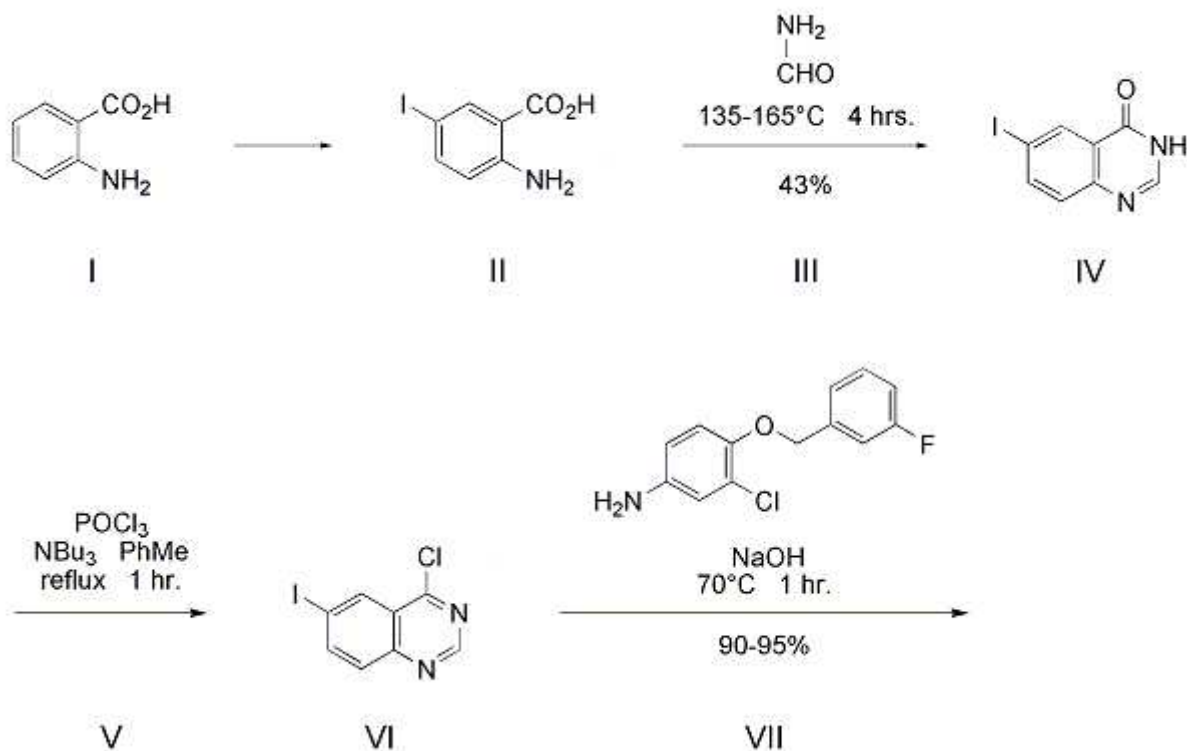
The compound is developed as the ditosylate salt (CAS-RN: 388082-78-8)

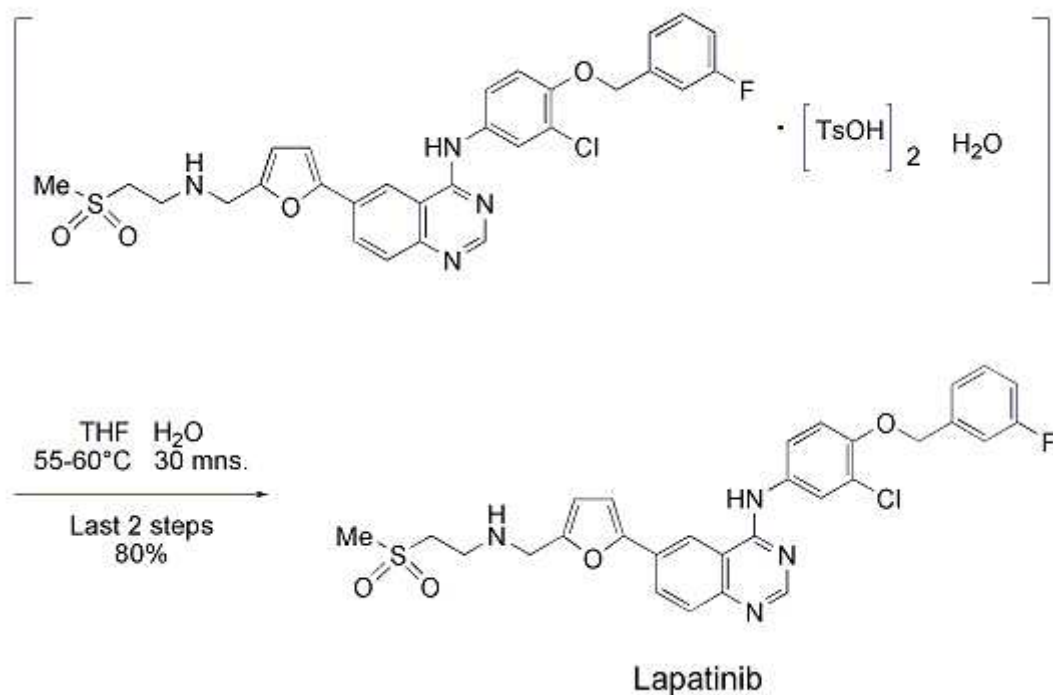
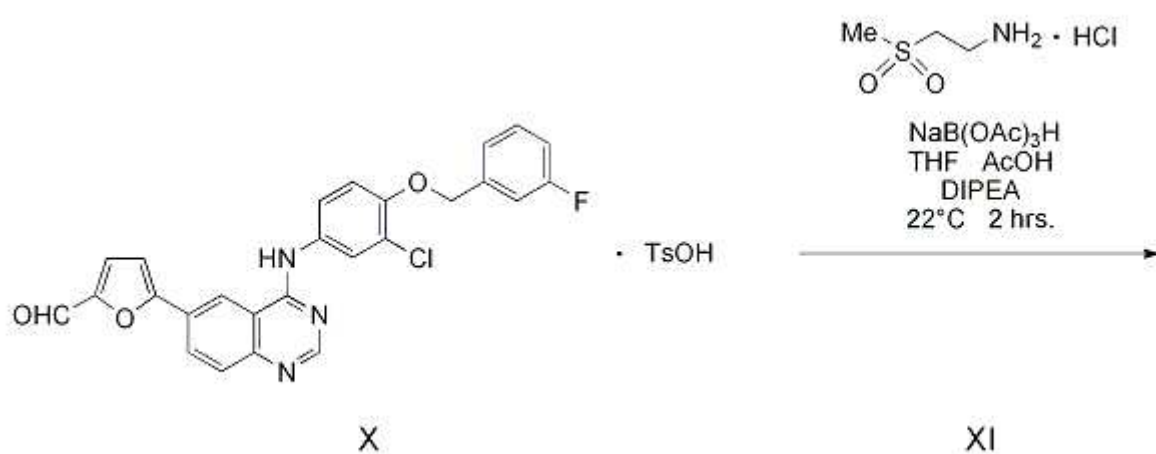
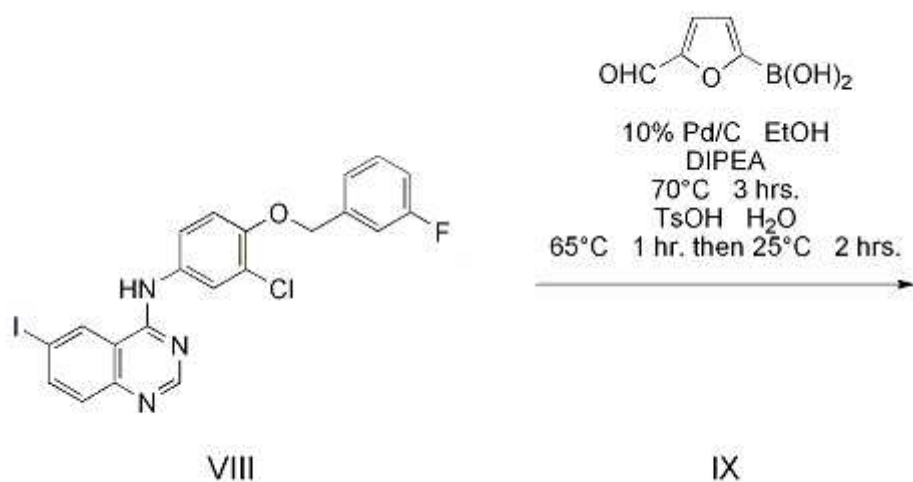
Tykerb (lapatinib ditosylate) is an epidermal growth factor receptor (EGFR) and ErbB-2 (Her2/neu) dual tyrosine kinase inhibitor, under development by GlaxoSmithKline as a treatment for solid tumours such as breast and lung cancer. This novel investigational agent has attracted considerable interest, 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.

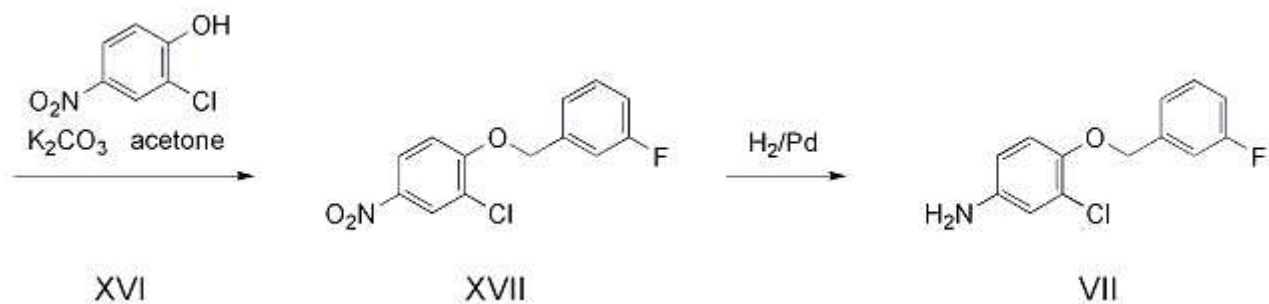
Tykerb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

- 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

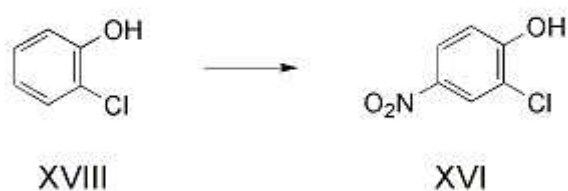




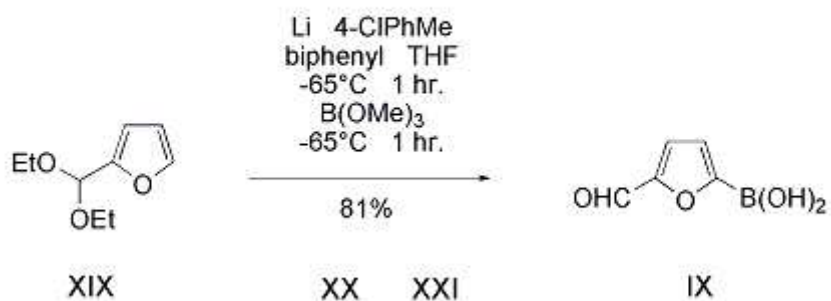
## Preparation of VII



#### Preparation of XVI



#### Preparation of 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-quinazoliny]-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