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Tarceva® – A New Approach for Treatment of Non-Small Cell Lung Cancer

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Abstract: 'How chemistry could make life easier' is exemplified by the small molecule erlotinib, the active principle of Tarceva®, providing a new approach for the treatment of non-small cell lung cancer.

Keywords: Aminoquinazoline · Lung cancer · Process chemistry · Tarceva®

Introduction

Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. One emphasis constitutes oncology in which Roche provides products and services for early detection, prevention, diagnosis, and treatment of cancer. Among the drug products of great demand are the monoclonal antibodies MabThera/Rituxan (rituximab) for non-Hodgkin's lymphoma, Herceptin (trastuzumab) for HER2-positive breast cancer, the first anti-angiogenic agent Avastin (bevacizumab) so far approved for colorectal cancer. Drugs with small molecules as active ingredients are Xeloda (capecitabine) for metastatic breast cancer, and adjuvant colon cancer, and Tarceva for non-small cell lung cancer (NSCLC) which is subject of this contribution.

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Tarceva

Tarceva (erlotinib) was discovered as part of OSI Pharmaceuticals' cancer research alliance with Pfizer [1]. In 2000 OSI gained full development rights of erlotinib enabling Pfizer to meet the U.S. Federal Trade Commission (FTC) antitrust requirements for its merger with Warner Lambert. In 2001, OSI entered into concurrent agreements with Roche globally, and Genentech within the United States, for the continued development and commercialization of erlotinib. The approval to treat locally advanced or metastatic NSCLC was granted in the European Union in September 2005 and in the US in November 2004. Tarceva is an oral tablet taken once a day and has the potential to treat many types of solid tumors.

Lung cancer is the most common cancer worldwide with 1.2 million new cases annually [2], and someone, somewhere dying of the disease every 30 seconds [3]. NSCLC accounts for almost 80% of all lung cancer cases. Tarceva works differently from other chemotherapy by specifically targeting tumor cells, inhibiting their formation and growth by intervening in the signaling pathway of the epidermal growth factor receptor (EGFR).

EGFR is stimulated when the epidermal growth factor (EGF) binds to it on the cell surface. The stimulated EGFR in turn activates the protein-tyrosine kinase in the cell initiating a signal transduction cascade which results in a variety of biochemical changes in the cell that ultimately lead to DNA synthesis and cell proliferation [4]. Erlotinib inhibits the activity of protein-tyrosine kinase hence interrupting the signal transduction pathway.

How does this brief biochemical description transform into clinical practice? The efficacy of Tarceva was demonstrated in a clinical phase III study, the BR.21 trial [5]. 731 people with advanced NSCLC, whose cancers had progressed after first- or second-line chemotherapy, participated in the trial. The study compared Tarceva to placebo. The key findings of the BR.21 study were:

- Treatment with Tarceva in patients with advanced NSCLC resulted in significantly longer survival compared to placebo, a 42.5% improvement (6.7 months *vs*. 4.7 months);
- 31% of patients receiving Tarceva were alive at one year compared to 22% on placebo;
- Patients receiving Tarceva had stability or control of their lung cancer related symptoms such as cough, shortness of breath and pain, for significantly longer;
- Patients also had a superior quality of life and improved physical function compared to those on placebo;
- The benefits of Tarceva were shown in a broad spectrum of patients.

Many people with advanced NSCLC do not receive chemotherapy. This can be for a variety of reasons, most often because they are too sick to cope with it. People whose cancer is not being treated receive best supportive care (BSC). BSC consists of drugs and other treatments used to optimize comforts and minimize disease symptoms. The portion of people who are receiving BSC after failure of one chemotherapy varies between 25 and 50% across the countries. Tarceva now provides a new treatment option for these patients.

Tarceva delivers effectiveness comparable to other chemotherapy but, importantly, without compromising tolerability and overall quality of life [5]. It also provides improved convenience benefits such as ease

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of administration, as it is taken orally and does not induce the typically distressing side-effects associated with chemotherapy, *e.g.* nausea, vomiting, and hair loss or neuropathy. Side effects observed for Tarceva were mild to moderate diarrhea and a reversible rash, both well manageable.

NSCLC was the first indication for which Tarceva gained marketing authorization. But it is expected that other types of cancer could be treated, thus more clinical studies are currently running. Due to Tarceva's new mode of action against cancer it is possible to extent its application in combinations with other drugs, *e.g.* like Avastin to search for synergistic effects.

In this contribution the enormous chemical effort to find a new molecule like erlotinib is not discussed, but the other role of chemistry is presented, *i.e.* the development of a chemical process to make erlotinib available in large quantities and proper quality.

Process Development of the Synthesis of Erlotinib

Erlotinib is a 4-aminoquinazoline hydrochloride salt carrying two different substituents (Fig. 1), apparent also in the full name: N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazoline hydrochloride. Inhibition of the EGF receptor tyrosine kinase by amino-quinazoline derivatives was first disclosed by the research groups of Zeneca and Parke-Davis [6].

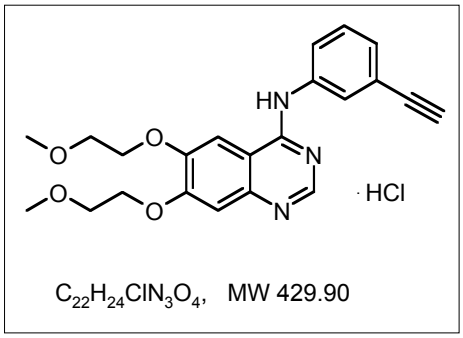


Fig. 1. Structure of erlotinib

Synthesis

When Roche entered into further development of erlotinib, a three-step synthesis was handed over by OSI. Thus considerable development work had been done already by the process research group of Pfizer, and vendors for the envisaged starting materials evaluated.

The synthesis (as shown in Scheme 1) started from quinazoline-4(3H)-one (**2**), and aminophenylbutinol (**3**). For these compounds several vendors were identified, but the discussions of the quality requirements at that time had not been completed. Due to the brevity of the synthesis **2** and **3** must have a high purity.

Quality of Quinazoline-4(3H)-one (2)

This compound was always obtainable in high quality. The synthesis started from ethyl-3,4-dihydroxybenzoate (**6**) (Scheme 2). The ether side chains were introduced, and the antranilic acid derivative **8** generated, which is a typical intermediate to prepare quinazoline-4(3H)-ones [7].

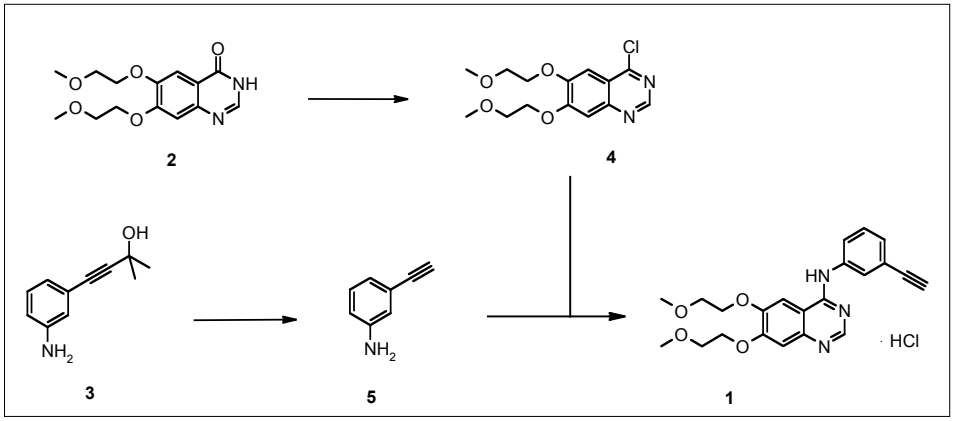
In one case traces of impurities (<0.1%) were observed in erlotinib which could be ascribed to corresponding impurities in **2**. After isolation by preparative high-pressure chromatography, these impurities were characterized by their mass spectra. These compounds showed structurally modifications in the ether side chains, *i.e.* the chemical step where the ether side chains were formed used a quality of 1-chloro-2-methoxy ethane presumably contaminated with ethylchloride and 1-(2-chloroethoxy)-2-methoxy-ethane to afford the corresponding pairs of positional isomers as impurities in **2** (Fig 2). The result of this investigation was communicated to the suppliers of **2** to control the quality of chloromethoxy ethane.

Quality of Aminophenylbutinol (3)

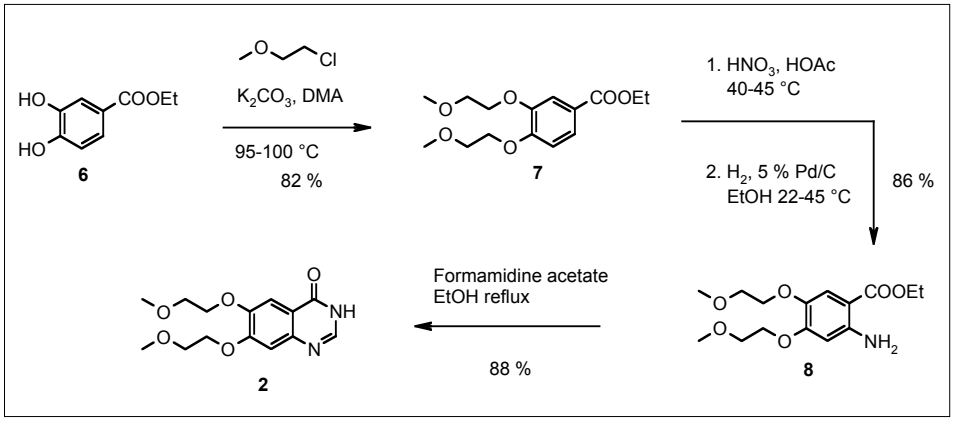
Aminophenylbutinol (**3**) was prepared by a Sonogashira coupling reaction [8] of corresponding N-substituted bromobenzenes and methylbutinol. Several companies disclosed process patents (Scheme 3) which gave indications about the impurity profile of **3**. Accurate analysis of **3** of different origin showed no positional isomers of **3**, and no residues of Pd, Cu, and Ph_3P. Thus aminophenylbutinol was obtained in sufficient quality from various suppliers.

Step 1: Process to Prepare Chloroquinazoline 4

So far two procedures had been used to prepare **4**, which were based on thionyl chloride/dimethylformamide or oxalyl



Scheme 1. Synthesis of erlotinib



Scheme 2. Synthesis of **2**

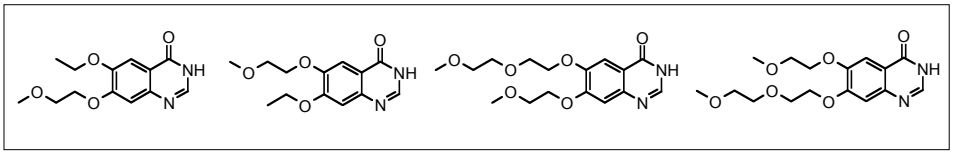
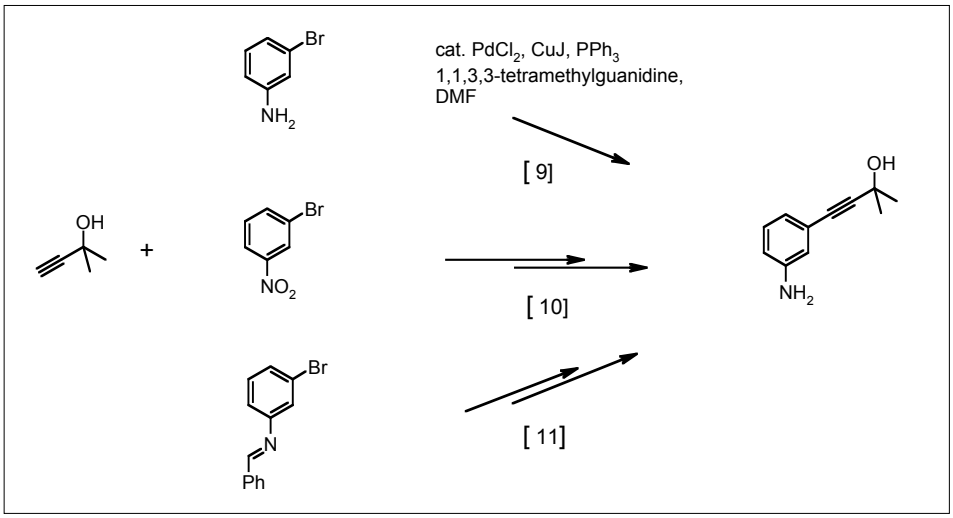
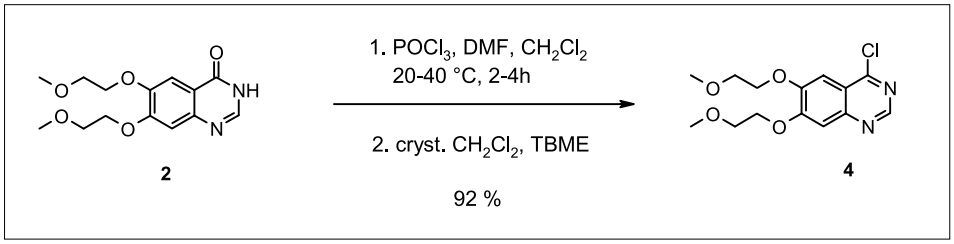


Fig. 2. Impurities of quinazoline-4(3H)-one



Scheme 3. Processes to form **3**



Scheme 4. Process to prepare chloroquinazoline **4**

chloride/dimethylformamide. Both procedures used dichloromethane as solvent and required 20 h reaction time for complete conversion of **2**. Observed issues with these protocols prevented further development.

$C_2O_2Cl_2$/DMF: the reaction mixture separated into two phases, a highly fluid one, and very viscous mass that stuck to the stirrer and the reactor wall, rendering the procedure impractical on large scale. The reason for this inhomogeneity of the reaction mass is the formation of the Vilsmeier salt (chloromethylenedimethylammonium chloride) which is insoluble in dichloromethane.

$SOCl_2$/DMF: in the course of the reaction an unstirrable gel-like mass with intense foaming was observed. In addition traces of dimethylcarbamoyl chloride (DMCC) were detected in the reaction mixture. Since DMCC is a known animal carcinogen and a potential human carcinogen [12] monitoring during the process at the level of only a few parts per billion would be mandatory.

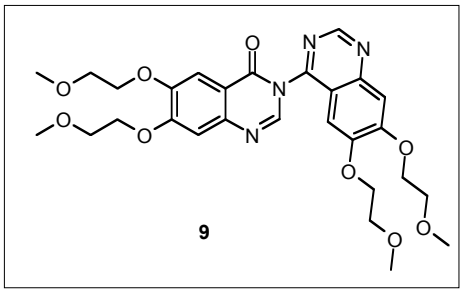


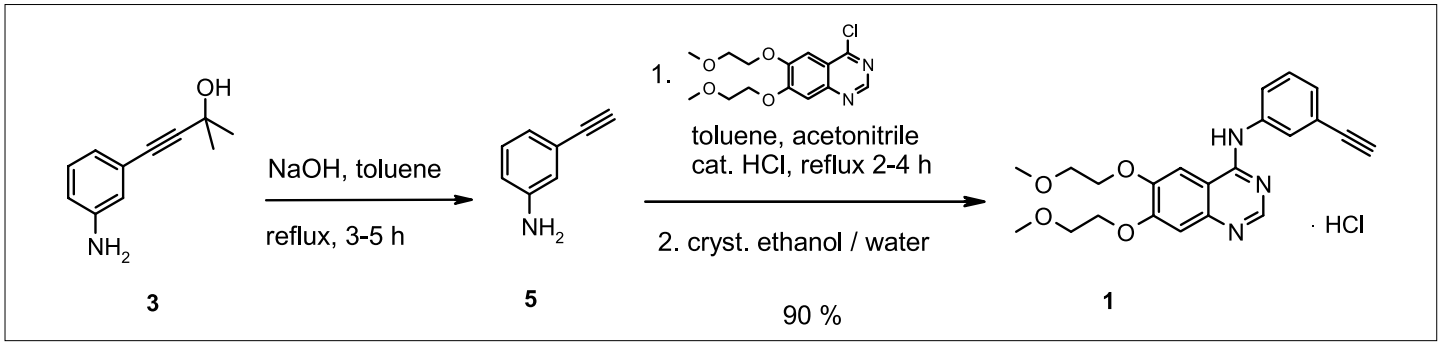
Fig. 3. Impurity of chloroquinazoline

Another common reagent often used to perform the chlorodehydroxylation of quinazoline-4(3H)-ones is phosphorous oxychloride ($POCl_3$) [13]. Very mild conditions were found that combined $POCl_3$ with DMF in dichloromethane as solvent. After 2–4 h reflux, conversion was complete (<2% of **2**). As expected no DMCC was detected. The reaction mixture was diluted with precooled water and the pH adjusted to 1.0 by adding aqueous NaOH solution, which allowed separation of unreacted **2** in the first extraction step. In the second extraction with water, a pH of 6–7 was adjusted by using a saturated bicarbonate solution. After phase separation the dichloromethane layer was washed salt-free with water. Crystallization of **4** was accomplished by adding *tert*-butyl methylether (TBME) to the concentrated, heated solution of **4** in dichloromethane, and subsequent cooling to –10 °C as shown in Scheme 4.

Compound **4** was obtained in high purity. Impurities were only observed in traces (<0.10%). Beside **2** the other impurity was identified as **9** by synthesis and NMR and IR spectroscopy (Fig. 3). Neither compound was detected in erlotinib.

Step 2: Deprotection of Aminophenylbutinol (3)

Aminophenylbutinol (**3**) was converted to ethinylphenylamine (**5**) by heating in toluene with sodium hydroxide pellets (Scheme 5). Liberated acetone was distilled off with toluene to achieve almost complete conversion of **3** (<0.1% area). This was important to avoid the presence of an impurity in erlotinib. Unreacted **3** also coupled with **4** to yield a compound that still carried the protection on the triple bond, which was difficult to remove in the final purification of erlotinib. Work-up of the deprotection reaction was done by adding water to dissolve sodium hydroxide, and separation of the water layer from the toluene layer. Compound **5** was not further isolated but used as toluene solution. The small amount of impurities formed by acetone in an aldol condensation (1–2% 2,5-dimethyl-hepta-2,5-dien-4-one) did not affect the quality of the final product.



Scheme 5. Deprotection of aminophenylbutinol **3** and coupling of **5** and **4**, followed by crystallization

Step 3: Coupling of 5 and 4 Followed by Crystallization

To couple choroquinazoline (**4**) with ethinylphenylamine (**5**), **4** was suspended in acetonitrile and **5** in toluene solution was added. A catalytic amount of hydrochloric acid accelerated the reaction, after 2–4 h heating **4** was consumed (<0.1 % area) – also shown in Scheme 5.

Erlotinib had a low solubility in the reaction mixture, after cooling to 20–30 °C crystalline erlotinib crude was filtered off, dried, and already obtained in high purity (99.9%).

The final crystallization of **1** served to adjust the solid-state properties for optimal processing of **1** to manufacture tablets. From three different polymorphs the thermodynamically most stable form A was chosen, obtained reliably by seeding a hot solution of **1** in an ethanol/water mixture with crystals of form A. Crystal growth was controlled by applying a temperature gradient when the mixture was cooled.

Beside the polymorphic form, a certain particle size and particle size distribution was important to run a robust process in tablet preparation.

Since safety of the processes is the most important criteria to assess whether a procedure could be scaled-up from laboratory to large plant equipment, all synthetic steps were carefully investigated with regard to the thermal and reactive hazards according to standards used in the fine chemicals industry [14]. The above-described conditions to perform the synthesis of erlotinib bear no safety issues.

The waste streams of the synthesis were also investigated. The wastewater streams were biodegradable, and therefore suitable for discharge into the chemical wastewater treatment plant. Organic solvents could be regenerated or safely incinerated.

Conclusion

Even with the short synthesis of erlotinib, important aspects of chemical process development in pharmaceutical industry could be addressed [15]: How to ensure a product of high quality? How to develop safe processes regarding thermal hazards, and toxic hazards? How to avoid environmental burden?

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