Synthetic Strategies in the Preparation of Osimertinib

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Abstract. Osimertinib is an oral small molecule epidermal growth factor receptor tyrosine kinase inhibitor and is mainly used clinically for the treatment of lung cancer. Lung cancer, as the cancer with the highest incidence and mortality rate in China, has a huge market demand for therapeutic drugs. However, the traditional synthetic process route has a low yield and serious pollution. In recent years, the development of new synthetic routes has become a research hotspot. This article mainly focuses on the synthesis of Osimertinib, with an emphasis on three aspects. This study examines the different synthetic routes of Osimertinib, comparing their efficiency and applicability. It also explores the novel catalysts which can be used in the synthesis process. Moreover, the derivatives of Osimertinib are also explored. By evaluating each synthetic route, this work aims to offer a strategic roadmap for future research endeavors and provide new ideas for the research on the synthetic process of this drug.

Keywords: Osimertinib, organic synthesis, catalyst.

1. Introduction

Lung cancer has the highest incidence among malignant tumors in China, and it is also one of the cancers with the highest mortality rate. The development and optimization of its therapeutic drugs has become a core challenge in the field of clinical medicine and medicinal chemistry. Traditional chemotherapy regimens, due to their limitations such as significant toxic and side effects and the tendency to induce drug resistance, are difficult to meet clinical needs. There is an urgent need to develop efficient and low-toxicity targeted therapy strategies. Therefore, exploring targeted drugs with low toxicity and side effects has become the focus of research.

Osimertinib, as a key targeted drug for lung cancer, has become the focus of the research field. Epidermal growth factor receptor (EGFR) mutation is an important target of lung cancer, so targeted therapeutic drugs for EGFR mutation are constantly developing. Osimertinib, as a third-generation tyrosine kinase inhibitor acting on EGDR, was approved by the U.S. Food and Drug Administration (FDA) in 2020 as an adjuvant targeted therapy drug after surgery for stage II-III patients with EGFR mutations, and it has shown excellent efficacy in the treatment of drug resistance caused by such mutations. The core mechanism of action is that the acrylamide portion of Osimertinib can form a covalent bond with the EGFR through addition reactions and undergo irreversible binding, thereby permanently inhibiting the activity of tyrosine kinase [1]. This study focuses on the initial synthesis method of Osimertinib, the improvement strategies of the synthesis method, and the synthesis methods of this type of derivatives, with the expectation of providing useful references for the further research and development of this drug.

2. The Synthesis of Osimertinib

2.1. Initial Synthetic Route

The initial synthetic method of Osimertinib was developed by AstraZeneca [2]. The specific reaction route is shown in Fig. 1. Firstly, the nucleophilic substitution reaction of indole and 2, 4-dichloropyrimidine is carried out to obtain intermediate 1, and intermediate 1 undergoes a methylation reaction to generate intermediate 2. Then 4-fluoro-2-methoxyaniline is nitrated to produce 4-fluoro-2-methoxy-5-nitroaniline. Next, intermediate 2 undergoes a nucleophilic aromatic substitution reaction with 4-fluoro-2-methoxy-5-nitroaniline to generate intermediate 3. Subsequently, in the polar aprotic solvent N, N-dimethylacetamide (DMA), intermediate 3 undergoes a nucleophilic substitution reaction with N, N, N'-trimethylethane-1, 2-diamine, replacing the halogen atoms on the benzene ring in the intermediate to form intermediate 4. Subsequently, in ethanol and water solvents, iron and ammonium chloride were used as reducing agents to reduce the nitro group in intermediate 4 to the amino group to obtain intermediate 5. Finally, acryloyl chloride reacts with the amino group to obtain the final product Osimertinib. The specific reaction route displays a total yield of approximately 39% and it has a general yield of 6%.

This synthetic route involves a total of 7 reactions. The final yield is only 6%, with low atomic economy and serious waste of raw materials. Among them, when intermediate 3 undergoes nucleophilic substitution to form intermediate 4, microwave heating is required. The purification of multiple intermediates needs to be carried out sequentially through ion exchange chromatography and column chromatography. The reaction conditions are rather harsh and the consumption time is long, which is not suitable for large-scale production. Furthermore, in terms of the usage of reaction reagents, the use of tetrahydrofuran (THF) during the methylation process is prone to form peroxides, posing certain safety risks. Furthermore, acryloyl chloride is used in the synthesis of the final compound. Acryloyl chloride is a highly toxic and corrosive reagent that may produce toxic by-products such as HCl. When iron and ammonium chloride are used as reduction systems for nitro reduction, it may not only cause environmental pollution but also lead to partial or incomplete reduction, such as the formation of azo compounds. These shortcomings further limit the large-scale application of this method.

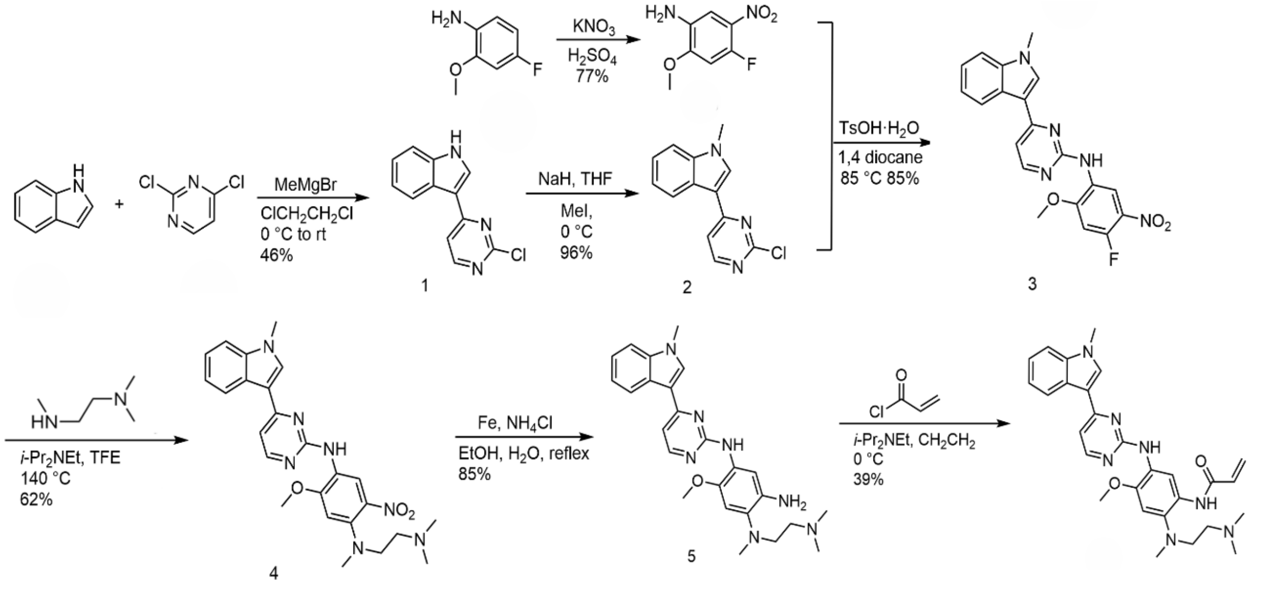

Figure 1. Initial synthetic route [2] (picture draw credit: original)

2.2. Improved Synthetic Route

2.2.1. Boc protection

In 2015, a synthetic improvement route was proposed by Liu et al [3]. The specific reaction route is shown in Fig. 2. Firstly, applying the idea of retrosynthetic analysis, Osimertinib can be broken into two key fragments, namely 3-(2-chloropyrimidin-4-yl)-1-methyl-1H-indole and trisubstituted N-aryl-acrylamide. This scheme focuses on optimizing the synthetic optimization route of trisubstituted N-aryl-acrylamide. This route takes 4-fluoro-2-methoxy-1-nitrobenzene as the starting material. Firstly, the nitro group is reduced to obtain the amine, and then the intermediate 6 is obtained through nitration reaction. Subsequently, the amino group is protected by di-tert-butyl pyro carbonate (Boc_2O). Since amino protection can reduce the electron-donating effect, intermediate 6 is more likely to undergo nucleophilic substitution to form intermediate 7. Then, by nucleophilic substitution of the fluorine group with N, N, N'-trimethylethane-1,2-diamine, intermediate 8 is obtained. The nitro group was reduced by Pd/C catalyst to obtain aromatic amine, and then acylation was carried out to obtain intermediate 9. After removing the Boc-group, trisubstituted N-aryl-acrylamide can be formed in this step. Finally, 3-(2-chloropyrimidin-4-yl)-1-methyl-1H-indole and trisubstituted N-aryl-acrylamide are reacted in the presence of 4-methylbenzenesulfonic acid hydrate at 50-65℃ for 3-8 h, and Osimertinib could be obtained. The total yield of the reaction was 65.4%.

The yield of this reaction route is relatively high, and the total yield has been significantly improved compared with the original route. For the step of obtaining intermediate 9 from Intermediate 8 by reaction, the method of hydrogenation reduction with Pb/C catalyst is adopted, which avoids the use of iron and ammonium chloride in the original research route, eliminates the complex operation of post-treatment with ion exchange resin after the reaction, and increases the yield of this step from 85% in the original research route to 95%. At the same time, it reduces the high-temperature requirement of the original research route for this step. It is conducive to industrial production. However, due to the protection strategy of Boc-protection, the synthetic route becomes more complex and cumbersome, and the economy is poor. Moreover, the success rate of using and removing the Boc-group is relatively low, and the demand for the dosage of di-tert-butyl pyro carbonate is very precise, otherwise, by-products are very likely to be generated, which will have a significant impact on the subsequent purification.

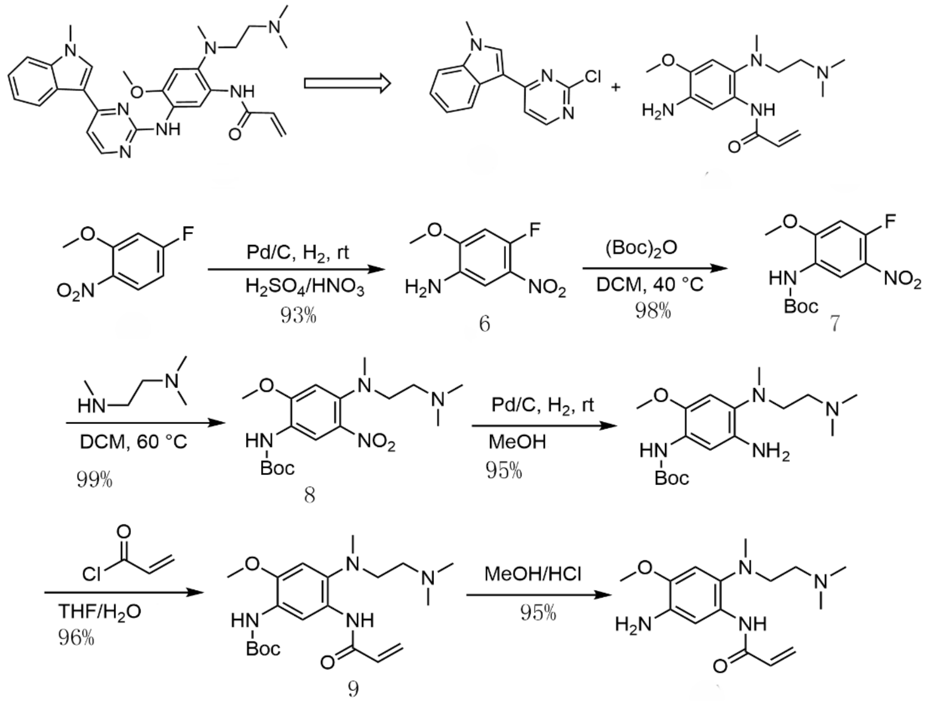

Figure 2. Boc protection synthetic route [3] (picture draw credit: original)

2.2.2. Convergent synthetic route

A new method for synthesizing Osimertinib using a convergent synthetic route was proposed by Zhu et al [4]. As Using 4-fluoro-2-methoxyaniline as the raw material, the raw material is first subjected to nitration reaction to obtain intermediate 6 as shown in Fig. 3. Subsequently, cyanamide is used to induce guanidination reaction in intermediate 6, and then nucleophilic substitution is carried out with N, N, N'-trimethylethane-1,2-diamine to obtain intermediate 10. The 1-(1-Methyl-1H-indol-3-yl) ethan-1-one is methylated with dimethyl sulfuric and then subject to the DMF-DMA reaction to obtain intermediate 11. Then intermediate 10 and intermediate 11 undergo a cyclization. After being heated at 100℃ for 12 h, intermediate 12 is obtained. Finally, intermediate 12 undergoes catalytic hydrogenation under the catalysis of Raney Ni to reduce the nitro group, and then it undergoes amidation reaction with acryloyl chloride to finally obtain Osimertinib. The total yield of the reaction is 40.4%.

This route adopts the convergent synthesis method, effectively avoiding the problems of intermediate degradation and low efficiency caused by long steps in linear synthesis reactions. Using Raney Ni as the catalyst, the reaction selectivity is good, which can avoid the occurrence of side reactions, such as the reduction of indole rings, and the product purity is high. The HPLC purity of Osimertinib after recrystallization is as high as 99.1%, which is sufficient to meet the purity requirements of industry.

Based on this route, in 2021, Pinelopi Voulgari et al. proposed a synthetic method for optimizing this route [5]. This method uses intermediate 6 as the raw material and uses iodomethane instead of dimethyl sulfuric in the methylation step. The subsequent synthetic routes of intermediate 11 and the final product are basically the same. However, when intermediate 10 reacts with intermediate 11, the compound providing alkaline conditions is changed from sodium hydroxide to potassium carbonate. It should be noted that the Raney Ni catalyst was replaced with a Pd/C catalyst for the catalytic hydrogenation. The total yield of this reaction is 68%. The specific reaction route is shown in Fig. 3. In this figure, condition (1) marks the original reaction conditions of the convergent reaction, while condition (2) corresponds to the optimized conditions.

Compared with the low yield of the traditional route, the final total yield of this reaction is 68%, which greatly improves the total yield of the reaction. In traditional processes, the guanidination reaction of intermediate 6 is carried out using cyanamide, water, ethanol and hydrochloric acid, with a reaction duration of up to 24 h. After optimization, this route uses an excess of cyanide as the solvent, enabling the quantitative generation of guanidinium and shortening the reaction time to 2 hours. The use of relatively mild reagents such as iodomethane and potassium carbonate reduces high-temperature and highly toxic reagents, making the reaction safer and more environmentally friendly. The drawbacks of this route are equally obvious. Due to the excessive use of cyanide, although the yield is increased and the reaction time is shortened, but it will increase the burden of separation and the environment during industrial scale-up. Moreover, the synthesis reaction of intermediate 10 and intermediate 11 still takes as long as 12 h, which affects the industrial production efficiency. Although the optimized synthetic route reduces the usage of highly toxic reagents, reagents such as DMF are still inevitable, and environmental protection issues still exist.

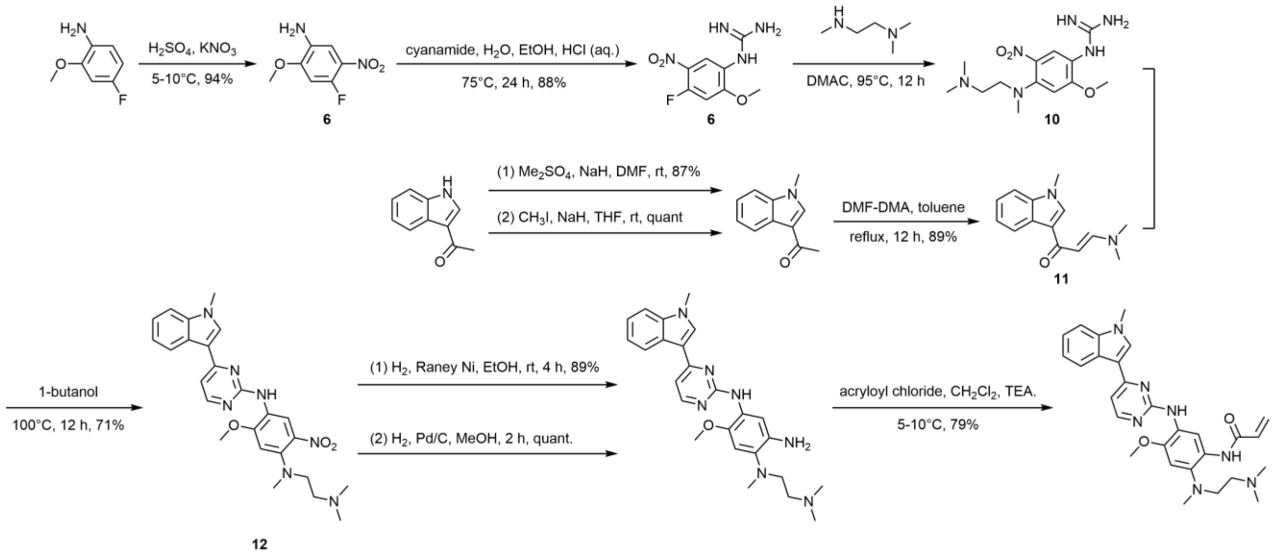

Figure 3. Convergent synthetic route [4, 5] (picture draw credit: original)

3. The Application of New Catalysts

In recent years, with the deepening of the concept of green chemistry and the development of precise catalytic technology, the key steps in the synthesis of Osimertinib have gradually abandoned traditional highly polluting reagents and instead relied on new catalytic systems to achieve efficient and low-toxicity conversion. Various new types of catalysts have also been frequently applied in the synthesis of Osimertinib. Among them, the more representative one is the method of reducing the nitro group in intermediate 4 to an amino group using a graphene-palladium catalyst to generate intermediate 5 [6]. The reducing agent of this reaction is hydrogen. Under conditions of 14-40°C, the reaction can occur when the aqueous solution of the reactants is illuminated with an LED light of 400-700nm. This reaction only takes 15 to 30 min with a yield of over 95%. It can be operated under normal temperature and pressure, making it easy to expand production in industry. The catalyst can be recycled more than five times, effectively reducing production costs. A method to react intermediate 5 with acrylic acid to generate Osimertinib using molecular sieve catalyst was also proposed by Cui Zhaohua et al [7]. The reaction was carried out by microwave heating in an alcohol solvent using one type of HY zeolite, 13X-APG zeolite or 10X zeolite. This reaction process has significant advantages. Acrylic acid is used to replace the highly toxic acryloyl chloride in the original route, and the final yield can reach up to 97.9%, achieving a green and efficient reaction in this step.

4. Synthesis of Derivatives

Although Osimertinib has a remarkable therapeutic effect, its cardiotoxicity problem restricts its clinical application. To this end, researchers have developed novel derivatives through structural modification to balance the targeting activity and safety. Gao et al. proposed five derivatives based on Osimertinib to reduce toxicity and improve selectivity [8]. As shown in Fig. 4, these five derivatives are respectively one N-oxide derivative, two fluorinated derivatives, and two fluorinated N-oxide derivatives. Firstly, N-oxide derivative, whose purpose is to increase solubility and bioavailability, and to reduce the N-demethylation metabolic pathway in the body. The reactants of this reaction are meta-chloroperoxybenzoic acid (m-CPBA) and Osimertinib. As an oxidizing agent, m-CPBA can selectively oxidize tertiary amines to form N-oxides (compound 14) in this reaction. Secondly, fluorinated derivatives can be obtained by adding fluorine atoms to the indole ring of Osimertinib. Introducing fluorine atoms onto the indole ring aims to enhance molecular stability and improve its binding ability with EGFR. 5-fluoro-1-methyl-1H-indole and 7-fluoro-1-methyl-1H-indole are used as starting materials to undergo aromatic nucleophilic substitution reactions with the Osimertinib mother nucleus under alkaline conditions, forming 5-fluoro-1-methyl-1H-indole derivative of Osimertinib (compound 15) and 7-fluoro-1-methyl-1H-indole derivative of Osimertinib (compound 16). In addition, researchers also attempted to obtain double-modified derivatives by superimposing fluorination and N-oxidation double modification strategies. It combines two strategies to enhance the anti-cancer activity and selectivity of the derivatives. Using compound 15 and compound 16, the tertiary amines were oxidized by the same m-CPBA oxidation method as compound 14 to form N-oxides (compound 17 and compound 18). Through experiments such as in vitro cell proliferation inhibition experiments and in vivo mouse transplanted tumor models, it was found that N-oxide derivative (compound 14) enhances the anti-tumor activity and metabolic stability in vivo while improving bioavailability, while fluorinated derivative and fluorinated N-oxide derivative were found in the experiments to possibly reduce the selectivity of the drug.

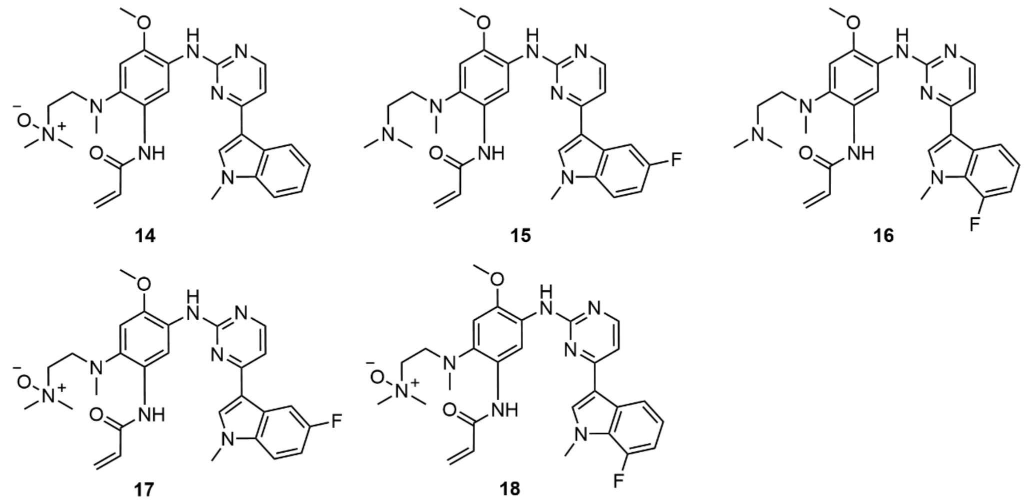

Figure 4. Synthesis of derivatives [8] (picture draw credit: original)

5. Conclusion

This work summarizes the original research route of Osimertinib, three improved routes, the use of two different catalysts, and the synthesis of five derivatives. Each reaction has, to a certain extent, improved various problems of the original research route, such as low reaction yield and the reaction route not conforming to green chemistry. However, each route still has certain problems. The Boc protection method has an overly long reaction route, the convergent synthetic route has a relatively low yield, and its improved method has a longer reaction time. Although the use of new catalysts can better solve the above problems, they can only be applied in certain specific reactions and have certain limitations. The synthesis of its derivatives provides a new idea for future improved synthetic routes. In conclusion, in future research on the synthesis of Osimertinib, efforts should be made to actively seek and utilize various efficient and environmentally friendly new catalysts, and explore more effective Osimertinib derivatives.

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