Jestr

Journal of Engineering Science and Technology Review 15 (3) (2022) 55 - 62

JOURNAL OF
Engineering Science and Technology Review

Research Article

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Design and Optimization of Synthetic Process for Afatinib Dimaleate

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Received 19 May 2022; Accepted 18 July 2022

Abstract

The growth and proliferation of tumor cells can be effectively inhibited by Afatinib dimaleate, which is a second-generation targeted drug, inducing an excellent inhibitory effect on various tumors. Consequently, the synthesis methods and quality control have gained considerable attention. This study analyzed and compared the existing synthesis methods and routes, particularly the problems in the selection of starting materials, yield, impurities, and process control. The limitations of the existing synthetic routes and the insufficient synthetic control conditions were studied by innovating synthetic routes (e.g., raw materials, reaction types, added method, reaction sequences, and catalysts), optimizing process conditions (e.g., molar ratio, sequence of addition material and reactions, reaction temperature, solvent, reaction time, and purification method), and employing quality control to improve the quality and yield of Afatinib dimaleate. Additionally, compatible synthetic route was proposed based on literature review, laboratory test, and pilot-scale experiment for industrial production, and the influencing factors and reaction conditions were optimized. The results show that Afatinib dimaleate is synthesized from 4-fluoro-2-aminobenzoic acid after a six-step reaction, including cyclization, nitration, substitution, reduction, condensation, and salification, with a total yield of 41.60% and 99.48% content of the related substances of the product. The structure of product was confirmed by ^{1}HNMR, ^{13}CNMR, MS, and IR. The design of the synthetic route is reasonable, because it does not require column chromatography, it involves simple post-treatment processes, it is easy to control, and the process yield is stable. The proposed method is advantageous for industrial production and provides a good reference for the design, optimization, and quality evaluation of the synthetic route of Afatinib dimaleate.

Keywords: Afatinib dimaleate, Synthetic route, 4–fluoro-2-amino benzoic acid

1. Introduction

Lung cancer is the most common malignant tumor, and its incidence rate and mortality increase rapidly, which seriously endangers human health. Molecular targeted drugs are one of the best anticancer drugs so far, and these drugs can effectively inhibit the growth and proliferation of tumor cells. Advanced non-small cell lung cancer (NSCLC) is a study hotspot of new anti-tumor drugs, and many innovative drugs are available. Among these drugs, Afatinib[1-3] is a second-generation targeted drug, which is a powerful and irreversible dual inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor erbB-2 (HER2) tyrosine kinase, that is developed by Boehringer Ingelheim, Germany. As a new generation of oral small molecule tyrosine kinase inhibitor (TKI) and the first irreversible ErbB family blocker, it can act on the entire ErbB family, including EGFR. Unlike the first-generation reversible EGFR TKI, Afatinib irreversibly binds to EGFR to block the signal pathway of cancer cells and inhibit tumor growth.

Afatinib dimaleate is chemically known as (Z)-but-2-enedioic acid;(E)-N-[4-(3-chloro-4-fluoroanilino)-7-[(3S)-oxolan-3-yl]oxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide. It has a molecular formula of $C_{24}H_{25}ClFN_5O_3 \cdot 2C_4H_6O_4$ and molecular weight of 718.083g/mol. It appears as a white to brownish yellow powder, and it is soluble in water. It was listed in the United States in July 2013 and has been approved in more than 70 countries around the world for the treatment of NSCLC patients with EGFR mutations. With the expansion of the application scope and population of afatinib, the demand for drugs has also increased. The research on the optimization of drug synthesis process and quality control has also become a hot spot. Many processes are involved in the synthesis of Afatinib dimaleate. Based on the route developed by the original research company, afatinib is prepared from 2-amino-4-halogenated-benzoic acid through cyclization, nitration, two-step substitution, reduction, and condensation. The shortcomings of the existing synthetic routes of afatinib dimaleate mainly include reaction steps, synthetic raw materials, ratio, reaction type, reaction sequence, reaction solvent, reaction time, purification method, yield and selectivity, economic cost, and impurity control. The existing synthetic methods and routes have many deficiencies. The development, innovation, and optimization of the synthetic routes and process conditions of Afatinib dimaleate need to be determined. The development and application of the synthetic methods are conducive to the simplification of industrial production steps, mild reaction conditions, simple purification methods, high yield, and high product purity.

At present, scholars have extensively studied the synthetic route of Afatinib[4-12], performed quality control, , and optimized the process conditions. Sun Bing et al. used 4-(3-chloro-4-fluorophenylamino)-6-nitro-7-fluoroquinazoline as the starting material and performed nucleophilic

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doi:10.25103/jestr.153.07

substitution, reduction, amidation, and salification to obtain Afatinib dimaleate. However, the structure of the starting material is relatively complex and easily produces impurities, and the yield is low. Yu Qian et al. used 6-amino-7-hydroxy-3,4-dihydroquinazolin-4-one and acetyl chloride as starting materials and carried out acetylation, chlorination, hydrolysis, Mitsunobu, acylation, and condensation to obtain afatinib maleate with low yield and high production cost. Changmao Biochemical Engineering Co., Ltd. improved and optimized the chlorination, amination, etherification, and reduction reactions in the synthetic process of Afatinib and improved the yield and purity of the product. The process operation is simplified, the production cost is reduced, and the post-treatment is convenient, resulting in high practicability. However, it has not applied for patent protection. Li Wenqian et al. used 2-amino-4-chlorobenzoic acid as raw material. After cyclization, nitration, chlorination, and amination, the key compound 4-[(3-chloro-4-fluorophenyl) amino]-6-nitro-7-[(s)-tetrahydrofuran-3-yloxy]-quinazoline was prepared by one pot two-step method. Afatinib was synthesized by reduction, amidation, and Horner-Wadsworth-Emmons reaction. Many impurities were obtained, and the structure was not clear. Tu Yuanbiao and others used 4-fluoro-2-aminobenzoic acid and formamidine acetate as starting materials for the preparation of Afatinib by cyclization, nitration, chlorination, condensation, and nitroreduction, followed by condensation and Wittig-hornor reaction. However, the synthetic route has high cost and low yield. In the preparation method of Suzhou Mingrui Pharmaceutical Technology Co., Ltd. and Xu Xuenong afatinib, 6-amino-7-hydroxy-3,4-dihydroquinazolin-4-one and (s)-3-hydroxytetrahydrofuran undergo etherification reaction to produce 6-amino-7-[(s)-(tetrahydrofuran-3-yl) oxy]-3,4-dihydroquinazolin-4-one(III). Compound III is acylated with 4-(n,N-dimethylamino)-2-ene-butyryl chloride to produce 6-([4-(n,N-dimethylamino)-1-oxo-2-butene-1-yl] amino)-7-[(s)-(tetrahydrofuran-3-yl)oxy]-3, 4-dihydroquinazolin-4-one (IV). Compound (IV) is condensed with 4-fluoro-3-chloroaniline to obtain Afatinib. The preparation method has the advantages of simple and economic process and environmental protection, making it suitable for industrial amplification. However, the production cost is high, and it easily produces many impurities. The process for the preparation of aminocrotonylamino substituted quinazoline derivates in WO2007085638A1 describes the synthesis of Afatinib dimaleate, which is the original discovery route. The raw materials used in this route have a simple structure and are easy to obtain, but the subsequently introduced groups are large and have many impurities. However, the patent of this synthetic method route is still in the protection period. At the same time, patent protection is avoided by using this route as a reference route only and avoiding design and innovation. The synthetic route developed by US20050085495A1 /WO20050037824A2 uses 2-amino-4-chlorobenzoic acid as raw material, which is subjected to cyclization, nitration, halogenation, substitution, reduction, acylation, amination, and salification. This process has a long reaction route, low yield, and high cost. For the WO2007085638A1 patent, 7-chloro-6-nitroquinazolin-4 (3H)-one is used as raw material. The cost and impurity content of the six-step reaction are high, and the total yield is less than 40%. For the WO2014183560A1 patent, methyl 3-amino-4-hydroxybenzoate is used as raw material. The cost of production of the seven-step reaction is high, and the total yield is approximately 37%. For the WO2014180271A1 patent, 4-hydroxybenzonitrile is used as raw material. The total yield of the eight-step reaction is low, and many impurities are produced.

The above results mainly aimed to determine the synthetic route of Afatinib dimaleate, but limited studies have on the optimization, innovation and quality control of its synthetic route, especially the study on the innovation of starting materials, control of reaction influencing factors, purification methods, and reaction sequence. Considering the influence of patent protection, limited studies have focused on generic drugs. In the present study, based on literature review, laboratory test, and pilot scale experiment, we have established the quality control and optimization of influencing factors, the synthetic route, optimized reaction conditions, and purification methods suitable for industrial production of Afatinib dimaleate. Starting from the innovative and designed synthetic route, the reaction sequence, reaction conditions and purification methods are discussed, and the synthetic route and the proposed methods of Afatinib dimaleate are established. This study provides basis for the optimization and test of synthesis control factors.

The rest of this study is organized as follows. The second section describes the synthetic route of Afatinib dimaleate with 4-fluoro-2-aminobenzoic acid as the starting material and constructs the control method of the synthetic process. In the third section, after comparison and optimization, the synthetic route of Afatinib dimaleate was selected, and the material ratio and reaction time of cyclization reaction were optimized in terms of starting materials, reaction steps, operability of production process, and cost analysis. The optimization of reduction reaction conditions and the improvement of post-treatment methods have innovated the synthetic route and operation method of Afatinib dimaleate. The last section summarizes this study and gives the relevant conclusions.

2. Materials and methods

2.1 Instruments and reagents

Nicolet 170 SX type infrared spectrometer (KBr tablet);BRUKER AV-500 nuclear magnetic resonance instrument (DMSO-d6+TFA-d); AGILENT 1200 LC-MSD mass spectrometer; Elementar Vario EL Ⅲ type element analyzer. Reactor is show in Fig.1. The others analytical reagents of analysis and synthesis are used.

Fig. 1. Reactor

2.2 Selection and design of synthetic route

Based on the existing synthetic routes [12-20], the process control parameters were subjected to laboratory screening and optimization, and a synthetic route with industrialization production was determined. 4-Fluoro-2-aminobenzoic acid reacts with formamidine acetate was used to synthesize

compound B; compound B was used to synthesize compound C by nitration; compound C reacted with 3-chloro-4-fluoroaniline to synthesize compound D; compound D reacted with 3-hydroxytetrahydrofuran to synthesize compound E; compound E was used to synthesize compound F under the catalysis of Pd/C; compound F reacted with crotonic acid to synthesize compound A; compound A reacted with methylamine to synthesize Afatinib dimaleate, which is the refined product of Afatinib. The proposed route is shown in Fig. 2.

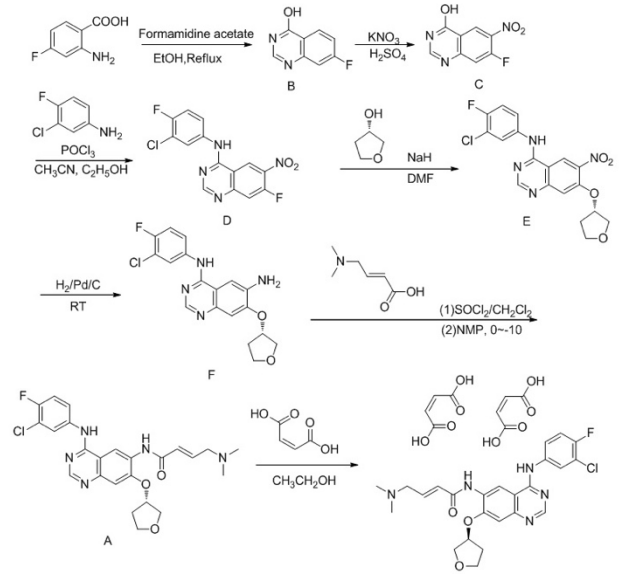


Fig. 2. Synthetic Route of Afatinib dimaleate

2.3 Steps and control of synthesis processes

(1) Synthesis of compound B

In total, 100 g of 4-fluoro-2-aminobenzoic acid (644.64 mmol) and 1.2 L of anhydrous ethanol were charged into a reactor, the mixture was stirred for 10min at room temperature. A total of 387 g formamidine acetate (6,446.4 mmol, 4-fluoro-2-aminobenzoic acid:formamidine acetate =1:10 (mol/mol)) was added into the mixture, which is heated until refluxed for 12h after completion of the reaction, as indicated by TLC results. When the reaction was completed, the reaction solution was cooled to room temperature and added with 1.5 L of purified water. When a large amount of solid was produced, the solution was stirred for 1 h. Solids by vacuum filtration were washed with water, and the wet solid was dried at 50 °C for 10 h, yielding 104 g of gray white solid compound B (633.62 mmol), with a mass yield of 98.29%. Compound B is show in Fig.3.

Fig. 3. Compound B

(2) Synthesis of compound C

Approximately 1.5 L of concentrated sulfuric acid was added into a reactor, and the mixture was stirred in an ice bath for 20 min, added with 100 g (609.25 mmol) of compound B and 132.2g potassium nitrate (1,218.5 mmol, compound B: KNO_3 =1:2,(mol/mol)) by batch, and stirred in an ice bath for 1 h. The solution was heated to room temperature and stirred for 10 h. The reaction was monitored by TLC, and then poured into ice water after completion. The temperature was kept at 0 °C until a large amount of solid was separated out. The solution was processed by vacuum filtration to obtain the solid. The solid mixed with 2.2 L of ethyl acetate was stirred for 1 h. Then, the solid obtained by vacuum filtration was washed with water and dried by blasting at 50 °C, yielding 112 g of light yellow solid (compound C, 535.54 mmol) with a mass yield of 87.90%. Compound C is show in Fig.4.

Fig. 4. Compound C

(3) Synthesis of compound D

Approximately 90 g (430.35 mmol) of compound C and 1 L of acetonitrile were added into the reactor. The mixture was stirred for 10 min at room temperature, and then slowly added with phosphorus oxychloride (602.49 mmol, compound C: phosphorus oxychloride =1:1.4 (mol/mol)) and triethylamine (602.49 mmol) by drops. The solution was continuously stirred at room temperature for 1 h when a large amount of white smoke was generated in the reaction system, and the reaction system was heated until refluxed for 12 h. The reaction was monitored by TLC, and the reaction solution was cooled to room temperature when the raw materials disappeared. 3-Chloro-4-fluoroaniline (516.42 mmol, compound C:3-chloro-4-fluoroaniline =1:1.2 (mol/mol)) was dissolved in 10 times anhydrous ethanol, and then added into the reaction mass. Then, the solution produced a large amount of yellow precipitate. Approximately 500 mL of water and 0.5 M liquor sodium hydroxide were added into the reactor to quench the reaction, the pH was adjusted to 8–9, and the solution was stirred at room temperature for 1 h. The solid obtained by vacuum filtration was washed with water and blast dried at 55 °C to furnish 126 g of yellow solid (compound D, 374.24 mmol) with mass yield of 86.96%. Compound D is show in Fig.5.

Fig. 5. Compound D

(4) Synthesis of compound E

In total, 30.6 g of 3-hydroxytetrahydrofuran (347.52 mmol, compound D:(s)-hydroxy-tetrahydrofuran =1:1.3 (mol/mol)) and 1 L of N,N-dimethylformamide (DMF) were added into the reactor, and the mixture was stirred at −10 °C for 30 min. Then, sodium hydride (401.00 mmol) was added to the solution by batch, and the mixture was stirred for 1 h at −10 °C. Approximately 90 g of compound D (267.32 mmol) was added into the reaction system, the temperature was maintained at −10 °C, the mixture was stirred for 2 h, and the reaction was monitored by TLC. When the reaction was finished, 2 L of purified water was added, and the reaction was stirred at 10 °C for 20 min. Liquor hydrochloric acid solution (2 N) was added to adjust the solution pH to 7−8. The reaction mass produced a large amount of solid orange precipitate under vacuum; 1.2 L of methanol was added, the mixture was stirred for 1 h, and the solid obtained via vacuum filtration was washed with water and blast dried at 50 °C, yielding 93 g of yellow solid (compound E, 229.75 mmol) with a mass yield of 85.95%. Compound E is show in Fig.6.

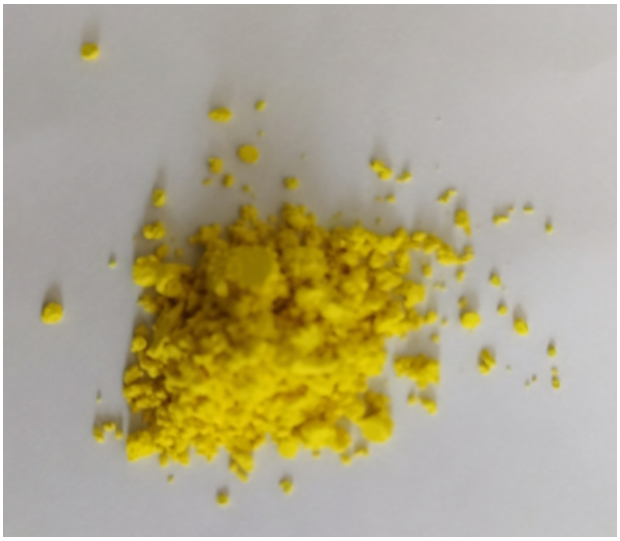


Fig.6. Compound E

(5) Synthesis of compound F

Approximately 80 g of compound E (197.64mmol), 1.2 Lof tetrahydrofuran, and 8 g Pd/C (19.76 mmol, compound E:Pd/C=1:0.1(mol/mol)) were added into the reactor. Hydrogen was passed into the solution, which was stirred at room temperature for 12 h. The completion of the reaction was monitored using TLC. The reaction solution was subjected to vacuum filtration when the raw materials disappeared to remove Pd/C. the reaction solution was concentrated and dried, 1.5 L of anhydrous methanol was mixed with the solution, and it was stirred of 1.5 h. The solid obtained by vacuum filtration was washed with water and dried at 45 °C under vacuum condition to obtain 64 g of white solid (compound F, 170.76 mmol) with a mass yield of 86.40%. Compound F is show in Fig.7.

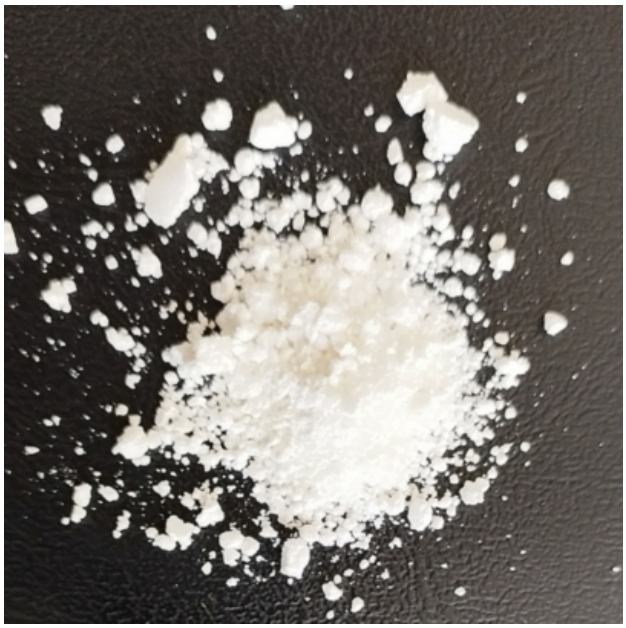


Fig.7. Compound F

(6)Synthesis of Product A

Approximately 41.4 g of dimethylaminocrotonic acid hydrochloride (320.18 mmol, compound F: dimethylaminocrotonic acid hydrochloride =1:2 (mol/mol)), 700 ml of dichloromethane and 4 ml of DMF were added into the reactor. The mixed solution was stirred at −10 °C for 30 min. Then, 38.1 g of thionyl chloride (320.18 mmol, compound F: thionyl chloride =1:2 (mol/mol)) was added dropwise into the reactor, and the temperature was controlled at −5 °C. The reaction solution was stirred for 10 min, heated up to 30 °C, and stirred for 1h. Next, the reaction solution was concentrated to dry, and 60 g of compound F (160.09 mmol) and 1 L of tetrahydrofuran were added into reactor. The solution was stirred at room temperature, and then 1.2 L N-methylpyrrolidonewas added the solution, which was stirred at −5 °C for 30 min. Dichlorosulfoxide tetrahydrofuran solution was added dropwise, and the temperature was kept at −5 °C for 3 hrs. Approximately 500 ml of purified water was added into the reaction solution for quenching reaction, and the solution was extracted with ethyl acetate for three times. The solution was concentrated to three fourths of the volume of ethyl acetate, the temperature was controlled at 0 °C, cyclohexane was added into the solution for crystallization, and the solid obtained by filtration was washed with water and dried

under vacuum at 45 °C to afford 58 g of white solid compound A (119.36 mmol) . The mass yield was 74.56%. The total yield was 41.60%. Compound A is show in Fig.8.

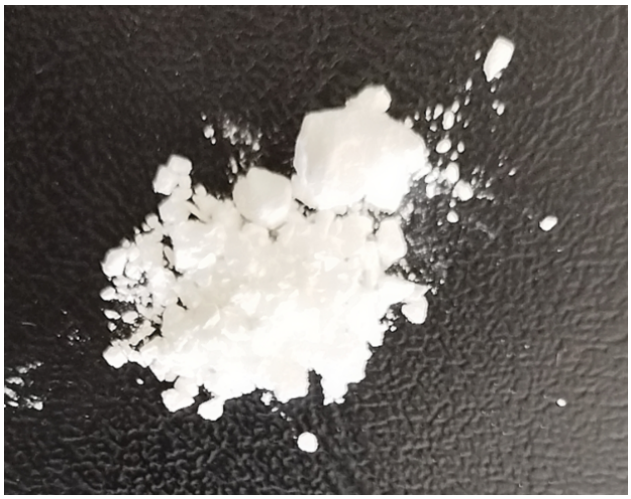


Fig.8. Compound A

(7) Salification of product A

Approximately 1,000 ml of anhydrous ethanol and 80 g of compound A were added into the reactor, the solution was stirred at 40–45 °C for 40 min, and the temperature was kept at 40 °C. Then, 40 g maleic acid and 300 ml of anhydrous ethanol were added into the solution, which was stirred at 50 °C for 15 min. The filtrate was kept at 40 °C and is stirred for 30 min. Then, the solution was cooled to 10 °C, stirred, and crystallized for 10 h. The solid was washed with 100 ml of anhydrous ethanol, and the obtained solid was vacuum-dried at 45 °C for 16 hrs to obtain 86 g of Afatinib dimaleate.

3 Result Analysis and Discussion

3.1 Selection of synthetic route

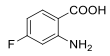
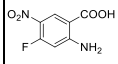
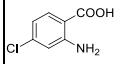
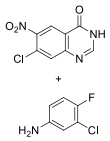
The production efficiency can be improved, and unnecessary losses can be reduced by considering simple operation, green process, cost saving, less environmental pollution, and production safety as the main indices for the route selection of drug synthesis process development. Afatinib dimaleate was synthesized from 4-fluoro-2-aminobenzoic acid by cyclization, nitration, substitution, reduction, and condensation in this study[12-20]. Potassium nitrate was used as the nitration reagent in the nitration process instead of using mixed acids (nitric acid and concentrated sulfuric acid) to avoid a large amount of waste acid. The post-treatment of the waste acid is troublesome, and the safety cannot be guaranteed in the production process. However, the use of potassium nitrate as the nitration reagent not only has mild conditions, but also has high selectivity of nitration products. In the process of (s)-hydroxy tetrahydrofuran substitution, sodium hydride is used as the dehydrogenation reagent, resulting in high yield and avoiding pungent smell caused by the metal base of tertbutyl alcohol. In the reduction reaction, this route uses the traditional H_2-Pd/C as the reduction reagent, which has the characteristics of short reaction time, high efficiency, green safety, no pollution, and simple post-treatment. Considering the difficulty of post-treatment in the condensation process, this study was aimed to optimize the conditions for the condensation process.

3.2 Optimization of synthesis conditions

(1)Selection of starting materials for synthetic route

The raw materials for the synthesis of Afatinib dimaleate should have a simple structure, low cost, good selectivity, and they should be easy to obtain and be conducive to the introduction of groups. The study compared the original materials, reaction steps, and operability of production process and performed a cost analysis of the following synthetic routes. The results are shown in the Table.1.

Table 1. Synthetic route comparison

SR	Optimal route	route1	route2	route3	Contrastive research
SM					structure, reactivity, selectivity, cost, accessibility, and ease of operation in the reaction process
RS	6	6	8	7	The fewer steps, the simpler the process, and the less impurities are introduced, which is conducive to the subsequent process
PO	better operability	Complex synthesis processes	and low purification yield	Complex synthetic processes and with many impurities	optimal route have better operability
PC	8-10w/kg	18-20w/kg	12-15w/kg	10-24w/kg	optimal route can saving cost

Note: Synthetic route(SR); Starting materials (SM) ; Reaction steps(RS); Processes operability(PO); Production costs(PC)

(2) Optimization synthesis process of compound B

4-Fluoro-2-aminobenzoic acid reacted with methyl acetate, and anhydrous ethanol was used as the solvent and heated up to reflux for approximately 12 h. Purified water was added dropwise after cooling to room temperature. Then, the solid was separated. The solution was stirred for 1 h and filtered, and the solid was washed. The ratio of 4-fluoro-2-aminobenzoic acid to methyl acetate affects the yield. By taking the yield as the assessment index, the ratio of reaction substances was optimized. The results are shown in the Fig.9. The ratio of reactants is 10 (mol/mol), and the reaction time is 12 h.

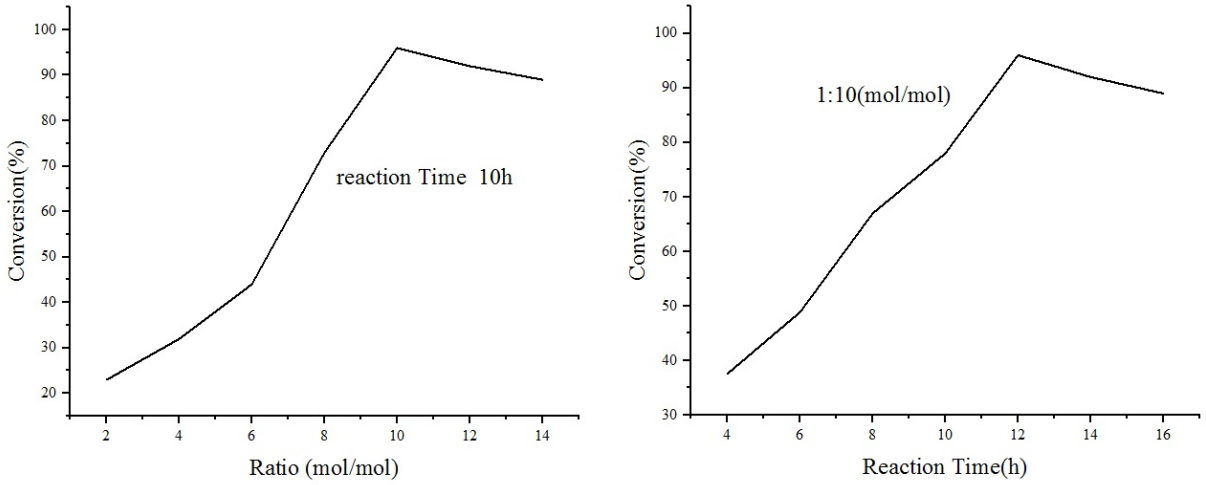


Fig.9. Effect of reaction time and conversion of compound B

(3) Selection of nitrification method for compound C

Two nitrating reagents, namely, H_2SO_4 - HNO_3 and KNO_3 - H_2SO_4, were investigated. The effects of molar ratio, impurity content, and reaction time of nitrating agent were studied. As shown in the Fig.10, the yield of nitration of KNO_3 - H_2SO_4 is higher than that of H_2SO_4 - HNO_3, and it decreased when the reaction time exceeded 12 h and slightly changed when the reactant ratio (mol) was 2. The optimal nitration conditions are as follows: nitration reagent, KNO_3 - H_2SO_4; reaction time, 12 h; and reactant ratio (mol) 2.

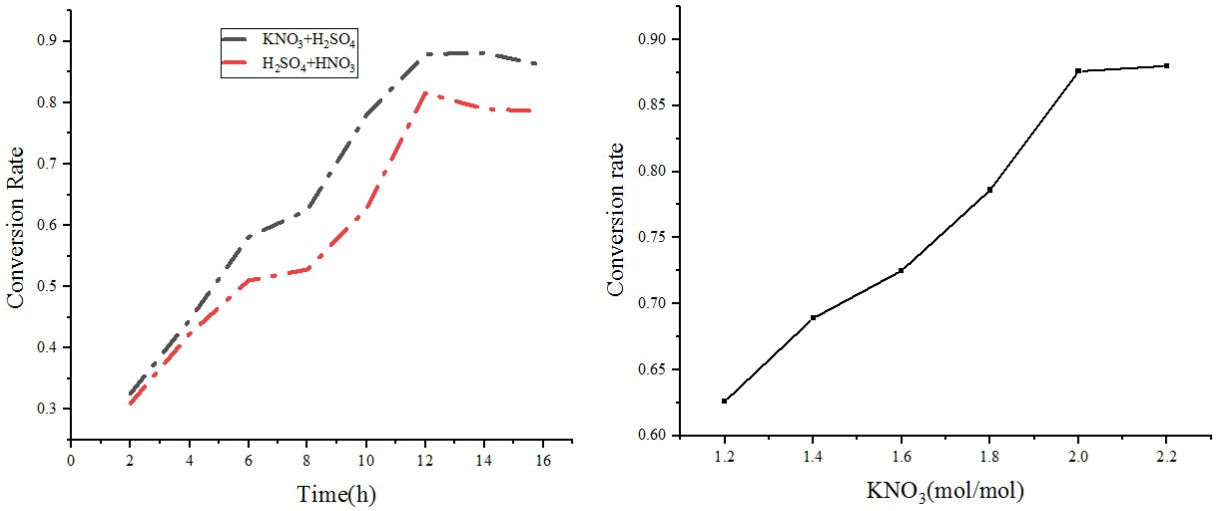


Fig.10. Selection of nitrification methods and influencing factors

(4) Control of the synthesis of compound E

Compound D was etherified with (s)-hydroxy-etrahydrofuran. The effects of temperature, catalyst, and its dosage on the reaction were studied. The optimization results are shown in Table.2. Under the optimized conditions of NaH-DMF, the reagent ratio (mol) was 1:1.5, the reaction time was 4 h, and the yield of the reaction was higher than 85%.

Table. 2. Optimization of control factors for etherification reaction

Catalyst	Reaction time (h)	Dosage of catalys (mol/mol)	Conversion(%)	Content (%)
NaH-DMF	2	1:1.5	68	78
t-BuOK-DMF	2	1:1.5	65	75
NaH-DMF	4	1:1.5	86	97
t-BuOK-DMF	4	1:1.5	82	90
NaH-DMF	6	1:1.5	78	89
t-BuOK-DMF	6	1:1.5	69	87

(5) Control reduction process of Compound F

The reduction methods include 10%Pd / C - H_2 , Fe-HCl, Fe / CH_3COOH , Raney / Ni - NH_4Cl , NaH-THF, and $NaBH_4$ - $NiCl_2$. The above methods were studied and compared with the results in the Table.3 and Fig.11, in which the reduction method of 10%Pd / C - H_2 is reliable, the reaction time is approximately 5 h, and the yield is the highest.

Table. 3. Effect of reducing agent on compound F

Reducing agent	Reaction time (h)	Results	Conversion (%)
10%Pd / C - H_2	4	The reaction liquid is black, the reaction is complete, and TCL impurity spots are relatively few	82
Fe/HCl	4	Incomplete reaction, TCL has many impurity spots	68
Fe / CH_3COOH	4	Incomplete reaction, TCL has many impurity spots	73
Raney / Ni - NH_4Cl	4	Incomplete reaction, TCL has many impurity spots	72
NaH-THF	4	Incomplete reaction, TCL has many impurity spots	79
$NaBH_4$ - $NiCl_2$	4	Incomplete reaction, TCL has many impurity spots	77

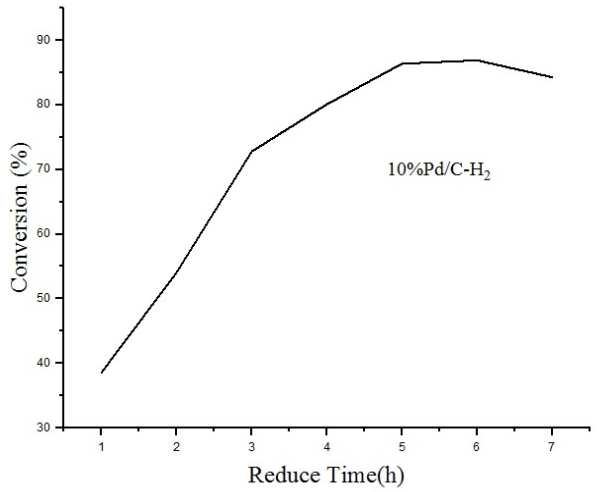


Fig.11. Effect of reaction time and conversion of compound F

(6)Preparation process control of compound A

The condensation process was divided into two steps, namely, the preparation of acyl chloride and the completion of the condensation process. However, the stability of acyl chloride in air is poor, resulting in low condensation yield and difficult post-treatment. In this study, the process optimization was carried out from the reaction of the material for preparing acyl chloride with the product A (Afatinib).

Table 4. Optimizate the synthetic condition of Afatinib dimaleate

Factor	**Crotonic acid hydrochloride** \ $SOCl_2$		
Material ratio	1:1	1:1.5	1:2
Yelid	11%	53%	76%
Post-treatment	Oily substance	Light grey solid	White solid

Based on the data in Table.4, when the material ratio of crotonic acid hydrochloride and $SOCl_2$ was 1:2, product with good properties can be obtained, and the yield reached 76%. To further verify the purity analysis by HPLC, we used a chromatographic column of C18 with dimensions of 4.6 mm×250 mm, 5 μm. The mobile phase consisted of 0.02 mol/L liquor potassium dihydrogen phosphate (2 mol/L sodium hydroxide solution, pH=6.0), the detection wavelength was 245 nm, and the injection volume was 20 μL. By using the area normalization method, the content of related substances was determined to be 99.48%. The results are shown in Fig.12.

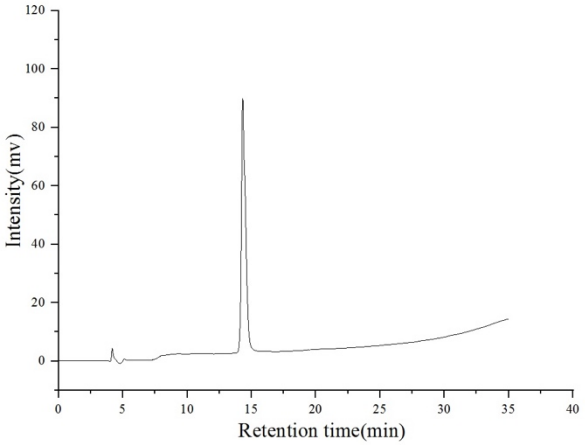


Fig.12. HPLC Spectrum of Afatinib dimaleate

(7) Salifying process control of compound A

Different salts have different solubility and crystallization tendency. Large-scale production process can be simplified using different physical and chemical characteristics. In the salt formation process, the beating method was used to remove the impurities adsorbed on the crystal solid surface. The impurities on the crystal solid surface can be removed, and the product was filtered and separated after full contact with the solvent. After beating, the solid was washed and dried. The refining and purification method improved the purity of the product and reduces the introduction of impurities.

4 Conclusions

To innovate and optimize the synthetic route of Afatinib dimaleate, we developed an innovative synthetic route and optimized the synthetic process, resultingi n stable quality, high yield, and moderate economic cost of Afatinib dimaleate. The selection and establishment of the synthetic route for Afatinib dimaleate and the influencing factors of

the process were optimized via literature analysis, small-scale experiment and pilot test. The parameters adjusted include the ratio of reactants, added sequence and method of raw material, the reaction time, the purification method, and the process control by taking the yield and impurity content as the inspection indicators. The following conclusions could be drawn:

(1)The proposed synthesis method of Afatinib dimaleate can be employed. 4-Fluoro-2-aminobenzoic acid was selected as the original material via cyclization, nitration, etherification (substitution), reduction, and condensation reactions.

(2)More than 45% of total conversion rate was achieved, it reduced the cost and impurity content, and the content reached 99.5%.

(3)The influencing factors for the synthetic route such as reactant ratio, reaction time, and purification method were optimized, and the yield and quality stability of the product were ensured.

In this study, small-scale and pilot scale experiments were combined with theoretical study to innovate the synthetic route for Afatinib dimaleate. The reaction conditions and process control methods in each step of the established reaction route ensured stable yield and reliable quality of product. This study has certain reference significance for improving the quality and reducing the cost of Afatinib dimaleate. However, the structure, reaction conditions, and purification methods of the impurities need to be further studied because of the lack of actual data for impurity control during the synthesis processes to improve the understanding of impurities generated during the synthesis of Afatinib dimaleate, improve the product quality, reduce the costs, and provide technical support for the subsequent preparation production.

Acknowledgements

This work was supported by science and technology innovation project of Xuzhou City(KC19204) and QingLan teaching team project of Jiangsu Province.

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