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Fast and Efficient Synthesis of Racemic Baloxavir Catalyzed by Strong Solid Acid under Microwave Conditions

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Abstract: The compound (±)-12aR-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-7-hydroxy-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione is the intermediate of baloxavir marboxil. In the literature, traditional heating methods and common acid catalysts are used, which result in long reaction times and a low yield. Therefore, finding an efficient and environmentally friendly synthetic route is necessary. In this study, (±)-12aR-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-7-benzyloxy-3,4,12,12a-tetrahydro-1h-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione (compound 3) was synthesized using a sulfonate resin solid acid catalyst (HND-580) under microwave conditions. The benzyl group was removed without further purification, and an intermediate, racemic baloxavir, was obtained under microwave irradiation. The total yield of the two steps was 78%. This method greatly reduces the reaction time and improves production efficiency.

Keywords: baloxavir marboxil; intermediate; synthesis; sulfonate resin solid acid; microwave irradiation

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1. Introduction

Influenza is a contagious disease infection that is caused by the influenza virus. It has high morbidity and mortality rates worldwide, and its spread and the economic losses caused are among the highest of infectious diseases [1]. Vaccinations and drug treatments are the main measures used to deal with influenza viral infections. However, vaccines have limitations in the scope of their use. Therefore, it is essential to develop drugs for the treatment of influenza viral infections. M2 ion channel inhibitors and neuraminidase inhibitors are the most often utilized anti-influenza virus medications in clinical practice [2,3]. Because of the continuous mutation and recombination of influenza viruses, medical chemists have explored anti-influenza drugs for new targets or mechanisms of action. In March 2018 and October 2018, baloxavir marboxil (trade name: Xofluza) was launched in Japan and the United States, respectively. Most influenza viruses, including oseltamivir-resistant and avian strains (H_7N_9 and H_5N_1, respectively), have shown good antiviral activity with baloxavir marboxil [4–13].

As a new anti-influenza drug with a novel mechanism of action against influenza viruses A and B, the synthesis of baloxavir marboxil has received extensive attention. Many synthetic routes have been developed worldwide based on the structural characteristics of baloxavir marboxil and combined with retrosynthetic strategies [14–20]. In all synthetic routes, triazine fragments and sulfur-containing fragments are prepared separately, and then these two fragments undergo dehydration condensation, debenzylation, and esterification to obtain the final product, baloxavir marboxil. The synthesis process improvements reported in the literature have focused mostly on triazine or sulfur-containing fragments. However, for the intermediate (±)-12aR-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-7-hydroxy-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]p-

yrido[2,1-f][1,2,4]triazine-6,8-dione (hereinafter referred to as (±) baloxavir, Figure 1), process improvement reports are few, and the application of new reaction equipment and the use of catalysts have not yet been reported.

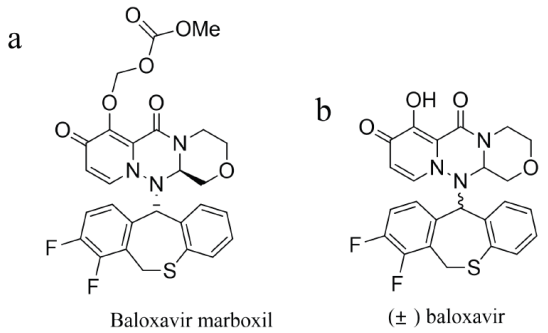
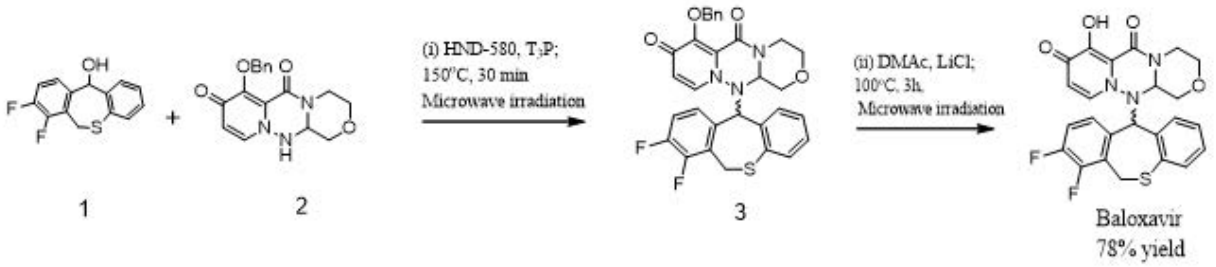


Figure 1. (**a**) Structure of baloxavir marboxil and (**b**) (±)-12aR-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-7-hydroxy-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione (abbreviated as (±) baloxavir).

In the synthesis of baloxavir marboxil, the yield of (±) baloxavir directly restricts the yield of the entire synthesis route. The synthesis process of (±) baloxavir, first reported by Shionogi Co. [21], was separated into two steps. In the condensation step, (±)-12aR-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-7-benzyloxy-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione (hereinafter referred to as compound 3) was obtained from 7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-ol (compound 1) and 7-(benzyloxy)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione (compound 2) after a long reaction time (more than 10 h) with only about 50% yield. At the same time, the separation and purification processes were difficult due to there being more impurities. Zheng et al. [22] synthesized compound 3 under anhydrous, anaerobic conditions through the Mitsunobu reaction. The previously described by-product, triphenylphosphine oxide, in the dehydration condensation reaction is difficult to separate. As reported by Tang et al. [23] who obtained analogues of compound 3 in sealed tubes with a conversion rate of only about 50%. Tang et al. [24] obtained analogues of compound 3 in reaction conditions with conventional heating with a conversion rate of only about 46%.

The conventional heating method is not always efficient due to poor heat transfer and uneven temperatures. Microwave synthesis refers to a technology used in modern organic/inorganic synthesis research based on microwave irradiation, which has the characteristics of rapid heating, homogeneity, and high product selectivity. In 1986, Gedye et al. [25] compared esterification, hydrolysis, oxidation, and nucleophilic substitution reactions carried out under microwave heating and conventional conditions. They found that permanganate was carried out in a sealed tube of a microwave oven. The oxidized toluene to the benzoic acid reaction was five times faster than that via conventional reflux, and the reaction of 4-cyanophenate with benzyl chloride was 240 times faster.

In order to find an efficient and environmentally friendly synthetic route, the microwave irradiation method was adopted in dehydration condensation and debenzylation (Scheme 1). Compound 3 was obtained from the dehydration condensation of compound 1 and compound 2. Compound 3 was further debenzylated without purification to obtain a light yellow solid (±) baloxavir. Meanwhile, sulfonic acid resin solid acid catalysts were used in dehydration condensation reactions for the first time in this study.



Scheme 1. (±) Baloxavir was prepared by microwave heating (compound 1: 7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-ol; compound 2: 7-(benzyloxy)-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione; compound 3: (±)-12aR-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-7-benzyloxy-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione).

2. Materials and Methods

2.1. Instruments and Reagents

Compound 1 was homemade [17], and compound 2 was purchased from Vcare Pharmatech (Nanjing, China). An ethyl acetate solution of 1-propyl phosphoric anhydride was obtained from Macklin Biochemical Co., Ltd. (Shanghai, China). The HND series resins were developed by Nankai University (Tianjin, China), and the Amberlyst series resins were developed by DuPont (Wilmington, DE, USA). The microwave reactor was an XH-800SP Nanocube multifunctional microwave hydrothermal parallel synthesizer. The circulating water vacuum pump was an SHB-III (Zhengzhou Great Wall Technology Industry and Trade Co., Ltd., Shenzhen, China). The electric heating blast drying oven was a GZX-9240MBE (Shanghai Boxun Industrial Co., Ltd., Shanghai, China). The electronic balance was a PB3002-S (Mettler Toledo, Columbus, OH, USA). The high-performance liquid chromatographer was an Agilent-1200 (Agilent Technologies, Santa Clara, CA, USA). A Bruker (Karlsruhe, Germany) nuclear magnetic resonance (NMR) instrument and a Bruker mass spectrometer were used for characterization.

2.2. Experimental Method

Synthesis of (±) baloxavir: A 100 mL microwave reactor was charged with compound 1 (2.64 g, 10 mmol), compound 2 (3.27 g, 10 mmol), and HND-580 (0.132 g) and were added into a 100-mL microwave reactor. Then, 50 wt% 1-propyl phosphoric anhydride ethyl acetate solution (20 mL) was added into the microwave reactor. The reaction temperature was irradiated for 30 min at a temperature of 150 °C. After completion of the reaction, the reaction solution was poured into ice water and filtered, and the catalyst was recovered. The catalyst was extracted with dichloromethane and combined with the organic phases. The mixture was washed with a saturated sodium bicarbonate aqueous solution and a saturated sodium chloride solution successively and was dried with anhydrous sodium sulfate to obtain a light yellow solid, compound 3 (483.4900 g/mol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, 2H), 7.28–7.38 (m, 3H), 7.02–7.11 (m, 3H), 6.95–7.02 (m, 2H), 6.68 (t, 1H), 6.41 (d, 1H), 5.76 (d, 1H), 5.65 (d, 1H), 5.43 (d, 1H), 5.20–5.26 (m, 2H), 4.68 (d, 1H), 4.44 (d, 1H), 4.01 (d, 1H), 3.88 (d, 1H), 3.73 (d, 1H), 3.29–3.39 (m, 2H), and 3.00 (t, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.16, 154.38, 151.19 (d), 140.32 (d), 137.29, 136.49 (d), 135.87, 134.49, 133.40, 129.67, 128.94, 128.79,128.46, 128.35, 128.13, 128.03, 127.77, 126.51, 125.41, 124.81 (d),116.46 (dd), 113.23 (d), 74.72, 73.15, 72.88, 69.41, 68.18, 65.50, 61.99, 45.47, and 25.48 (dd). MS (ESI) calcd for $C_{24}H_{19}BrF_2N_3O_4S$ $[M + H]^+$ 564.2071, found 563.1549.

Compound 3 was added to a 100 mL microwave reactor without further purification. Then, 20 mL of dimethylacetamide (DMAC) and 2.53 g of anhydrous lithium chloride were added. The reaction temperature was set to 100 °C, the maximum power was 300 W, the heating time was 10 min, and the reaction time was 3 h. After the reaction, water was added to the reaction solution, and the pH of the reaction solution was adjusted to about

6 with 1 M of diluted hydrochloric acid. The solution was filtered. The filter cake was washed with water and dried to obtain a light yellow solid. The solid was then dissolved in chloroform, isopropyl ether was added to precipitate a solid, and the mixture was filtered. A light yellow solid baloxavir was obtained with a yield of 78%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14–7.06 (m, 3H), 7.06–7.00 (m, 2H), 6.84 (m, 1H), 6.68 (m, 1H), 5.77 (m, 1H), 5.28 (m, 2H), 4.66 (m, 1H), 4.58 (m, 1H), 4.06 (m, 1H), 3.95 (m, 1H), 3.80 (m, 1H), 3.63 (m, 1H), 3.48 (m, 1H), and 3.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.99, 161.75, 154.14, 138.33, 135.72, 132.88, 131.42, 130.37, 128.79, 128.04, 125.83, 125.45, 124.15, 124.02, 116.84, 116.66, 114.61, 111.54, 77.20, 75.77, 70.34, 69.49, 66.61, 45.88, and 23.27. HRMS (ESI) calcd for $C_{24}H_{19}F_2N_3O_4S$ $[M + H]^+$ 484.1142, found 483.1064. M.p. 230 °C (decomposition).

3. Results and Discussion

In the initial attempt, (±) baloxavir was synthesized without acid catalysts following the process reported in the literature [22,23]. However, it was found that there was almost no expected product. Compared with the condition without catalyst, traditional sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid were used as catalysts, and there was no significant increase in yield (Table 1, entry 1 and 2).

Table 1. Screening of catalyst.

No.	Catalyst	Catalyst Amount [a]	Reaction Temperature (°C) [b]	Temperature Rise Time (min)	Response Time (min)	(±) Baloxavir Yield [c,d]
1	Methanesulfonic acid	5%	150	50	30	40%
2	p-toluenesulfonic acid	5%	150	50	30	45%
3	Amberlyst15	5%	150	50	30	22%
4	Amberlyst16	5%	150	50	30	28%
5	Amberlyst31	5%	150	50	30	29%
6	Amberlyst33	5%	150	50	30	33%
7	Amberlyst35	5%	150	50	30	72%
8	Amberlyst36	5%	150	50	30	67%
9	Amberlyst39	5%	150	50	30	34%
10	Amberlyst40	5%	150	50	30	53%
11	Amberlyst70	5%	150	50	30	24%
12	Amberlyst131	5%	150	50	30	26%
13	HND-8	5%	150	50	30	20%
14	HND-580	5%	150	50	30	75%
15	HND-582	5%	150	50	30	41%
16	HND-583	5%	150	50	30	46%
17	HND-586	5%	150	50	30	65%
18	HND-587	5%	150	50	30	55%

[a] Reaction conditions: compound 1 (1 mmol), compound 2 (1 mmol), propylphosphonic acid anhydride (T_3P, 55 mmol). The amount of catalyst is the weight percentage of compound 1. [b] Under microwave heating. [c] The yield is the combined yield of the two reaction steps for compounds 3 and (±) baloxavir. [d] The reaction conditions of (±) baloxavir were determined as follows: DMAc, anhydrous lithium chloride, and compound 3 were added to a microwave reactor. The reaction temperature was set to 100 °C, the maximum power was 300 W, the heat time was 10 min, and the reaction time was 3 h.

Solid super acids show high activities for various reactions, including olefin double-bond isomerization, alcohol dehydration, olefin alkylation, acidification, and esterification [26–28]. Amberlyst series resins are a type of macroreticular polystyrene-based ion exchange resin with a very acidic sulfonic group invented by DuPont. As a result, it is a great source of powerful acid. It is easy to use, readily removed from the reaction system, and regenerated quickly. It has been reported that Amberlyst-15 could catalyze the nucleophilic substitution of allylic alcohols [29]. Thus, Amberlyst-15 was tried first. Although a lot of compound 1 was left in the dehydration reaction, the residue was easy to deal with and applied to the next step directly without further purification. The total yield of the two steps was 22% (Table 1, entry 3). Encouraged by this result, Amberlyst series resins were

screened systematically. Table 1 shows that the yields catalyzed by Amberlyst-15, -16, and -131 were below 30%. This may be related to their breakdown at 150 °C. The matrixes of Amberlyst-31 and -33 are kinds of gels without pores, which is unbeneficial to catalysts. Amberlyst-35, -36 and -40 had good results due to their high capacity and thermal stability. Although Amberlyst-70 was stable up to 190 °C, its yield was only 24%. Pore structure was proposed to be the most important factor in this reaction.

Nankai University has developed HND series resins, which are cheaper than Amberlyst ones. Similar to Amberlysts, the yields of the HND series increased with the service temperature. Among them (Table 1, entries 13–18), HND-580 has as high a yield as Amberlyst-35. Therefore, the low-cost and easy-to-obtain HND-580 was chosen as the catalyst.

These data in Table 1 show that the reaction effect of the sulfonic acid catalyst was much worse than that of the solid acid catalyst, and there were many by-products. The solid acid catalysts HND-580 and Amberlyst-35 had better catalytic effects.

After determining the type of catalyst, the dosage of the solid acid catalyst HND-580 was further screened. The data in Table 2 show that with the increase in the amount of the catalyst HND-580, the yield also increased. When the dosage of HND-580 (entry 4) was 5%, the yield was 78%. The catalyst dosage was determined to be 5% based on the environmental and economic benefits. Furthermore, the effects of the reaction temperature (entries 4–6), heating time, and reaction time (entries 7–13) were also explored. A higher temperature causes resin breakdown and produces side effects.

Table 2. Screening of reaction conditions.

No.	Catalyst	Catalyst Amount [a]	Reaction Temperature (°C) [b]	Temperature Rise Time (min)	Response Time (min)	(±) Baloxavir Yield [c]
1	HND-580	1%	150	50	30	18%
2	HND-580	2%	150	50	30	31%
3	HND-580	3%	150	50	30	57%
4	HND-580	5%	150	50	30	78%
5	HND-580	5%	140	50	30	61%
6	HND-580	5%	160	50	30	66%
7	HND-580	5%	150	10	40	65%
8	HND-580	5%	150	20	30	72%
9	HND-580	5%	150	30	20	71%
10	HND-580	5%	150	40	10	56%
11	HND-580	5%	150	50	0	58%
12	HND-580	5%	150	60	0	59%
13	HND-580	5%	150	50	20	70%

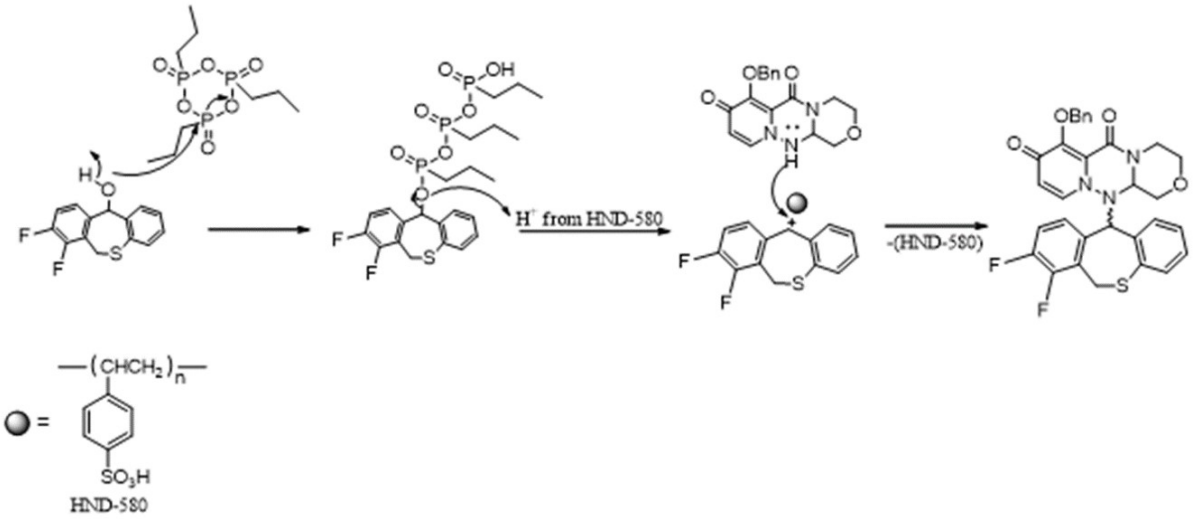
[a] Reaction conditions: compound 1 (1 mmol), compound 2 (1 mmol), propylphosphonic acid anhydride (T_3P, 55 mmol). The amount of catalyst is the weight percentage of compound 1. [b] Under microwave heating. [c] The yield is the combined yield of the two reaction steps for compounds 3 and baloxavir.

Conversely, a lower temperature is not a favourite for this reaction. The data in Table 2 show that the yield was optimal when heating and reaction times were 50 min and 30 min, respectively. More by-products were detected by thin-layer chromatography if the time was prolonged.

It was speculated that the reaction mechanism for compound 1 was esterified with propylphosphonic acid anhydride (T_3P). HND-580 was an excellent source of strong acids. The carbocation of compound 1 was obtained by the reaction of an ester with acid in HND-580 pores. Then the nitrogen anion of compound 2 attacked the carbocation, and compound 3 was obtained after dehydrogenation (Scheme 2). The pore structure of HND-580 was favorable for the reaction.

Following the literature of Shionogi Co., Osaka, Japan [21], the amount of 1-propylphosphoric anhydride (molar ratio) was 55 times that of compound 1, and the yield of (±) baloxavir was 75% (Table 3, entry 3). The excessive dosage not only resulted in the reaction product turning into a scorched and viscous substance, which is not conducive

to subsequent processing, but also led to higher production costs. When the amount of 1-propylphosphoric anhydride required was reduced from 55 times to 2 times that of compound 1 and diluted with acetate (Table 3, entry 2), not only did the yield increase to 78%, but the post-processing was also simple, and the production costs were greatly reduced.



Scheme 2. Dehydration condensation reaction mechanism.

Table 3. Screening of dosage of 1-propylphosphoric anhydride.

NO.	Compound 1	Compound 2	Dosage of 1-Propylphosphoric Anhydride	(±) Baloxavir Yield [a]
1	1 mmol	1 mmol	2 mmol	73%
2	1 mmol	1 mmol	2 mmol + 2 mL ethyl acetate	78%
3	1 mmol	1 mmol	55 mmol	75%

[a] The yield is the combined yield of the two reaction steps for compounds 3 and (±) baloxavir.

After determining the reaction conditions of compound 3, the reaction conditions of (±) baloxavir were further screened. The effects of the reaction temperature and reaction time were explored. The data in Table 4 show that the yield was optimal when the reaction temperature was 100 °C and reaction time was 3 h. If time was prolonged and the temperature was increased, more by-products were detected by thin-layer chromatography. Therefore, the reaction conditions of (±) baloxavir were determined as follows: DMAc, anhydrous lithium chloride, and compound 3 were added to a microwave reactor. The reaction temperature was set to 100 °C, the maximum power was 300 W, the heat time was 10 min, and the reaction time was 3 h.

Table 4. Screening of (±) baloxavir [a].

NO.	Reaction Temperature (°C) [b]	Reaction Time (h) [b]	(±) Baloxavir Yield [c]
1	80	3	10%
2	80	4	25%
3	100	1.5	40%
4	100	3	78%
5	100	4	79%

[a] Reaction conditions: compound 1 (1 mmol), compound 2 (1 mmol), propylphosphonic acid anhydride (T_3P, 2 mmol), 2 mL ethyl acetate. The amount of catalyst is 5% of compound 1. [b] Under microwave heating. [c] The yield is the combined yield of the two reaction steps for compounds 3 and (±) baloxavir.

After optimization of the synthesis route, the feed amount was increased to gram level (i.e., 10 mmol of compound 1, 10 mmol of compound 2, and 5% solid acid catalyst HND-580, 20 mmol of 1-propylphosphoric anhydride, and 20 mL ethyl acetate solution) in the

microwave reactor at 150 °C. A light yellow solid compound 3 was obtained. Compound 3 was mixed with anhydrous lithium chloride in dimethylacetamide (DMAC) without further purification and heated at 100 °C in the microwave reactor for 3 h. A light yellow solid, (±) baloxavir, was obtained with a yield of 78%.

The purity of baloxavir was 92.57% by HPLC (Figure 2, the chromatographic column used was ZORBAX SB-Phenyl C18, 4.6 × 250 mm, 5 µm. Experimental conditions: detection wavelength was set at 210 nm, column temperature was 30 °C, the flow rate was 1.0 mL/min, the sample size was 10 µL, mobile phase A: 0.1% phosphoric acid solution (pH = 4.0), B: methanol, gradient elution was carried out).

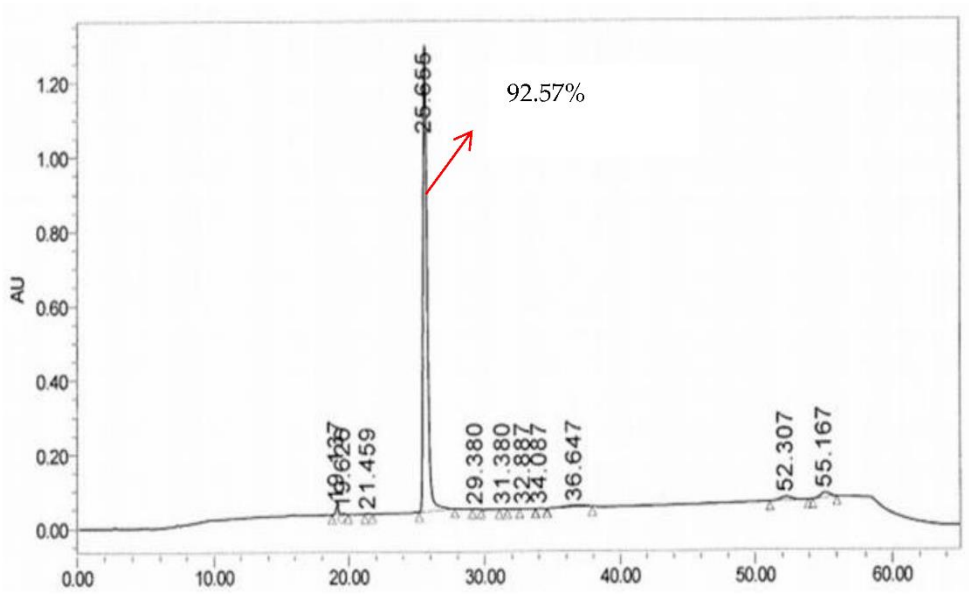


Figure 2. HPLC of Baloxavir.

4. Conclusions

This study developed an efficient and green synthesis method of the intermediate ((±) baloxavir) of baloxavir marboxil. Microwave irradiation and a solid acid catalyst (HND-580) were used, the reaction time was significantly shortened, and the total yield of the two steps was 78%, which is about 40% higher than that in the literature. Compared with methanesulfonic acid and p-toluene sulfonic acid, HND-580 is safe and easy to handle. It reduces costs and pollution through the recycling of catalysts. Microwave irradiation allowed for rapid heating, uniformity, and high product selectivity, which greatly shortened reaction times, reduced the generation of by-products, and improved product quality. At the same time, dehydration and debenzylation were combined into a one-step reaction, which not only improved production efficiency but also reduced the input of the workforce and material resources. The approach developed in this study effectively improves the atomic economy and realizes the rational use of resources. Furthermore, it is easy to perform, safe, and environmentally friendly, and the production efficiency is high. Thus, it is conducive to industrialized production.

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