An Efficient Synthesis of Ivacaftor

Rui Zhang, Guanyu Han, Luobin Jiang, Yao Shen, Rui Yang, Yongjun Mao,* and Hang Wang

College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, Shanghai 201620, China
*E-mail: yongjun.mao@hotmail.com

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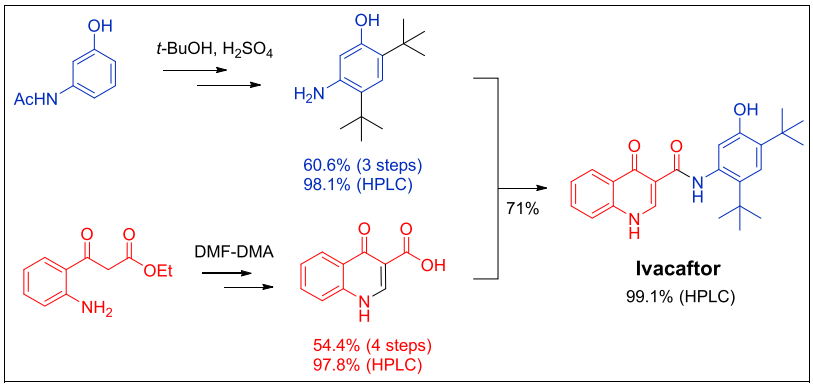

New and practical synthetic route of ivacaftor is described on a grams scale. An electrophilic addition of two *t*-butyl groups to the aromatic ring is adopted to prepare 5-amino-2,4-di-*t*-butylphenol in 61% yield over three steps with 98.1% purity (high-performance liquid chromatography). An intramolecular cyclization of ethyl 3-(2-aminophenyl)-3-oxo-propanoate with dimethylformamide-dynamic mechanical analysis is used to prepare 4-oxo-1,4-dihydroquinoline-3-carboxylic acid in 54% yield over four steps. Ivacaftor is obtained by condensation of the two parts in 71% yield with 99.1% purity (high-performance liquid chromatography).

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INTRODUCTION

Ivacaftor (VX-770, Kalydeco™) **1**, as shown in Figure 1, is a drug used to treat cystic fibrosis in people with certain mutations in the cystic fibrosis transmembrane conductance regulator gene [1,2]. It was developed by Vertex Pharmaceuticals and approved by the FDA in January 2012 [3]. The combination drug lumacaftor/ivacaftor (Orkambi™) is also used to treat cystic fibrosis, was approved by the FDA in 2015 [4].

With regarded to the synthesis of ivacaftor, it can be envisioned as a combination of two structural fragments, 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**) and 5-amino-2,4-di-t-butylphenol (**3**), as shown in Figure 1.

A couple of methods have been reported for the synthesis of compound **3** and the methyl carbonate derivative **8**, as depicted in Scheme 1 [5–7]. 2,4-Di-*t*-butylphenol (**4**) is adopted as the starting material, via protection, nitration, ester hydrolysis, and reduction to give the final product **3**. Compound **8** is obtained from intermediate **6** through catalytic hydrogenation. The main drawback of the nitration of **5** to **6** methodology is poor selectivity and low yield (29%). Compound **6** is isolated by column chromatography, which is not suitable for scale-up preparation.

The reported approach to the synthesis of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**) are mainly *via* Gould-Jacobs procedure, heating diethyl 2-((phenylamino) methylene)malonate (**9**) with diphenyl ether at 230–240°C for several hours to give ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate in moderate yield [8,9], as shown in Scheme 2. Compound **2** is obtained through ester hydrolysis. The high temperature required for the cyclization step lead to a fussy and hard operation. Furthermore, diphenyl ether is a high boiling solvent difficult to recover, harmful to environment and may also cause allergies to people handling it.

RESULTS AND DISCUSSION

In order to develop practical method for preparation of ivacaftor, 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**) and 5-amino-2,4-di-*t*-butylphenol (**3**) are prepared in new route, as shown in Schemes 3 and 4.

As depicted in Scheme 3, the electrophilic addition of *t*-butyl group to benzene ring was adopted to prepare compound **3** after optimization [10,11], as shown in Table 1. *N*-(3-hydroxyphenyl)acetamide (**11**) was prepared from 3-aminophenol (**10**), which was treated with *t*-butanol and concentrated H_2SO_4 in CH_2Cl_2 at room temperature for 48 h to give compound **12** in 74% yield after purified by recrystallization [12,13]. 5-Amino-2,4-di-*t*-butylphenol (**3**) was obtained by acid hydrolysis

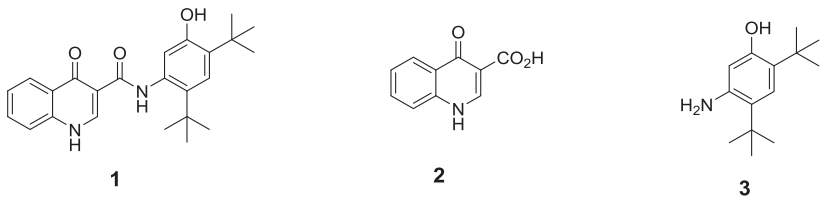
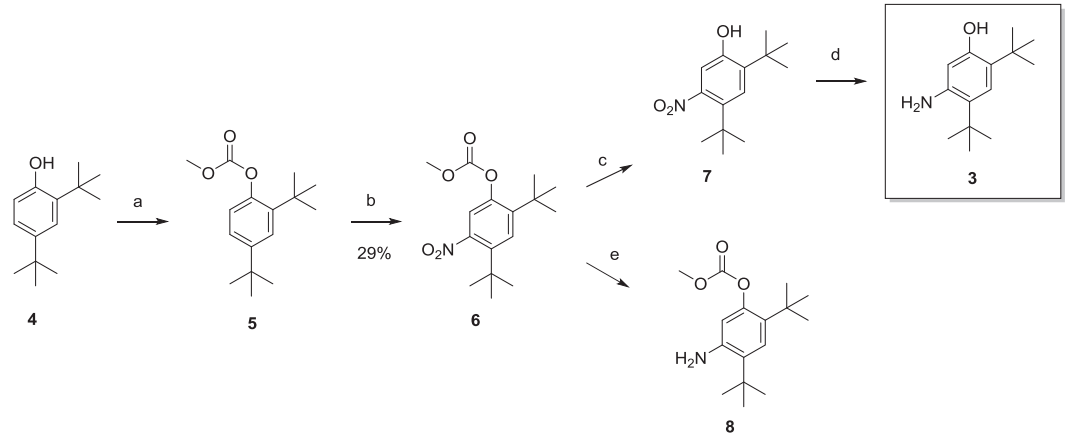
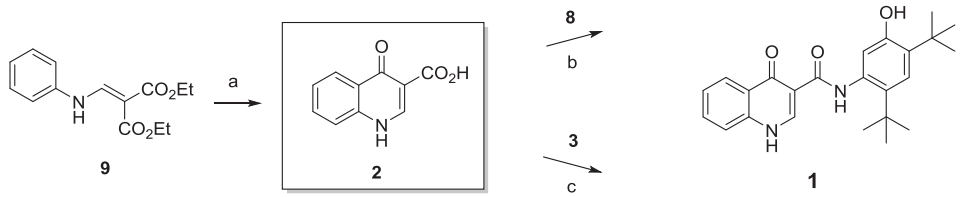


Figure 1. Chemical structures of Ivacaftor (**1**), (**2**) and (**3**).

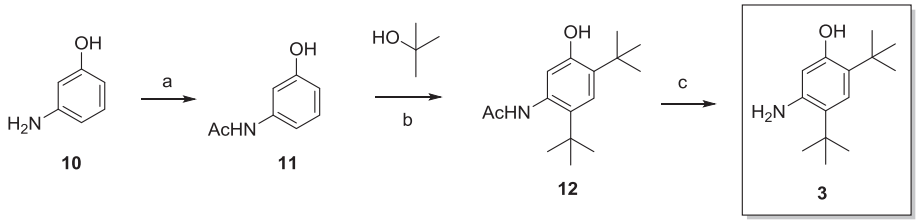
Scheme 1. Reagents and conditions: (a) CH_3CO_2Cl, Et_3N, DMAP, CH_2Cl_2; (b) HNO_3, H_2SO_4, 29% via column chromatography; (c) KOH, MeOH; (d) HCO_2NH_4, Pd/C, EtOH; (e) H_2, Pd-C, MeOH, rt.



Scheme 2. Reagents and conditions: (a) (i) PhOPh, 230–240°C, 40–60%; (ii) NaOH, EtOH, reflux; (b) (i) 1,3,5,2,4,6-trioxatriphosphorinane (T3P), pyridine, 2-MeTHF, 50°C, 8 h, 70%; (ii) NaOMe, rt; (c) HBTU, Et_3N, DMF, 71%.



Scheme 3. Reagents and conditions: (a) Ac_2O, HOAc, 50°C, 2 h, 92%; (b) H_2SO_4, CH_2Cl_2, rt, 48 h, 74%; (c) HCl, EtOH-H_2O, 89%.



of **12** in good yield and 98.1% purity [high-performance liquid chromatography (HPLC)].

As shown in Scheme 4, the intramolecular cyclization of ethyl 3-(2-aminophenyl)-3-oxo-propanoate (**15**) and *N,N*-dimethylformamide dimethyl acetal dimethylformamide-dynamic mechanical analysis (DMF-DMA) was used to prepare ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (**16**) [14,15]. 2-Nitrobenzoic acid (**13**) was reacted with *N,N*'-Carbonyldiimidazole (CDI) and ethyl potassium malonate to give the intermediate **14** in good yield [16]. Compound **15** was obtained by catalytic hydrogenation of **14** in high yield, which was treated with DMF-DMA in toluene at 100°C to give **16** in 73% yield after purification by recrystallization. Compound **2** was then

Scheme 4. Reagents and conditions: (a) (i) CDI, MeCN; (ii) ethyl potassium malonate, $MgCl_2$, Et_3N, rt − 35°C; (iii) 3 N HCl, 82%; (b) H_2, Raney-Ni, THF, rt; (c) DMF-DMA, toluene, 100°C, 6 h, 73%; (d) NaOH, EtOH-H_2O, reflux, 2 h, 91%; (e) EDCI, HOBt, Et_3N, DMF, rt, 71%.

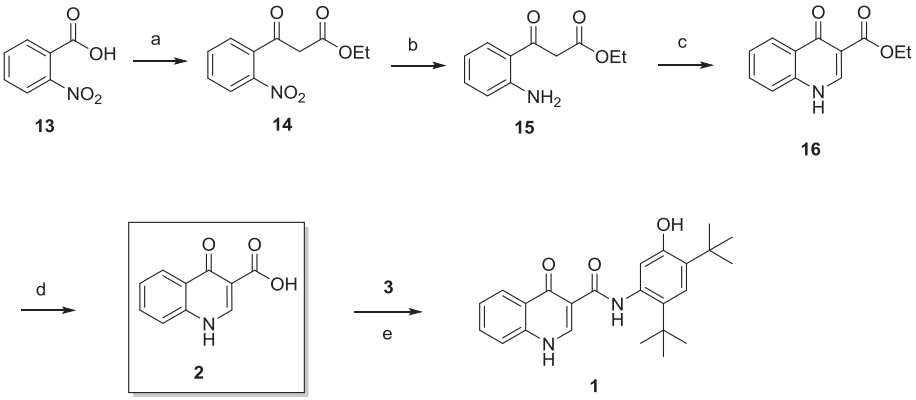


Table 1

The Optimization Methods of Preparation Compd. 12 from 11.

Item	Alkylating agent	Catalyst acid	Solvent	Time	Temp.	Result
1	2-chloro-2-methylpropane	$AlCl_3$	dichloromethane	4 h	rt	No product
2	2-chloro-2-methylpropane	H_2SO_4	toluene	4 h	rt − 60°C	No product
3	*t*-butanol	$AlCl_3$	dichloromethane	12 h	0°C − rt	No product
4	*t*-butanol	H_2SO_4	toluene	12 h	0°C − rt	Insoluble
5	*t*-butanol	H_2SO_4	dichloromethane	24 h	rt − 40°C	<50% yield
6	*t*-butanol	H_2SO_4	dichloromethane	48 h	rt	74% yield
7	*t*-butanol	H_2SO_4	dichloromethane	4 days	rt	73% yield

obtained after ester hydrolysis, which reacted with 5-amino-2,4-di-*t*-butylphenol (**3**) directly using EDC/HOBt as the condensing agent to give the final product ivacaftor (**1**) in 71% yield and 99.1% purity (HPLC) after purified by recrystallization [17,18].

In summary, we have developed a new and practical synthetic route of ivacaftor (**1**). On the one hand, an electrophilic addition of *t*-butyl group to benzene ring is adopted to prepare 5-amino-2,4-di-*t*-butylphenol (**3**) in 61% yield over three steps from 3-aminophenol and 98.1% purity (HPLC). On the other hand, an intramolecular cyclization of ethyl 3-(2-aminophenyl)-3-oxo-propanoate (**15**) with DMF-DMA is used to prepare 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**) in 54% yield over four steps. Lastly, compound **2** was condensed with **3** to give ivacaftor (**1**) in 71% yield and 99.1% purity (HPLC), and the overall yield of **1** from compound **13** is 39%. Purification methods of the intermediates involved in the route were also given.

EXPERIMENTAL

All commercially available chemicals and solvents were used as received without any further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker UltraShield 400 Plus spectrometer using tetramethylslane or trimethylsilyl as an internal standard. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Shenguang WRS-1B melting point apparatus and are uncorrected. The HPLC results were generated using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump.

N-(3-Hydroxyphenyl)acetamide (11). A mixture of 3-aminophenol (109.1 g, 1.0 mol) and HOAc (700 mL) was stirred and heated to 50°C. Ac_2O (112.3 g, 1.1 mol) was added to the reaction solution over 1 h and stirred at the temperature for another 1 h. It was cooled to room temperature, and poured slowly into ice-water (3 L) while stirring constantly. The solid formed was filtered off and washed with cold water (300 mL × 2), dried at 45°C for 6 h to afford **11** (139.0 g, 92%) as a white solid, mp 146–148°C. ^{1}H NMR [dimethyl sulfoxide (DMSO)-d_6, δ]: 2.01 (s, 3H), 6.42 (m, 1H), 6.92 (m, 1H), 7.04 (m, 1H), 7.18 (m, 1H), 9.33 (s, 1H), 9.78 (s, 1H); electrospray ionization-mass spectrometry (ESI-MS) (*m*/*z*) 152.2 $(M + H)^+$.

N-(2,4-di-tert-butyl-5-hydroxyphenyl)acetamide (12). Concentrated H_2SO_4 (176.4 g, 1.8 mol) was added slowly to the stirred solution of **11** (120.0 g, 0.79 mol), *t*-butanol (205.0 g, 2.77 mol) and CH_2Cl_2 (1.5 L) below 20°C. White sticky solid was formed immediately, and

the suspension was stirred quickly at room temperature for 48 h to give a white homogeneous suspension. The resulting white solid was filtered, washed with H_2O (400 mL × 2) and then mixed with 300 mL H_2O and stirred quickly. Saturated aqueous $NaHCO_3$ was added slowly to the mixture to adjust the pH ~ 6. The resulting white solid was filtered, washed with H_2O (400 mL × 2) and dried at 50°C for 5 h to give the crude product **12** (187 g), which was stirred and heated with 1:1 (*v*/v) hexane/EtOAc (500 mL) at reflux for 2 h then cooled to room temperature overnight, the resulting solid was filtered off and washed with 1:1 (*v*/v) hexane/EtOAc (200 mL × 2), dried at 40°C for 3 h to afford **12** (154.0 g, 74%) as a white solid, mp 91–94°C. ^{1}H NMR (DMSO-d_6, δ): 1.25 (s, 9H), 1.33 (s, 9H), 1.99 (s, 3H), 6.45 (s, 1H), 7.11 (s, 1H), 9.00 (s, 1H), 9.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.0, 30.9, 31.2, 35.4, 36.8, 110.3, 126.0, 131.5, 132.2, 132.6, 149.0, 169.3. ESI-MS (*m*/*z*) 264.3 $(M + H)^+$, 527.4 $(2 M + H)^+$, 549.4 $(2 M + Na)^+$.

5-amino-2,4-di-tert-butylphenol (3). Concentrted HCl (167.0 mL, 2.0 mol) was added to a suspension of **12** (135.0 g, 0.51 mol), EtOH (1.4 L) and H_2O (200 mL). The reaction mixture was stirred and heated to reflux for 6 h to give a clear solution. It was cooled to room temperature, and around 1 L solvent was recovered under reduced pressure. The residue was stirred at room temperature for 2 h. The resulting white solid was filtered, washed with cold water (200 mL × 2) and then mixed with 200 mL water and stirred quickly. Saturated aqueous $NaHCO_3$ was added slowly to the mixture to adjust the pH ~ 6 and the mixture was stirred for another 2 h. The resulting white solid was filtered, washed with cold water (200 mL × 2) and dried at 45°C for 5 h to afford the crude product (110 g), which was stirred and heated with 1:1 (*v*/v) hexane/EtOAc (350 mL) at reflux for 2 h then cooled to room temperature overnight, the resulting solid was filtered off and washed with 1:1 (*v*/v) hexane/EtOAc (100 mL × 2), dried at 40°C for 3 h to afford **3** (100.5 g, 89%) as a gray solid, mp 86–89°C. ^{1}H NMR (DMSO-d_6, δ): 1.32 (s, 9H), 1.34 (s, 9H), 6.79 (s, 1H), 7.19 (s, 1H), 9.78 (brs, 2H). ESI-MS (*m*/*z*) 222.3 $(M + H)^+$.

HPLC Conditions: Column: InertSustain C18 (250 mm × 4.6 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 30°C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 15 min; Mobile phase A: water; Mobile phase B: MeOH/AcOH = 100:0.1; Gradient program: Mobile phase A/Mobile phase B = 10/90: t_R = 5.404 min, purity: 98.1%.

Ethyl 3-(2-nitrophenyl)-3-oxopropanoate (14). Flask A: To a suspension of 2-nitrobenzoic acid (167.1 g, 1.0 mol) in CH_3CN (2 L) was added CDI (178.4 g, 1.1 mol) portion-wise, gas evolution was observed. This solution was stirred for 4 h at the ambient temperature.

Flask B: To a solution of ethyl potassium malonate (510.0 g, 3.0 mol) in CH_3CN (4 L) was added $MgCl_2$ (103.0 g, 1.08 mol) in portions over 15 min. The mixture was stirred at 35°C for 30 min and then cooled to 25°C and triethylamine (253.0 g, 2.5 mol) was added. The reaction mixture became very thick, and the slurry was stirred for 30 min.

The solution in flask A was then transferred to the slurry in flask B over 15 min. The reaction temperature rose to 35°C, and gas evolution was observed. The reaction mixture was stirred for 1.5 h, cooled to 5°C, and quenched with 3 N HCl (3 L), while maintaining the reaction temperature < 20°C. The resulting solution was distilled to remove CH_3CN and the resulting concentrate extracted with EtOAc (4 L). The organic phase was washed with water (2 L), saturated $NaHCO_3$ (2 L), and brine (2 L). The organic solution was concentrated under reduced pressure to give light yellow oil, which was solidified at room temperature to afford **14** (194.5 g, 82%) as a light yellow solid, mp 34–36°C. ^{1}H NMR ($CDCl_3$, δ): 1.33 (t, J = 7.2 Hz, 3H), 3.48 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 7.71 (m, 2H), 7.90 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.9, 49.0, 61.8, 124.1, 128.0, 130.9, 132.8, 134.7, 144.6, 166.5, 194.5. HRMS (ESI): Calcd for $C_{11}H_{11}NO_5$: 237.2110, Found 237.2105.

Ethyl 3-(2-aminophenyl)-3-oxopropanoate (15). Compound **14** (130.0 g, 0.55 mol) and Raney Ni (wet, 30 g) were added to THF (2 L), and stirred for 6 h at room temperature under hydrogen bag at atmospheric pressure to form a clear brown solution. The reaction mixture was then filtered through a celite pad, the filter cake was washed by THF (200 g × 2). The combined filtrate was concentrated to give the product **15** (114.0 g) as a light brown oil, which was used directly at the next step. ^{1}H NMR ($CDCl_3$, δ): 1.31 (t, J = 7.2 Hz, 3H), 3.44 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 6.68 (m, 2H), 7.30 (m, 1H), 7.86 (m, 1H), 8.77 (brs, 2H). ESI-MS (*m*/*z*) 207.0 $(M - H)^-$.

Ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (16). To a stirred solution of **15** (50.0 g, 0.24 mol) in toluene (600 mL) was added DMF-DMA (57.2 g, 0.43 mol). The mixture was stirred and heated to 100°C for 6 h and then cooled to room temperature. A gray suspension was formed and the resulting solid was collected by suction filtration, washed with 50% EtOH/H_2O (80 mL × 2), and dried at 60°C to give a gray solid. The crude product was stirred and heated with 1:1 (*v*/v) EtOH/EtOAc (160 mL) at reflux for 2 h then cooled to room temperature overnight, the resulting solid was filtered off and washed with 1:1 (*v*/v) EtOH/EtOAc (50 mL × 2), dried at 60°C for 4 h to afford **16** (38.0 g, 73%) as an light yellow solid, mp >250°C. ^{1}H NMR (DMSO-d_6, δ): 1.29 (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.2 Hz, 2H), 7.42 (m,

1H), 7.62 (m, 1H), 7.71 (m, 1H), 8.16 (m, 1H), 8.55 (s, 1H), 12.31 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5, 59.5, 110.0, 118.8, 124.6, 125.6, 127.4, 132.4, 139.1, 144.9, 164.9, 173.5. MS (ESI): *m/z* = 218.2 $(M + H)^+$.

HPLC Conditions: Column: InertSustain C18 (250 mm × 4.6 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 30°C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 15 min; Mobile phase A: water; Mobile phase B: MeOH; Gradient program: Mobile phase A/Mobile phase B = 10/90: t_R = 3.436 min, purity: 98.6%.

4-Oxo-1,4-dihydroquinoline-3-carboxylic acid (2). NaOH (13.8 g, 0.34 mol) was disolved in water (150 mL) and ethanol (250 mL) solution, and compound **16** (30.0 g, 0.13 mol) was added, and the resulting suspention was stirred and heated to reflux for 2 h to give a clear solution. Most of ethanol was removed under vacuum and the residue was adjusted with 6 N HCl to pH ~ 3, the resulting solid was filtered, washed with water (50 g × 2), and dried at 60°C for 5 h to give product **2** (22.3 g, 91%) as a white solid, mp >250°C. ^{1}H NMR (DMSO-d_6, δ): 7.60 (m, 1H), 7.82 (m, 2H), 8.29 (m, 1H), 8.88 (s, 1H), 13.45 (brs, 1H), 15.35 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 107.8, 119.6, 124.5, 125.1, 126.3, 144.0, 145.2, 166.6, 178.4. ESI-MS (*m/z*) 190.1 $(M + H)^+$.

HPLC Conditions: Column: InertSustain C18 (250 × 4.6 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 30°C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 15 min; Mobile phase A: water; Mobile phase B: MeOH/HCO_2H = 100:0.1; Gradient program: Mobile phase A/Mobile phase B = 10/90: t_R = 4.075 min, purity: 97.8%.

Ivacaftor (1). To a suspension of compound **2** (9.8 g, 0.052 mol) and **3** (11.5 g, 0.052 mol) in DMF (100 mL) was added triethylamine (22.0 mL, 0.16 mol). The mixture was stirred at room temperature, HOBt (10.8 g, 0.08 mol) and EDCI (15.3 g, 0.08 mol) were added successively. The reaction mixture was stirred at the ambient temperature overnight. The suspension was diluted with water (500 mL) to give a light yellow solid, which was filtered, washed by water (50 mL × 3), dried at 50°C for 4 h to afford the crude product **1** (19.0 g). The crude product was stirred and heated with 1:2 (*v*/v) MeOH/EtOAc (120 mL) at reflux for 1 h then cooled to room temperature overnight, the resulting solid was filtered off and washed with 1:2 (*v*/v) MeOH/EtOAc (20 mL × 2), dried at 50°C for 3 h to afford **1** (14.5 g, 71%) as an off-white solid, mp 124–128°C. ^{1}H NMR (DMSO-d_6, δ): 1.36 (s, 9H), 1.38 (s, 9H), 7.11 (s, 1H), 7.17 (s, 1H), 7.51 (m, 1H), 7.80 (m, 2H), 8.33 (m, 1H), 8.85 (m, 1H), 9.23 (s, 1H), 11.81 (s, 1H), 13.12 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.9, 31.1, 34.4, 34.8, 111.3, 116.4, 119.5, 124.2, 125.6, 126.0, 126.5, 132.0, 132.8, 133.3, 134.0, 139.6, 144.5, 153.7, 163.3, 176.9. HRMS (*m/z*): Calcd for $C_{24}H_{28}N_2O_3$: 392.4990, Found 392.4944.

HPLC Conditions: Column: InertSustain C18 (250 mm × 4.6 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 30°C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 15 min; Mobile phase A: water; Mobile phase B: MeOH/HCO_2H = 100:0.1; Gradient program: Mobile phase A/Mobile phase B = 10/90: t_R = 4.942 min, purity: 99.1%.

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