An Improved, Scalable and Impurity-Free Process for Lixivaptan

Shuai Mu,[a,c] Duan Niu,[c] Ying Liu,[c] Dashuai Zhang,[b] Dengke Liu,[c]* and Changxiao Liu[d]

[a]School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China
[b]Graduate School of Tianjin Medical University, Tianjin 300070, China
[c]Tianjin Key Laboratory of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research Tianjin 300193, China
[d]State Key Laboratory of Drug Delivery Technology and Pharmacokinetics, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, China
*E-mail: liudk@tjipr.com

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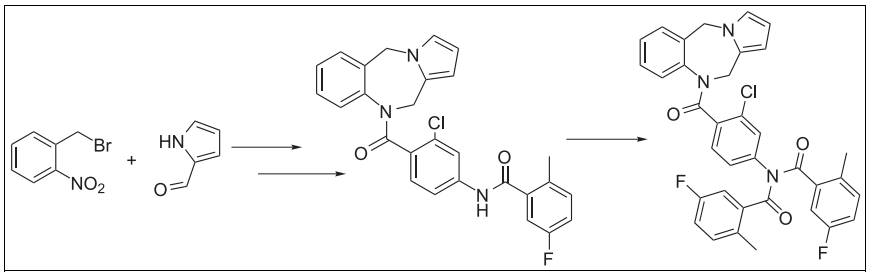


An optimized synthetic method in high efficiency has been developed for the synthesis of lixivaptan from 2-nitrobenzyl bromide and pyrrole-2-carboxaldehyde. The byproducts among this procedure and an unknown impurity in crude product were investigated. The byproducts were speculated by ^{1}H NMR or MS. The unknown impurity was characterized by ^{1}H NMR, ^{13}C NMR, and HRMS, confirming the structures as *N*-[3-chloro-4-(5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepine-10(11*H*)-ylcarbonyl)phenyl]-*N*-(5-fluoro-2-methylbenzoyl)-5-fluoro-2-methylbenzamide. Afterwards, the impurity was synthesized to make comparisons. The target product lixivaptan was obtained with 47.6% overall yield and 99.93% purity. This cost-effective and environmentally friendly process is suitable for scale-up production.

INTRODUCTION

Lixivaptan is an oral, nonpeptide vasopressin V2 receptor antagonist applied in the treatment of hyponatremia [1–6]. Recent reports demonstrated that it might have benefits to patients with congestive heart failure [7–10], cirrhosis [11], and syndrome of inappropriate antidiuretic hormone secretion [12,13]. It is chemically known as *N*-[3-chloro-4-(5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepine-10(11*H*)-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide, which is represented by chemical formula in Figure 1.

The reported two procedures (A and B) for synthesizing lixivaptan were shown in Scheme 1 [14–17]. Procedure A suffered from several drawbacks including the following: (i) use of pyrophoric reagents such as sodium hydride [15,18] resulted in the process industrially unattractive; (ii) poor volume efficiency; and (iii) partial dechlorination when Pd/C was used to catalyze the reduction of nitro [14]. Procedure B seemed to be more efficient than procedure A; however, it failed to obtain the desired purity of final product after successive recrystallization in different solvents such as methanol, ethyl acetate, chloroform–methanol, and hexane-ethyl acetate in our process development research. Upon the consideration for the commercial availability of the raw materials, the quality of the final product and the scale-up suitability, an improved synthetic route based on procedure A with an overall yield of 47.6% and purity of 99.93% was developed. The byproducts among this procedure and an impurity observed in the crude lixivaptan product were also investigated.

RESULTS AND DISCUSSION

The detailed modifications on procedure A were in reaction conditions a, b, and c, illuminated in Scheme 1. Our data indicated that the improved synthetic method was more efficient and scalable than conventional procedure A. The effects of variant reaction conditions in this modified procedure A on volume efficiency, yield, and purity were listed in Table 1.

In conventional procedure A, sodium hydride was used in the synthesis of **5**. Sodium hydride may ignite in air, especially upon contact with water to release hydrogen, which is also flammable, so extensively dried solvent was employed to ensure the safe operation. Moreover, the production yield and purity from conventional procedure were not satisfied for scale-up production. The effects of different bases were considered in this study for the improvement of conventional procedure (Table 2). It was found that the usage of anhydrous potassium carbonate

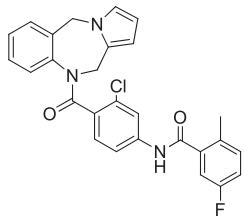


Figure 1. Chemical structure of lixivaptan.

instead of sodium hydride made the reaction controllable, with a total yield of more than 90%. The intermediate **5** could be used directly to the next reduction and cyclization step without further purification. The influence of different solvents was evaluated among tetrahydrofuran, dioxane, *N*, *N*-dimethylformamide, acetone, acetonitrile, and toluene; however, no significant difference in yield and product purity was observed.

Compound **6** was synthesized from **5** using a one-pot method. Possible reaction pathway was shown in Scheme 2. At room temperature, over 20 mL/g of ethyl acetate was required to dissolve compound **5**, but **5** changed more soluble (~5 mL ethyl acetate) at 60°C. The desired solubility in ethyl acetate of product **6**, the substrate does not need to be fully dissolved fortunately. The amount of solvent can be further reduced to 3 mL/g. The increase of the temperature slowed the absorption of hydrogen in turn, which extended the reaction time more than 24 h. A scalable method for the reduction and cyclization step was developed to overcome these disadvantages. In hydrogen atmosphere under a relatively higher pressure (0.1 ~ 0.2 MPa) and temperature (60°C), **6** was prepared from **5** with a yield of 90% and a purity of 99%.

Stannous chloride was industrially unattractive for the reduction of nitro. However, partial dechlorination (3 ~ 5%) was observed when Pd/C—H_2 in refluxing ethanol was introduced during preparation of **9**. In addition, the poor solubility of **9** in the solvent usually employed in the catalytic hydrogenation (such as methanol, ethanol, ethyl acetate, and tetrahydrofuran) suggested that it was difficult to separate the product from the reaction mixture. Finally, **9** was acquired by the reduction of **8** with Pd/C—H_2 in *N*,*N*-dimethylformamide at no more than 40°C, which reduced dechlorination (<2%), increased solubility, thereby improving the yield and purity of the product.

Scheme 1. Synthetic route for lixivaptan.

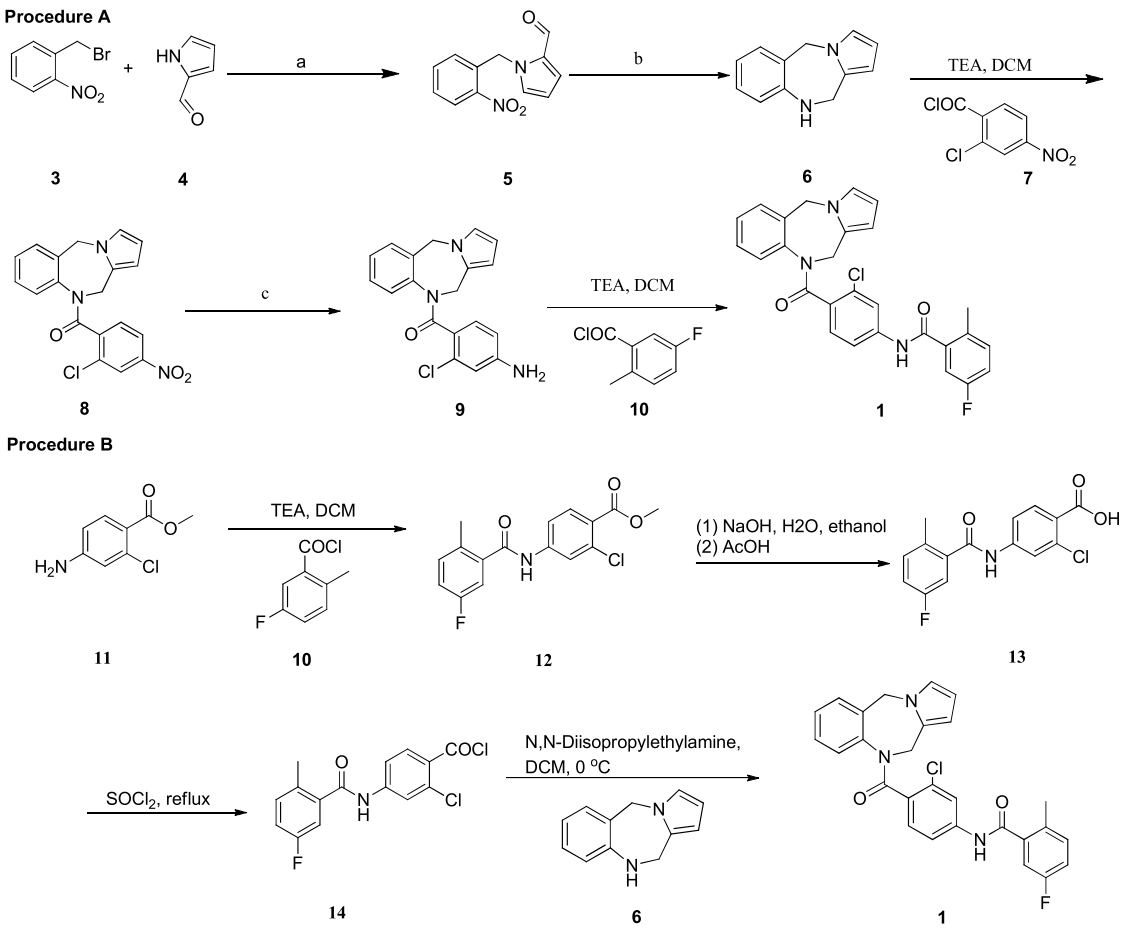


Table 1

Comparisons of solvent volume, yield, and purity.

Reaction conditions	Conventional procedure A			Improved procedure A		
	Solvent volume (mL/g)	Yield (%)	Purity[b] (%)	Solvent volume (mL/g)	Yield (%)	Purity (%)
a	23 (DMF)	95[a]	97.0	6 (THF)	92	99.5
b	26 (ethyl acetate and ethanol 1:1)	66	99.0	3 (ethyl acetate)	93	99.0
c	34 (ethanol)	—	96.2	3 (DMF)	87	98.8

[a]Reported in patents [17]. Experimental data is 60–70%.
[b]No purity data was reported by literatures; experimental data was listed instead.

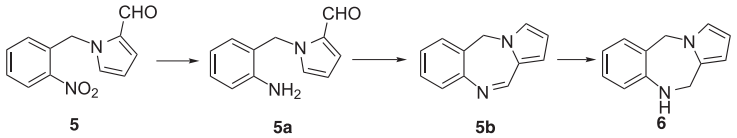
Table 2

Effects of different bases.[a]

Base	NaH	TEA	K_2CO_3	KOH	NaOH
Temperature (°C)	0	65	65	r.t.	r.t.
Reaction time (h)[b]	2	4	5	3	3
Yield (%)	63	88	92	70	76
Purity (%)	97.0	99.3	99.5	97.8	99.0

[a]The reactions were conducted in THF.
[b]Monitored by TLC every 30 min. Postprocessing time was not included.

Scheme 2. Possible pathway of the reaction from **5** to **6**.

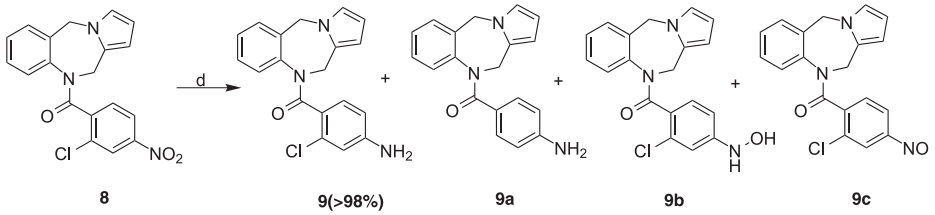


Except the dechlorination byproduct **9a**, another two byproducts **9b** and **9c** were also observed (Scheme 3) in the reaction process. It is because nitro reductions are known to proceed through various intermediates such as nitroso and hydroxylamine [19–21]. Compound **9b** was characterized by ^{1}H NMR; however, **9c** was characterized simply by MS because of the low level in crude intermediate **9**. Extending reaction time can effectively reduce the levels of **9b** and **9c**. Meanwhile, these byproducts can easily be removed by washing with hot ethanol.

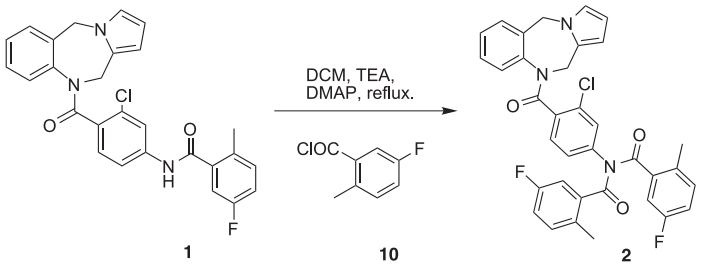
During the synthesis investigation, an impurity was observed in crude lixivaptan product. Then, the impurity was isolated from crude product via silica gel chromatography successfully and characterized by ^{1}H NMR, ^{13}C NMR, and HRMS, which confirmed the structure as *N*-[3-chloro-4-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10(11*H*)-ylcarbonyl) phenyl]-*N*-(5-fluoro-2-methylbenzoyl)-5-fluoro-2-methylbenzamide. Possible mechanism for the formation of the impurity was shown in Scheme 4. Theoretically, it is difficult to prepare imides from amides because of the strong electron-withdrawing effect from the carbonyl group. However, lixivaptan can be completely transformed into the impurity by the introduction of DMAP and increase of temperature. Comparison of the ^{1}H NMR, ^{13}C NMR, HRMS, and the HPLC spectrum of the impurity and the synthesized sample further verified the structure of the impurity.

The optimum reaction conditions were considered to eliminate the imide impurity. The introduction of the impurity was probably due to the excess of **10**. Temperature is another important factor for the generation of the impurity.

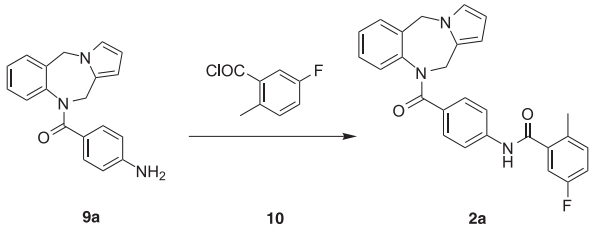
Scheme 3. Byproducts observed in the reaction from **5** to **6**.



Scheme 4. Synthesis of the impurity.



Scheme 5. Formation of the predictable impurity from the byproduct **9a**.



Finally, the product free from the impurity was prepared when the amount of **10** was added at 1 eq of **9**, and the reaction temperature was less than 0°C.

Another possible impurity **2a** (Scheme 5) was concerned because of the side reaction illustrated in Scheme 3, even though the impurity **2a** was not detected in the final product. After recrystallization in ethyl acetate and washed with methanol, the purity of the final product was 99.93% with a maximum single impurity level no more than 0.05%.

CONCLUSION

In conclusion, the synthetic process of lixivaptan has been improved for obtaining satisfied yields and quality by modification of the reaction conditions. All intermediates and the final product could be prepared with readily available, cost-effective, and environmentally friendly reagents and solvents; those made the method more suitable for large-scale industrial production than conventional method. Additionally, the byproducts among this procedure and an impurity in crude product were investigated. The byproducts were speculated by ^{1}H NMR or MS. The impurity was separated from the crude-synthesized lixivaptan and characterized by ^{1}H NMR, ^{13}C NMR, and HRMS, indicating the structure as *N*-[3-chloro-4-(5*H*-pyrrolo[2,1-*c*][1,4] benzodiazepine-10(11*H*)-ylcarbonyl)phenyl]-*N*-(5-fluoro-2-methylbenzoyl)-5-fluoro-2-methylbenzamide (**2**). Synthesis of the impurity further verified its structure. Meanwhile, optimum reaction conditions free from the byproducts and the impurity were developed.

EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers. All reactions were monitored by thin layer chromatography. Silica gel chromatography was conducted by Teledyne Isco COMBIFLASH Rf200 Purification System (petroleum ether and ethyl acetate, gradient elution); chromatographic analysis was performed with an Agilent 1260 equipped with a Grace C18 column (5 μ, 250 mm × 4.6 mm, Lot No. 55/182). ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER AV400 NMR. HRMS was detected on VG ZAB-HS. Melting points were observed on a YRT-3 Melting Point Tester (uncorrected).

1-(2-Nitrobenzyl)-2-pyrrolecarboxaldehyde (5). To a mixture of 2-nitrobenzyl bromide (455 g, 2.1 mol) and pyrrole-2-car boxaldehyde (200 g, 2.1 mol) in tetrahydrofuran (1200 mL) was added anhydrous potassium carbonate (440 g, 3.2 mol). Then, the mixture was heated to reflux and stirred for about 5 h. Then, the reaction mixture was poured into 2400 mL of water and stirred for an additional 0.5 h. Potassium carbonate was completely dissolved in water and yellow solid precipitated. After filtration, the resulting residue was vacuum dried to give desired product **5** as a light yellow solid (445 g, yield 92%), mp 135–137°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.85 (s, 2H), 6.39 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 1H), 6.44 (d, J = 7.6 Hz, 1H), 7.17 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 7.45 (s, 1H), 7.52–7.54 (m, 1H), 7.61–7.63 (m, 1H), 8.11 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 9.442 (d, J = 0.80 Hz, 1H).

10,11-Dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (6). Compounds **5** (400 g, 1.7 mol), 10% Pd/C (20 g), and ethyl acetate (1200 mL) were added into a 5-L high pressure reactor. At hydrogen atmosphere, the mixture was heated to 60°C, and the pressure was maintained at 0.1–0.2 MPa for 4 h. After the system was cooled to ambient temperature, the reaction mixture was filtrated to give colorless solution. Three quarters of the solvent was evaporated off under reduced pressure and white crystal precipitated. The desired product was obtained as white crystal (297 g, yield 93%), mp 152–154°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.33 (d, J = 4.8 Hz, 2H), 5.18 (s, 2H), 5.82 (t, J = 3.2 Hz, 1H), 5.86 (q, J = 1.6 Hz, 1H), 6.07 (t, J = 4.8 Hz, 1H), 6.38–6.46 (m, 2H), 6.72–6.73 (m, 1H), 6.87–6.94 (m, 2H).

2-Chloro-4-nitrobenzoyl chloride (7). *N*,*N*-Dimethylformamide (10 mL) was added into the mixture of 2-chloro-4-nitrobenzoic acid (322 g, 1.6 mol) and dichloromethane (900 mL) followed heating to reflux. Thionyl chloride (381 g, 3.2 mol) was added dropwise into the mixture and stirred for an additional 4 h. Then, the solution was concentrated in vacuo to afford 2-chloro-4-nitrobenzoyl chloride (**7**) as yellow oil, which was taken on to the next step without purification.

(2-Chloro-4-nitrophenyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-yl-methanone (8). Triethylamine (230 g, 2.3 mol) was added into a solution of **6** (280 g, 1.5 mol) in dichloromethane (1000 mL). After the mixture was cooled to 0°C, **7** dissolved in dichloromethane (500 mL) was added dropwise into the mixture and stirred for 5 h. Then, the mixture was washed successively with 1 mol/L hydrochloric acid and water. The organic layer was dried over anhydrous magnesium sulfate and evaporated to give brown oil. Methanol (1000 mL) was added to the oil and yellow solid precipitated. The intermediate **8** was afforded by filtration as yellow powder (470 g, yield 84%), mp 135–138°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.24 (br, 4H), 5.90 (t, J = 3.0 Hz, 1H), 6.01 (s, 1H), 6.83 (s, 1H), 7.03–7.08 (m, 2H), 7.11–7.15 (m, 1H), 7.40 (d, J = 7.2 Hz, 1H), 7.71 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H).

(4-Amino-2-chlorophenyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11H)-yl-methanone (9). The mixture of **8** (450 g, 1.2 mol) and 5% Pd/C (23 g) in *N*,*N*-dimethylformamide (1400 mL) was stirred at 35 ~ 40°C for 6 h under hydrogen atmosphere. Then, the insoluble solid was removed, and the resulting filtrate was poured into water (5000 mL) and white solid precipitated. The crude solid was stirred in refluxing ethanol for 0.5 h. After filtration and drying, compound **9** was obtained as white powder (360 g, yield 87%), mp 210–212°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.98 (s, 2H), 5.20 (s, 2H), 5.54 (s, 1H), 5.88–5.91 (m, 2H), 6.26 (s, 1H), 6.46 (s, 1H), 6.78s, 1H), 6.88 (d, J = 7.2 Hz, 1H), 6.99 (s, 1H), 7.13 (s, 2H), 7.38 (d, J = 4.4 Hz, 2H).

Separation of the byproducts (9a, 9b, and 9c). The crude solid of **9** was separated by preparative HPLC to afford the byproducts. **9a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.98 (br s, 2H), 5.23 (s, 2H), 5.49 (s, 2H), 5.91 (s, 2H), 6.30 (d, J = 8.4 Hz, 2H), 6.79–6.85 (m, 2H), 6.95 (d, J = 8.4 Hz, 2H), 7.11–7.19 (m, 2H), 7.46–7.48 (d, J = 6.4 Hz, 2H). **9b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.03–5.23 (m, 4H), 5.89–5.95 (m, 2H), 6.50 (s, 1H), 6.71 (s, 1H), 6.79 (s, 1H), 6.99–7.11 (m, 4H), 7.39 (s, 1H), 8.51 (s, 1H), 8.61 (s, 1H). **9c**: MS (ESI), $[M+H]^+$ *m/z*: 352.3.

5-Fluoro-2-methylbenzoyl chloride (10). Similar to the preparation of **7**, a mixture of 5-fluoro-2-methylbenzoic acid (200 g, 1.3 mol), dichloromethane (600 mL), and *N*,*N*-dimethylformamide (10 mL) was added thionyl chloride (310 g, 2.6 mol) and heated to reflux for 4 h. The solution was concentrated to afford 5-fluoro-2-me thylbenzoyl chloride (**7**) as chartreuse oil, which was taken on to the next step without purification.

Lixivaptan (1). To a mixture of **9** (360 g, 1.1 mol) in dic hloromethane (1500 mL), triethylamine (160 g, 1.6 mol) was added. Thereafter, **10** (184 g, 1.1 mol) dissolved in 400 mL of dichl oromethane was added dropwise into the reaction mixture followed stirring for 5 h under 0°C. Then, the mixture was washed successively with 1 mol/L hydrochloric acid and water. The organic layer was dried over anhydrous magnesium sulfate and concentrated to a residue as brown solid. Methanol (500 mL) was added to the residue and heated to reflux; then, the mixture was filtrated to give crude product, which was purified by recrystallization in ethyl acetate (1000 mL) after 2 h stirring. Finally, the sample was washed with methanol (500 mL) to give final product as white powder (355, yield 70%, purity 99.93%), mp 169–172°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.30 (s, 3H), 5.27 (br, 4H), 5.91 (s, 1H), 5.99 (s, 1H), 6.82 (s, 1H), 7.05–7.14 (m, 3H), 7.23 (t, J = 8.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 3H), 7.39–7.51 (m, 3H), 7.84 (s, 1H), 10.50 (s, 1H). HRMS (ESI), calcd: $C_{27}H_{21}ClFN_3O_2$ $[M+H]^+$ *m/z*: 474.1379, found: 474.1385.

Isolation of the impurity (2). The recrystallization mother liquor of lixivaptan was concentrated and separated by silica gel chromatography to afford the impurity, mp 203–207°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.23 (s, 6H), 5.22 (br, 4H), 5.89 (t, J = 3.0 Hz, 1H), 5.99 (s, 1H), 6.81 (s, 1H), 6.85-6.92 (m, 2H), 7.08–7.19 (m, 5H), 7.28–7.35 (m, 2H), 7.56–7.59 (m, 2H), 7.71 (s, 1H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ: 18.4, 45.0, 49.3, 106.8, 108.6, 113.9, 114.1, 117.5, 117.7, 122.2, 124.8, 127.4, 127.9, 128.1, 128.3, 128.4, 129.0, 129.7, 130.2, 132.4, 132.5, 132.5, 132.6, 135.3, 135.9, 136.3, 136.3, 139.4, 158.4, 160.8, 166.1, 170.4. HRMS (ESI), calcd: $C_{35}H_{26}ClF_2N_3O_3$ $[M+H]^+$ *m/z*: 610.1704, found: 610.1699. HPLC retention time: 12.06 min (methanol: H_2O = 4 : 1, flow rate 0.5 mL/min).

***N*-[3-Chloro-4-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10(11*H*)-ylcarbonyl)phenyl]-*N*-(5-fluoro-2-methylbenzoyl)-5-fluoro-2-methylbenzamide (2)**. Compound **7** (2.2 g, 12.7 mmol) was added to the mixture of lixivaptan (5 g, 10.6 mmol) in dichloromethane (30 mL) with triethylamine (1.6 g, 15.8 mmol) and DMAP (0.25 g). The mixture was refluxed for 4 h, and the reaction solution was washed successively by 1 mol/L hydrochloric acid and water. The organic phase was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by recrystallization (petroleum ether/ethyl acetate = 50/50, v/v, 20 mL) to give compound **2** as yellow solid (3.9 g, 60%), mp 203–207°C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.23 (s, 6H), 5.25 (br, 4H), 5.89 (s, 1H), 5.99 (s, 1H), 6.81 (s, 1H), 6.85–6.92 (m, 2H), 7.08–7.19 (m, 5H), 7.25–7.35 (m, 2H), 7.54–7.63 (m, 2H), 7.71 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 18.4, 45.0, 49.3, 106.8, 108.6, 113.9, 114.1, 117.4, 117.6, 122.1, 124.8, 127.4, 127.9, 128.1, 128.3, 128.4, 128.9, 129.7, 130.2, 132.4, 132.4, 132.5, 132.6, 135.3, 135.9, 136.2, 136.3, 139.4, 158.4, 160.8, 166.1, 170.4. HRMS (ESI), calcd: $C_{35}H_{26}ClF_2N_3O_3$ $[M+H]^+$ *m/z*: 610.1704, found: 610.1699. HPLC retention time: 12.04 min (methanol: H_2O = 4 : 1, flow rate 0.5 mL/min).

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