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Scale-Up Synthesis of Antidepressant Drug Vilazodone

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ABSTRACT: A scale-up synthesis of antidepressant drug vilazodone was accomplished in five steps. Friedel−Crafts acylation of 1-tosyl-1*H*-indole-5-carbonitrile with 4-chlorobutyryl chloride, selective deoxygenation in $NaBH_4/CF_3COOH$ system coupled with ethyl 5-(piperazin-1-yl)-benzofuran-2-carboxylate hydrochloride, one-step deprotection and esterolysis, and the final ammonolysis led to the target molecule vilazodone in 52.4% overall yield and 99.7% purity. This convenient and economical procedure is remarkably applicable for scale-up production.

INTRODUCTION

Vilazodone (Figure 1), a dual selective serotonin reuptake inhibitor (SSRI) and serotonin 5-HT_{1A} receptor partial agonist,

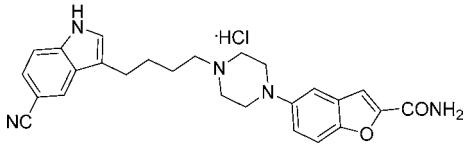

Figure 1. Vilazodone (**1**).

is a novel antidepressant drug recently approved by the Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD).[1] The reported synthetic approaches,[2] however, proceed with complicated workups, laborious purification procedures, fairly expensive or unfriendly catalysts, such as sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) and 1-methyl-2-chloropyridinium iodide (Mukaiyama reagent), and merely 3.5% overall yield. Although the further modifications of the above procedures have also been published in many patents,[3] all these approaches suffer from several drawbacks, including low overall yields, complicated purification process, and the employment of some expensive, unstable, or environmentally unfriendly reagents and catalysts. Thus, there still remains a high unmet need for a high-yield process applicable to the multikilogram production of vilazodone. Herein we described the development of a scalable synthesis of vilazodone (**1**) in a fairly high overall yield.

RESULTS AND DISCUSSION

Initial Synthesis of 1, Vilazodone. The synthesis of 3-acylindoles is often complicated by the fact that indole displays ambident reactivity leading to competing substitution at nitrogen. For example, the synthesis of 3-(4-chlorobutanoyl)-1*H*-indole-5-carbonitrile **2a** (73%) (Scheme 1) in a mixture of isobutyl-$AlCl_2$ and 4-chlorobutyryl chloride would unavoidably produce N-substituted indoles, such as 1-(4-chlorobutanoyl)-1*H*-indole-5-carbonitrile (**2b**), which was difficult to separate chromatographically.

Additionally, the following selective deoxygenation of the keto function group of 3-(4-chlorobutanoyl)-1*H*-indole-5-carbonitrile (**2a**) furnishes the product 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile (**3a**) in a low yield (26%), and the resulting solid **3a** is difficult to purify chromatographically.[2] We postulated that the significantly low yield and laborious purification process reported in the literature might result from the over-reduction of indole to indoline by a variety of hydride sources in the presence of various acids, such as Et_3SiH in CF_3COOH (TFA),[4] $NaBH_4$ in carboxylic acid or TFA,[5] $NaCNBH_3$ in acetic acid or TFA,[6] or Me_2SiHCl in Lewis acids, like $InCl_3$[7] (Scheme 2). The partial protonation of N-unprotected or N-alkylindoles in acid media might underlie the over-reduction of the compound **2a**. In order to demonstrate this hypothesis, we tried different reducing agents under acid media to reduce the molecule **2a**. As indicated in Table 1, the compound **2a** was indeed over-reduced into indoline by most of reductants, and accordingly the product **3a** was obtained at a very low yield, which simultaneously required laborious separation procedures. For instance, a large portion of compound **2a** would be reduced to the molecule **3b** (the indoline structure), while a small quantity of compound **2a** was converted to the desired product **3a** in the conditions of the $NaBH_4$/TFA system.

Finally, the intermediate **5a** is synthesized from **3a** and commercially available **4** (the synthesis is also published[8]) in 32% yield. Although **5a** could be obtained by this method in moderate yield, the process obviously was not amenable to industrial manufacturing due to the involvement of column chromatography. Furthermore, the costly catalyst 1-methyl-2-chloropyridinium iodide (Mukaiyama reagent) used in the literature to synthesize the target molecule vilazodone might further impede large-scale production. Thus all these undesired results prompted us to search for an alternate route.

Process Development for the Preparation of 1, Vilazodone. In contrast, herein we identified an efficient synthetic route to vilazodone, starting from N-protected 5-cyanoindole since indoles bearing strong electron-withdrawing groups, such as *p*-toluenesulfonyl or phenylsulfonyl functional groups, are resistant to C-3 protonation and thus effectively inert to over-reduction (Scheme 3).[9] The synthesis of N-protected 5-cyanoindole was quite convenient to proceed with

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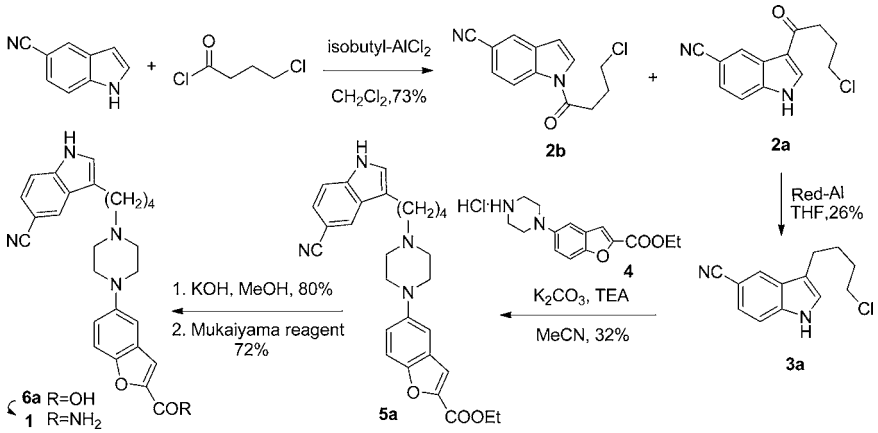
Scheme 1. Initial Synthesis of 1, Vilazodone



Scheme 2. Over-Reduction of Indole to Indoline under the Acidic Conditions

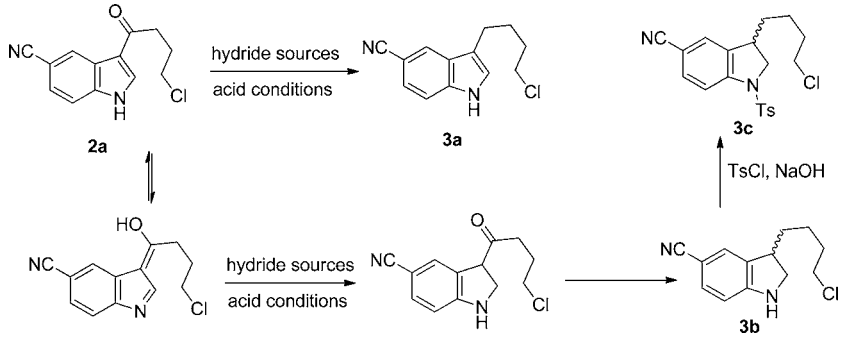


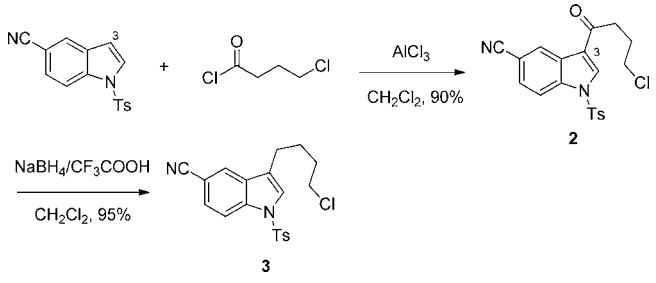
Table 1. Reduction of Compound 2a with Reducing Agents under Different Acid Conditions

entry	subject	conditions[a]	products	ratio	yield[b]
1	**2a**	$NaBH_4$/TFA	**3a:3b**	1:4	31%
2	**2a**	$NaBH_4$/HOAc	--[c]	--	--
3	**2a**	$NaBH_3CN$/TFA	**3a:3b**[d]	>1:10	56%
4	**2a**	$NaBH_3CN$/HOAc	**3a:3b**[d]	>1:10	22%
5	**2a**	$HSi(C_2H_5)_3$/TFA	**3a:3b**	1:8	69%
6	**2a**	Red-Al/THF	--	--	--

[a]Conditions were typically the reducing agents dissolved in acid solutions at 0 °C to which was added compound **2a** in CH_2Cl_2 solution, and the reaction mixture was stirred at rt for 6 h. [b]Isolated total yield of indole and indoline derivatives. [c]"--" represents that no product is produced. [d]Minute amount of **3a** is formed.

an excellent yield (98%).[10] This simple protection provided several major benefits.

Scheme 3. Alternative Synthesis of the Key Intermediate 3



First, the Friedel–Crafts reaction would selectively substitute at C-3 position of indole ring without any N-substituted byproduct. The product **2** could readily be prepared through recrystallization in *n*-propanol. Moreover, the electron-withdrawing effect of protecting groups, such as tosyl group or phenylsulfonyl group, would prevent the over-reduction of indole to indoline by reducing agents under acidic conditions, and therefore the selective deoxygenation of the keto group was accomplished with decent yields under mild conditions (Scheme 3).

For further optimization of this condition, we had explored a variety of reducing agents under different acid media to reduce the keto group of N-protected indole **2**. The results, summarized in Table 2, indicated that most of the reducing agents under acidic conditions could selectively deoxygenize the ketone group without any over-reduction byproducts.[11] Compared with acetic acid (HOAc), the trifluoroacetic acid (TFA) displayed much better characteristics for the accomplishments of the initial reduction of the ketone carbonyl by the stronger trifluoroacetoxyborohydride, acid-catalyzed protonation of the resultant alcohol, and loss of water. Finally, $NaBH_4$/TFA system was adopted by us thanks to its excellent yield (95%) and relevant low cost.

The important intermediate 3-(4-chlorobutanoyl)-1-tosyl-1*H*-indole-5-carbonitrile (**2**) was prepared by stirring a mixture of 1-tosyl-1*H*-indole-5-carbonitrile and 4-chlorbutyryl chloride in the presence of the catalyst $AlCl_3$ at the ambient temperature for 8 h. The reaction mixture was then poured into ice water, followed by extraction with CH_2Cl_2. The combined organic phase was washed with brine, dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and

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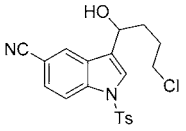
Table 2. Reduction of Compound 2 with Reducing Agents under Acid Conditions

Entry	Subject	Conditions[a]	Product	Ratio	Yield[b]
1	**2**	$NaBH_4$/TFA	3	+[c]	95%
2	**2**	$NaBH_4$/HOAc	--[d]	--	--
3	**2**	$NaBH_3CN$/TFA	3	+	91%
4	**2**	$NaBH_3CN$/HOAc			46%
5	**2**	$HSi(C_2H_5)_3$/TFA	3	+	85%

[a]Conditions were typically the reducing agents dissolved in acid solutions at 0 °C to which was added compound **2a** in CH_2Cl_2 solution, and the reaction mixture was stirred at rt for 6 h. [b]Isolated yield. [c]"+" means only product **3** is produced. [d]"--" represents that no product is obtained.

Scheme 4. Scale-Up Synthesis of 1, Vilazodone

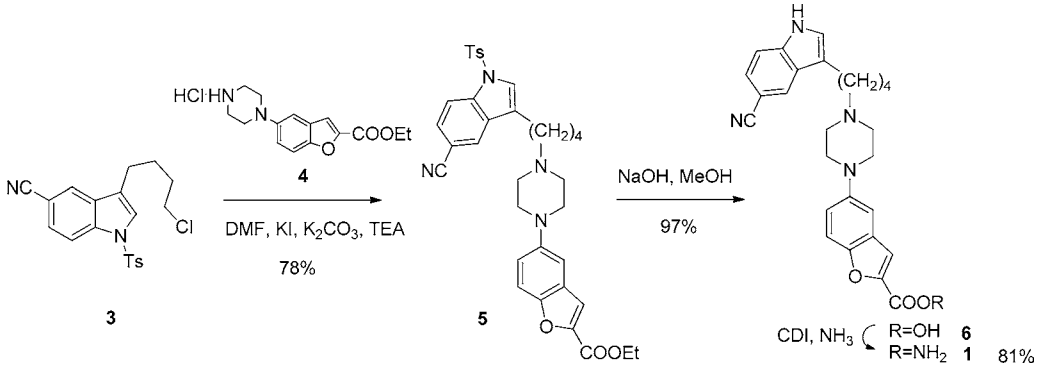
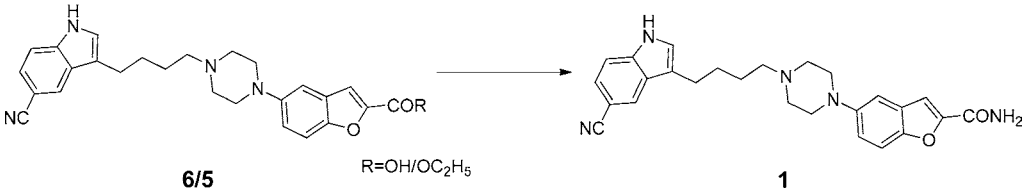


Table 3. Reaction Condition Optimization of Ammonolysis in the Synthesis of Vilazodone



entry	subject	conditions[a]	yield
1	**6**	Mukaiyama reagent/NH_3(g)	72%[b]
2	**6**	CDI/NH_3(g)	81%
3	**6**	EDCI, HOBt/NH_3(g)	75%
4	**6**	PyBOP/NH_3(g)	70%
5	**6**	$SOCl_2$/NH_3(g)	<5%
6	**6**	$C_2Cl_2O_2$/NH_3(g)	<5%
7	**6**	$POCl_3$/NH_3(g)	23%
8	**5**	NH_3(g)	--[c]

[a]Conditions were typically as follows: the compound **6** was dissolved in DMF at rt, to which were added coupling agents, and then NH_3(g) was introduced for 30 min; or the compound **6** was suspended in DCM at 0 °C, to which were added different chlorinating agents. The mixture was stirred at rt for 2 h, and then NH_3(g) was introduced for 15 min; or compound **5** was dissolved in MeOH, to which NH_3(g) was introduced. [b]The yield is cited from ref 2a. [c]"--" represents that no vilazodone is obtained.

purified via recrystallisation from *n*-propanol to yield **2** (90%) with analytical purity. The subsequent selective deoxygenation of **2** was carried out in the $NaBH_4/CF_3COOH$ system. Initially, $NaBH_4$ was added slowly into the CF_3COOH solution under the protection of nitrogen gas, which was followed by the addition of a solution of **2** in CH_2Cl_2. After the reaction mixture was stirred at room temperature for 6 h, it was poured into ice water and extracted with CH_2Cl_2. The combined organic phase was washed successively with Na_2CO_3-saturated aqueous solution and brine, dried with anhydrous sodium sulfate,

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filtered, and concentrated. The crude product was recrystallized from methanol to afford **3** in 95% yield with analytical purity.

In the synthesis of the intermediate **5**, the Finkelstein conditions[12] were employed since iodine is a good leaving group. This led cleanly to compound **5** and meanwhile shortened the reaction time significantly. We have also evaluated a range of acid scavengers (TEA, K_2CO_3, pyridine, DIPEA, NMM) and their different combinations. Surprisingly, we had noted that the addition of both TEA and K_2CO_3 led cleanly to product **5**. Therefore, this optimized process consists of stirring a mixture of the intermediate **3**, compound **4**, TEA, K_2CO_3, and a catalytic amount of KI in DMF for 16 h at 85 °C (Scheme 4). The reaction mixture was then poured into ice water, and the resulting precipitate was filtered and dried under vacuum to furnish off-white solid **5**. The obtained solid was then dissolved in ethyl acetate (EtOAc) and converted to the corresponding hydrochloride salt after addition of HCl-saturated EtOAc solution in 78% yield.

It is worth noting that compound **5** could be transformed into molecule **6** through one-step esterolysis and deprotection of tosyl group in a NaOH/MeOH system with excellent yield (97%), which would not require additional procedures at the cost of lowering the yield or boosting the expenditure after introducing a protecting group. A mixture of **5** and NaOH in methanol was heated to reflux for 4 h and then cooled. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water. 15% aqueous hydrochloric acid was then added until complete precipitation (pH ≈ 7); the precipitate was filtered and dried under vacuum to afford **6** (97%) which was pure enough for the following step.

Finally, a range of experiments was carried out to optimize the aminolysis reaction in synthesizing vilazodone. As illustrated in Table 3, most condensing agents furnished the final product vilazodone in good yields, while the chlorinating agents gave poor results and the direct aminolysis failed to initiate the reaction. Thus, *N*,*N*′-carbonyldiimidazole (CDI) was finally employed as coupling agent in replacement of Mukaiyama reagent to synthesize vilazodone for its low price and environmentally friendly characteristics. The target compound vilazodone (**1**) was produced in good yield as well (81%). First, CDI was added into a solution of **6** in anhydrous DMF. After the reaction mixture was stirred for 1 h at rt, NH_3(g) was introduced for 30 min. The mixture was poured into ice water, and the precipitate was filtered and dried under vacuum to yield a crude product of vilazodone in free base form, which was followed by a further salt switch to hydrochloride through the addition of HCl-saturated EtOAc solution. Then the product hydrochloride was further purified by recrystallization from an ethanol/methanol (1:1) solution.

CONCLUSION

Our five-step approach furnished vilazodone with an overall yield of 52.4% and was, to the best of our knowledge, the most efficient route to date to synthesize the target molecule vilazodone in an economical and convenient manner. Furthermore, all intermediates and vilazodone could be prepared with readily available, inexpensive and environmentally friendly reagents and solvents via simple and straightforward workups, rendering this new process highly amenable to the large-scale production of vilazodone.

EXPERIMENTAL SECTION

General Methods. All chemicals and solvents were either purchased or purified by standard techniques and used without any further purification. TLC was carried out using Merck 25 DC-AlufolienKieselgel GF254 silica gel plates. Melting points were recorded on an RY-1 melting point apparatus and were uncorrected. MS spectra were acquired on Agilent 1100 series LC/MSD Tarp (SL). The ^{1}H NMR spectra were recorded on a BRUKER AV-300 or AV-500 NMR spectrometer using TMS as the internal standard. The HRMS spectra were acquired on a Waters Micros Q-TOF apparatus. Product purities were determined by HPLC conducted on an Agilent 1200 system using a reverse-phase C18 column, and MeOH−H_2O was used as the mobile phase.

1-Tosyl-1*H*-indole-5-carbonitrile. The 1-tosyl-1*H*-indole-5-carbonitrile was prepared similarly to the reported procedure of ref 6. Mp: 116−118 °C (lit.[13] 116−118 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 3.6 Hz, 1H), 7.55 (dd, J = 8.6 Hz, J = 1.4 Hz, 1H), 7.27 (d, J = 8.3 Hz, 2H), 6.72 (d, J = 3.6 Hz, 1H), 2.36 (s, 3H).

3-(4-Chlorobutanoyl)-1-tosyl-1*H*-indole-5-carbonitrile (2). To a solution of $AlCl_3$ (7.2 kg, 54 mol) in CH_2Cl_2 (120 L) were added 4-chlorobutyryl chloride and a solution of 1-tosyl-1*H*-indole-5-carbonitrile (8 kg, 27 mol) in CH_2Cl_2 (20 L). The reaction mixture was stirred at rt for 8 h. After completion of the reaction, the reaction mixture was poured into ice water (150 L) and extracted with CH_2Cl_2 (3 × 120 L). The combined organic layer was washed successively with Na_2CO_3-saturated aqueous solution and brine, dried overnight with anhydrous Na_2SO_4, filtered and concentrated to afford white crude product **2** (10.2 kg). The crude product was recrystallized from 1-propanol (150 L) to give analytical purity product **2** (9.7 kg, 90%) as white crystal. Mp 154−156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, J = 1.4 Hz, 1H), 8.36 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.62 (dd, J = 8.7 Hz, J = 1.4 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 3.69 (t, J = 6.3 Hz, 2H), 3.13 (t, J = 6.3 Hz, 2H), 2.40 (s, 3H) 2.21−2.30 (m, 2H). IR (KBr): 3310, 2946, 2227, 1663, 1608, 1540, 1458, 1389, 1173, 1134, 1086, 989, 823, 702, 672 cm^{-1}. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2O_3S$, 401.0721; found, 401.0722.

3-(4-Chlorobutyl)-1-tosyl-1*H*-indole-5-carbonitrile (3). To a stirred solution of CF_3COOH (150 L) under the protection of nitrogen at 0 °C was added $NaBH_4$ (11 kg, 300 mol) slowly. A solution of **2** (8 kg, 20 mol) in CH_2Cl_2 (200 L) was then added to this mixture under 15 °C. The reaction mixture was stirred for 6 h at ambient temperature, poured into ice water (500 L) and extracted with CH_2Cl_2 (3 × 150 L). The combined organic layer was washed successively with Na_2CO_3-saturated aqueous solution and brine (2 × 250 L), dried overnight with anhydrous Na_2SO_4, filtered and concentrated to afford white crude product **3** (7.8 kg). The crude product was recrystallized from methanol (300 L) to give **3** (7.3 kg, 95%) as white crystal. Mp: 110−112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.6 Hz, 1H), 7.46 (s, 1H), 7.25 (d, J = 8.3 Hz, 2H), 3.57 (s, 2H), 2.70 (s, 2H), 2.36 (s, 3H), 1.68−1.91 (m, 4H). MS (ESI, 70 eV): m/z = 385 [M − H]$^-$. IR (KBr): 3114, 2225, 1458, 1371, 1175, 1129, 811, 667, 590 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{19}ClN_2NaO_2S$, 409.0748; found, 409.0744.

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Ethyl 5-(4-(3-(5-Cyano-1-tosyl-1*H*-indol-3-yl)butyl)-piperazin-1-yl)benzofuran-2-carboxylate Hydrochloride (5). A mixture of **3** (5 kg, 13 mol), **4** (4 kg, 13 mol), K_2CO_3 (3.6 kg, 26 mol), TEA (3.6 L, 26 mol), catalytic amount of KI (0.2 kg, 1.3 mol) and DMF (150 L) was heated to 85 °C for 16 h and cooled. After cooling, the reaction mixture was poured into ice water (200 L) and the precipitate was filtered and dried under vacuum to give off-white crude product **5** (6.9 kg). To a solution of the crude product in EtOAc (100 L) was added HCl-saturated EtOAc solution until complete precipitation (pH = 2−3). The precipitate was filtered and dried under vacuum to give **5** (6.7 kg, 78%) as off-white solid. Mp: 194−196 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.23 (s,1H), 8.06 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.85 (s, 1H), 7.73 (d, J = 9.5 Hz, 1H), 7.64 (s, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.36 (s, 1H), 7.32 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 11.0 Hz, 2H), 3.57 (d, J = 11.0 Hz; 2H), 3.31 (t, J = 11.9 Hz, 2H), 3.18 (bs, 4H), 2.73 (s, 2H), 2.31 (s, 3H), 1.65−1.1.88 (m, 2H) 1.41−1.65 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H). IR (KBr): 3427, 2220, 1724, 1458, 1361, 1300, 1166, 816, 676, 600, 537 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{35}H_{37}N_4O_5S$, 625.2479; found, 625.2478.

5-(4-(3-(5-Cyano-1*H*-indol-3-yl)butyl)piperazin-1-yl)-benzofuran-2-carboxylic Acid (6). To a mixture of **5** (5 kg, 7.6 mol) was added NaOH (1.2 kg, 30 mol) in MeOH (50 L), and the mixture was heated to reflux for 4 h and then cooled. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water (50 L). The pH of the solution was adjusted to about 7.0 by the addition of 15% aqueous hydrochloric acid. After the complete precipitation, the precipitate was filtered and dried under vacuum to furnish **6** (3.25 kg, 97%) as off-white product. Mp: 192−194 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.50 (bs, 1H), 8.11 (bs, 1H), 7.60−7.51 (m, 3H), 7.43 (s, 1H), 7.40 (s, 1H), 7.25 (s, 2H), 7.12 (d, J = 7.5 Hz, 1H), 3.40−3.07 (m, 8H), 2.77 (s, 2H), 2.29 (s, 2H), 1.60−1.81 (m, 4H). MS (ESI, 70 eV): m/z = 441 [M − H]$^-$. IR (KBr): 3411, 2217, 1579, 1560, 1472, 1397, 1216, 805, 685, 563 cm^{-1}. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{27}N_4O_3$, 443.2078; found, 443.2076.

5-(4-(3-(5-Cyano-1*H*-indol-3-yl)butyl)piperazin-1-yl)-benzofuran-2-carboxamide (1). To a solution of **6** (3 kg, 11.3 mol) in anhydrous DMF (150 L) at 15 °C was added CDI (1.6 kg, 10.2 mol). The reaction mixture was stirred at ambient temperature for 1 h, followed by the introduction of NH_3(g) for 30 min. The mixture was then poured into ice−water (180 L). The precipitate was filtered and dried under vacuum to yield 2.7 kg of vilazodone in the form of free base. The free base was then dissolved in hot isopropanol (30 L), and HCl-saturated EtOAc solution was added until complete precipitation (pH = 2−3). The precipitate was filtered and dried under vacuum to furnish the crude product of vilazodone hydrochloride **1** as off-white solid. The product of vilazodone hydrochloride was then recrystallized from an ethanol−methanol solution (1:1; 10 L) to give the final pure product vilazodone hydrochloride as white needles (2.4 kg, 81%). HPLC analysis: 99.7%. Mp: 234−236 °C (became charred). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.49 (s, 1H), 11.81 (bs, 1H), 8.10 (s, 1H), 7.61 (brs, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 0.65 Hz, 1H), 7.41 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 7.40 (d, J = 2.6 Hz, 1H), 7.27 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 9.1 Hz, J = 2.4 Hz, 1H), 3.78−3.70 (m, 2H), 3.58−3.52 (m, 2H), 3.23−3.21 (m, 6H), 2.78 (t, J = 7.5 Hz, 2H), 1.85−1.78 (m, 2H), 1.61−1.75 (m, 2H). MS (ESI, 70 eV): m/z = 442 [M + H]$^+$. IR (KBr): 3458, 3128, 2216, 1674, 1597, 1400, 934 cm^{-1}. ^{13}C NMR (75 MHz, DMSO-d_6): 22.9, 23.6, 26.8, 46.9 (2C), 50.9 (2C), 55.4, 100.1, 108.5, 109.8, 112.2, 112.7, 115.3, 118.5, 121.0, 123.6, 124.1, 125.1, 126.9, 127.7, 138.0, 146.7, 149.5, 149.6, 160.0. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{28}N_5O_2$, 442.2238; found, 442.2234.

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Notes

The authors declare no competing financial interest.

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(11) In order to demonstrate that there are no indoline byproducts, *N*-tolylsulfonyl indoline structure **3c** was synthesized from molecule **3b** through a similar procedure to synthesize 1-tosyl-1*H*-indole-5-carbonitrile, and detailed comparison was made through NMR, MS and TLC characteristics between products **3** and **3c**. The characterization data of **3c**: ^{1}H NMR 7.73−7.69 (m, 3H), 7.52 (dd, J_1 = 9 MHz, J_2 = 3 MHz, 1H), 7.33−7.27 (m, 3H), 4.06 (t, J = 9 MHz, 1H), 3.69−3.63 (m, 1H), 3.50 (t, J = 6 MHz, 2H), 3.25−3.18 (m, 1H), 2.41 (s, 3H), 1.76−1.28 (m, 6H); MS (ESI, 70 eV) m/z = 389 $[M + H]^+$.

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