ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Article
pubs.acs.org/OPRD

Synthesis of Impurities of Pramipexole Dihydrochloride

Tianwen Hu,[†,‡,∥] Feipu Yang,[†,‡,∥] Tao Jiang,[†,‡] Weiming Chen,[§] Jian Zhang,[§] Jianfeng Li,[†] Xiangrui Jiang,[*,†] and Jingshan Shen[†]

[†]CAS Key Laboratory of Receptor Research, Drug Discovery and Design Center, Shanghai Institute of Materia Medica, Chinese Academy of Sciences (CAS), 555 Zuchongzhi Road, Shanghai 201203, China

[‡]University of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, China

[§]Topharman Shanghai Co. Ltd., Shanghai 201209, China

Supporting Information

ABSTRACT: Three impurities of pramipexole dihydrochloride were synthesized, and the possible generation mechanisms and the preparation methods of some impurities were reviewed. The desired configuration at C7 of **3** was built by a Mitsunobu reaction.

KEYWORDS: *pramipexole, Mirapex, impurities, synthesis, Mitsunobu reaction*

INTRODUCTION

Pramipexole dihydrochloride monohydrate (Figure 1), developed as a second-generation nonergot dopamine

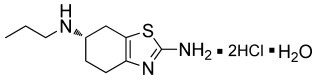


Figure 1. Structure of pramipexole dihydrochloride monohydrate.

receptor agonist by Boehringer Ingelheim, is the active substance in the anti-Parkinson drug Mirapex.[1,2] Pramipexole binds to the D_2 dopamine receptor subfamily with selectivity for the D_3 dopamine receptor.[3,4] It is well-established as a treatment option for motor symptoms at all stages of Parkinson's disease (PD).[5,6] Also, this drug is effective in the treatment of idiopathic and secondary restless legs syndrome (RLS) and in treatment-resistant patients as well.[7−12] The methods for synthesizing pramipexole disclosed in the original patent include three synthetic routes with 2,6-diamino-4,5,6,7-tetrahydrobenzothiazole as the common intermediate (Scheme 1).[13,14]

Seventeen impurities (Figure 2) were regulated in the quality inspection standards of pramipexole dihydrochloride tablets provided by the originator. Some of them originate from the manufacturing process of the active pharmaceutical ingredient (API). Others may be caused by oxidation or degradation of pramipexole in the process of preparation and storage.[15] For instance, Nishimura et al.[16] reported that **5** might be caused by photodegradation of pramipexole in the preparation and explained possible mechanisms for this in the solid state and the liquid state.

Pramipexole impurity standards are essential for the quality control of the API and tablets to ensure the safety and efficacy of the drug. To date, syntheses of some of these impurities have been reported. In 1986, Schneider and Mierau[17] provided synthetic routes for three impurities, namely, **Impurity A**, **Impurity D** (the *R* enantiomer of pramipexole), and **Impurity E**. Gegö et al.[18] reported the synthesis of **3**-**4**. Nishimura et al.[16] completed the synthesis of **5** in 2012. Jia et al.[19] reported the synthesis of **7**, and Wu et al.[20] reported the synthesis of **Impurity B**. However, synthetic methods for some of the other impurities have not been reported. Herein we report the synthesis of **3** and two other impurities (**1** and **2**).

RESULTS AND DISCUSSION

1, **2**, and **3** are generated by degradation of pramipexole. **1** and **2** may result from the mechanism of oxidation; **3** may be generated by replacement or condensation reactions between pramipexole and its oxidation impurities. Thus, the strategy of degradation and subsequent isolation was first tried to prepare these three impurities, but this approach failed.

Synthesis of 1. Compound **1**-**2** was obtained by bromination of **1**-**4** and subsequent replacement by thiourea (Scheme 2). **1**-**1** was then synthesized from **1**-**2** by the process of Gegö et al.[18] The desired compound **1** was furnished by the nucleophilic reaction between **1**-**1** and propylamine.

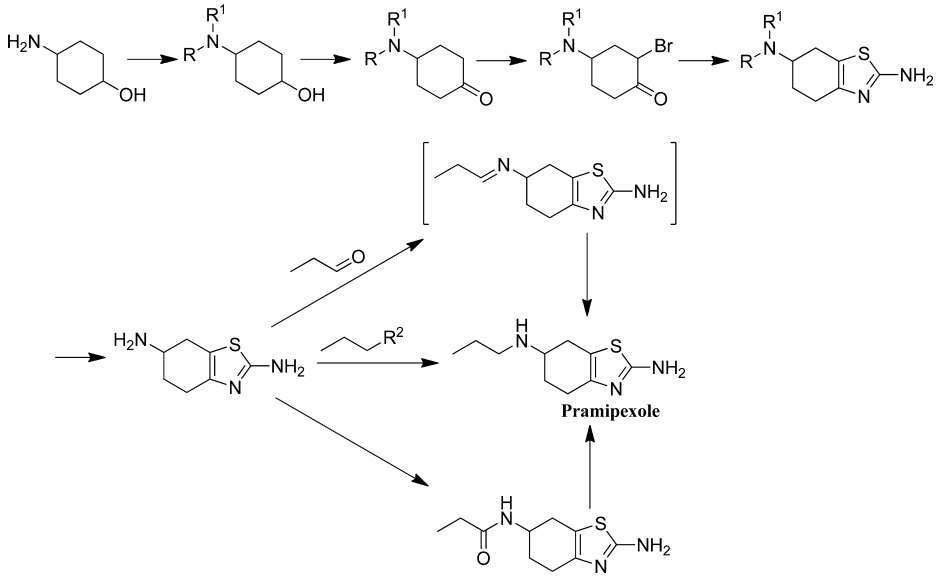
Synthesis of 2. Compound **2**-**3** was synthesized from **1**-**1** on the basis of the research of Gegö et al.[18] (Scheme 3). Propylation and subsequent reduction of **2**-**2** followed by selective reduction of **2**-**3** furnished **2**-**1** as a mixture of four stereoisomers. Finally, **2** was obtained by resolution using chiral chromatography.

Synthesis of 3. It was a challenge to construct the substituted tertiary C6 and C7 in **3** (Figure 2) and find a purification method for the highly polar final product. The asymmetric construction of the nitrogen-substituted tertiary carbon stereocenter was our foremost priority. With this intention, we made use of kinetic resolution and a Mitsunobu reaction to achieve the desired configuration.

Received: May 22, 2016

DOI: 10.1021/acs.oprd.6b00182
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 1. Three Synthetic Routes for Pramipexole[a]



[a]R = H and R^1 = protecting group or R and R^1 together form a protecting group. R^2 is a leaving group such as halide, OTs, or OMs.

Amine **3-4** was prepared from **2**−**3** through 4 steps according to literature (Scheme 4).[18] In the initial attempt, the amine **5** was reacted with propionaldehyde and $NaBH_4$ to obtain **3-4**. The structure of **3-4** monosulfate was determined by single-crystal X-ray diffraction, and the data indicated that the asymmetric carbons of **3-4** monosulfate had a (6*S*,7*S*) configuration (Figure 3). The absolute configuration of **3-5** was the same as that of **3-4** because the conversion from **3-5** to **3-4** did not involve a change in the configuration. After acetylation, intermediate **3-3** was obtained. The Mitsunobu reaction is commonly used for configuration inversion of chiral carbons.[21,22] **3-3** was coupled with protected pramipexole **4** to obtain **3-2**, which had our desired configuration, in the presence of DIAD and PPh_3 by the Mitsunobu reaction. Originally, we intended to cleave all of the amide bonds of **3-2** to get the desired product. However, a comprehensive study using various acidic conditions, such as HCl/ethanol, concentrated HCl, concentrated HBr, and HOAc/concentrated H_2SO_4, gave exclusively **3-1**. Stronger acidic and basic conditions were tried but failed to convert **3-1** to **3**, likely because of the chemical stability of the acetyl group on the secondary amine.

Stimulated by the failure of the initial route, an adjusted synthetic plan was carried out to complete the synthesis of **3** (Scheme 5). Selective propionylation of **3-5** using propionyl chloride in the presence of triethylamine produced amide **3-11**. Under the standard Mitsunobu reaction conditions, **3-10** was prepared from intermediates **4** and **3-11**. It was expected that **3-10** would be directly converted to **3-9**, but instead, only **3-8** was obtained. Subsequent selective alkylation using propionaldehyde by the same method as used to synthesize **3-4** generated the desired product **3**. To identify the absolute configuration of **3**, many methods were tried to obtain a single crystal of **3**, but all of them failed. The absolute configurations of C6 and C7 in **3-5** are same as in **3-4** and are retained in the subsequent propionylation. The configuration of C7 in **3-11** was inverted in the Mitsunobu reaction to generate **3-10** (Scheme 5), and there was no major influence on the configurations of C6 and C7 in the following steps. Therefore, it was deduced that **3** has a (6*S*,7*R*) configuration.

CONCLUSION

Total syntheses of **1**, **2**, and **3**, which are important and valuable for the quality control of drug manufacturing, have been accomplished. After the unsuccessful initial trial, the optimized synthetic method for **3** was feasible and allowed to give a sufficient amount of **3** efficiently. The configuration of C7 in **3** was deduced to be (6*S*,7*R*) from the chemistry leading from **3-5** to **3** and the single-crystal X-ray diffraction analysis of the sulfate of **3-4**, which is another impurity.

EXPERIMENTAL SECTION

General Procedures. All of the commercially available materials and solvents were used without any further purification. Thin-layer chromatography (TLC) analyses were performed on Merck silica gel 60 F254 plates. ^1H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AMX-400 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan MAT-95/711 spectrometer. Reversed-phase HPLC analyses were performed on an Agilent 1100 HPLC system with a diode array detector (area normalization).

*2-Bromocyclohexane-1,3-dione (**1-3**).* To a solution of **1-4** (50 g, 446 mmol) in acetic acid (535 mL) was added bromine (23 mL, 446 mmol) dropwise for 3 h. The reaction mixture was stirred for an additional 1 h and then filtered. The precipitate was washed twice with petroleum ether to afford **1-3** (64.8 g). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.63 (s, 1H), 2.61 (t, J = 5.9 Hz, 4H), 2.03 (p, J = 5.9 Hz, 2H). MS (ESI, ev): m/z = 191.9 $[M + H]^+$.

*2-Amino-5,6-dihydrobenzothiazol-7(4H)-one Dihydrobromide (**1-2**).* A mixture of **1-3** (120 g, 628 mmol) and thiourea (57.3 g, 753 mmol) in ethanol (600 mL) was refluxed for 3 h under N_2. Then the reaction mixture was cooled to room temperature and filtered to yield yellow solid **1-2** (109 g). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.65 (s, 4H), 2.71 (t, J = 6.1

DOI: 10.1021/acs.oprd.6b00182
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

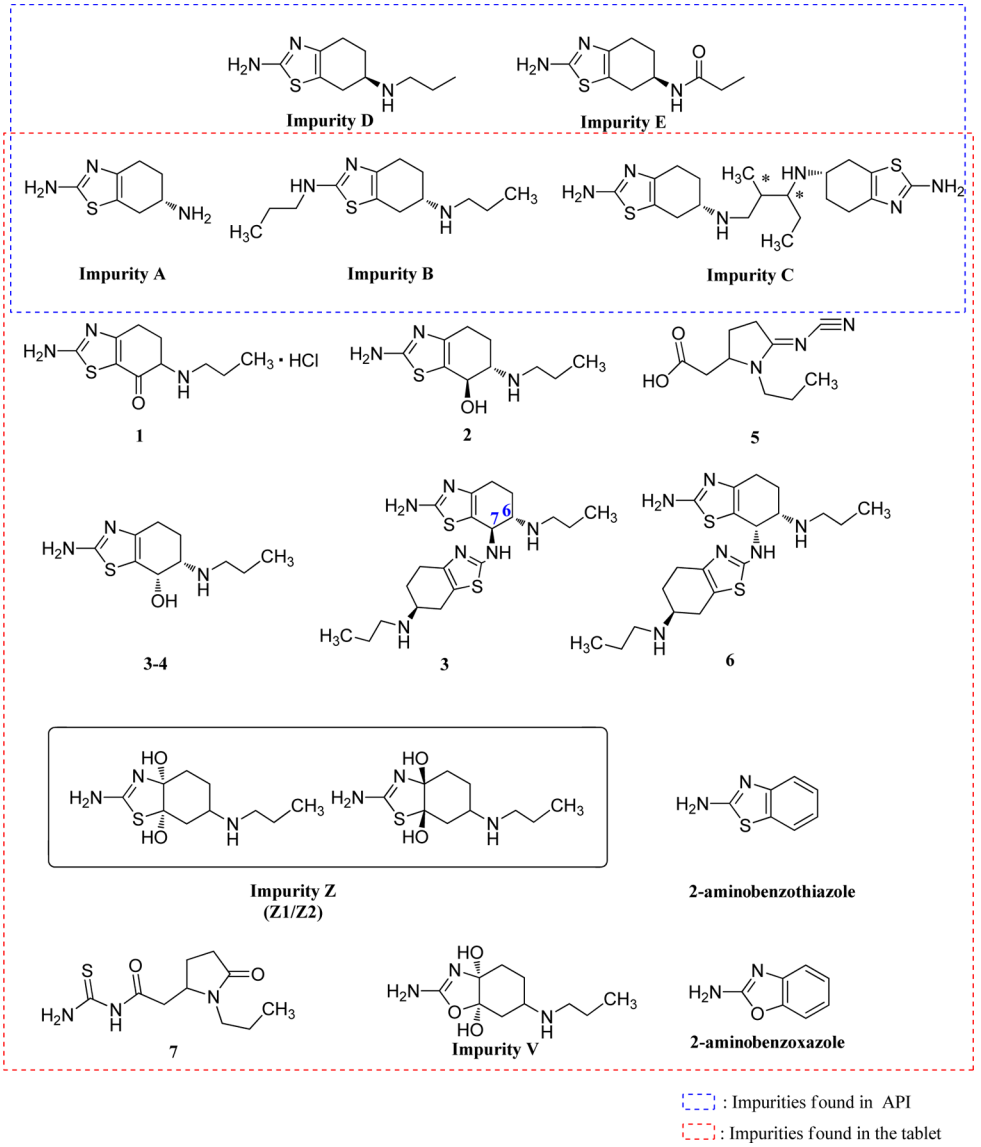
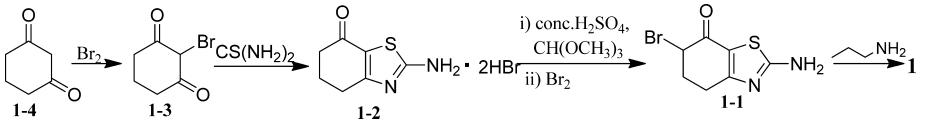
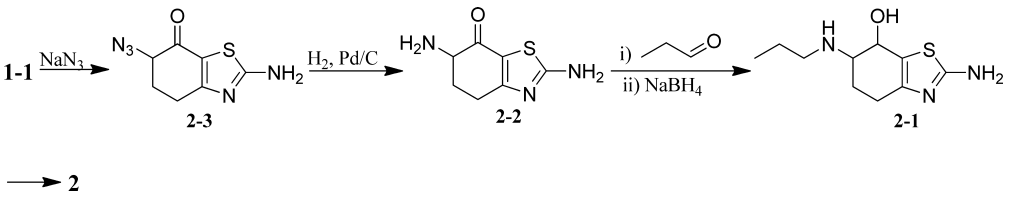


Figure 2. Structures of the 17 impurities found in the API and tablet.

Scheme 2. Synthetic Route for 1



Scheme 3. Synthetic Route for 2

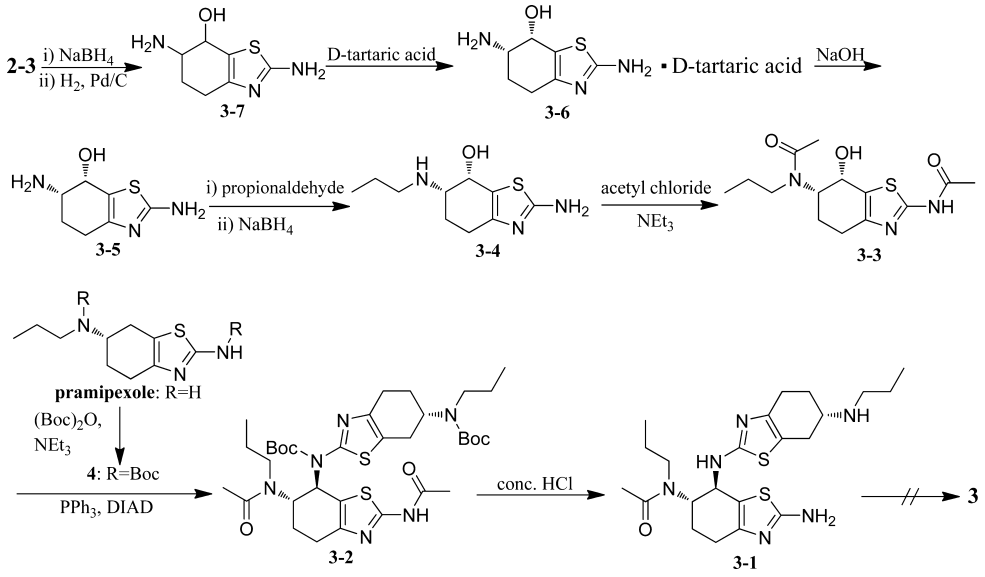


Hz, 2H), 2.40 (m, 2H), 2.01 (m, 2H). MS (ESI, ev): m/z = 169.11 $[M + H]^+$.

*2-Amino-6-bromo-5,6-dihydrobenzothiazol-7(4H)-one (**1-1**).* To a solution of **1-2** (50 g, 122 mmol) in methanol (340 mL) was added concentrated H_2SO_4 (18.13 mL) at 18−23 °C. When **1-2** was dissolved completely, trimethyl orthoformate (14.64 mL, 131 mmol) was added to the solution. The reaction mixture was stirred for an additional 90 min at 20−23 °C and then cooled to 0−5 °C. Bromine (6.26 mL, 122 mmol) was added dropwise at 0−5 °C within 45 min to 1 h,

DOI: 10.1021/acs.oprd.6b00182
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 4. Initial Synthetic Route for 3



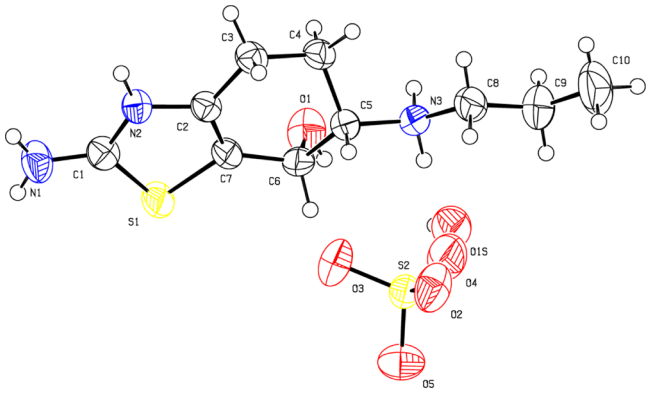


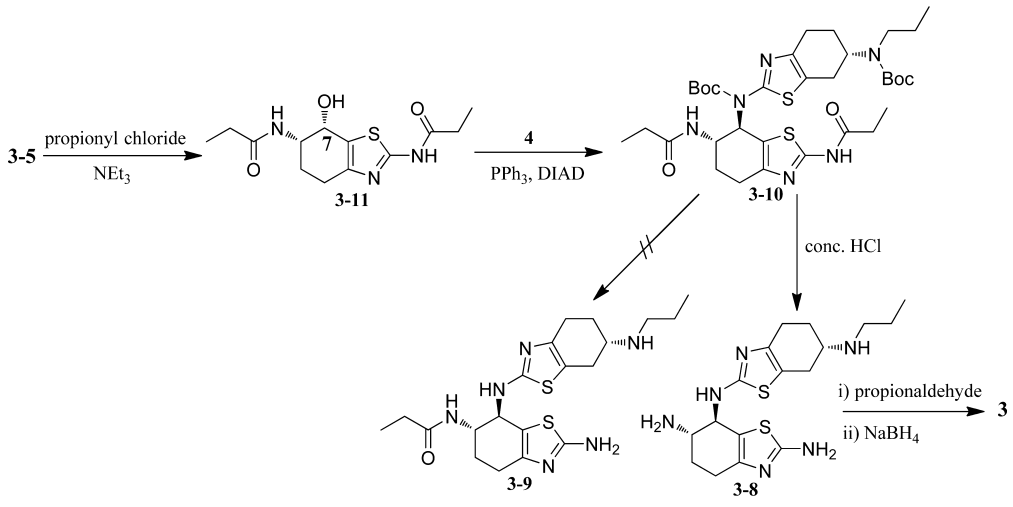
Figure 3. X-ray structure of **3-4**.

after which the reaction mixture was stirred for 2 h at that temperature and then allowed to warm slowly to room temperature during the night. The next day, water (450 mL) was added. Then the mixture was warmed to 45−50 °C and kept that temperature for 1 h. The resulting mixture was cooled to 0−5 °C and neutralized with saturated $NaHCO_3$ solution. The precipitate was filtered and washed with water to give **1-1** (64 g). The structural data for **1-1** were identical with those reported in the literature.[17]

*2-Amino-6-(propylamino)-5,6-dihydrobenzothiazol-7(4H)-one (**1**).* A mixture of **1-1** (5.38 g, 21.8 mmol), K_2CO_3 (3.0 g, 21.8 mmol), and propylamine (1.79 mL, 21.8 mmol) in CH_3CN (50 mL) was stirred at 50 °C. When the starting material was consumed, the mixture was purified to give **1** (700 mg). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.36−3.41 (m, 1H), 2.70−2.92 (m, 2H), 2.53−2.67 (m, 2H), 2.32−2.40 (m, 1H), 1.78−1.92 (m, 1H), 1.48−1.61 (m, 2H), 0.93 (td, J = 1.1 Hz, 7.4 Hz, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 184.04, 178.19, 170.88, 117.92, 61.24, 26.85, 20.83, 11.23. MS (ESI, ev): m/z = 226.11 $[M + H]^+$.

*2-Amino-6-azido-5,6-dihydrobenzothiazol-7(4H)-one (**2-3**).* To a solution of **1-1** (26.6 g, 107 mmol) in a mixture of DMF (300 mL) and water (100 mL) was added NaN_3 (8.4 g, 129 mmol) in portions. The reaction mixture was stirred for 3 h. NaN_3 (2.1 g, 32.3 mmol) was added again. Then the

Scheme 5. Successful Synthetic Route for 3



DOI: 10.1021/acs.oprd.6b00182
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

mixture was warmed to room temperature and stirred overnight. Water (520 mL) was added the next day, and the mixture was stirred for 30 min. The precipitate was filtered and washed with water (100 mL × 2) to give **2-3** (21.6 g). The structural data for **2-3** were identical to those reported in the literature.[17]

*2,6-Diamino-5,6-dihydrobenzothiazol-7(4H)-one (**2-2**).* To a solution of **2-3** (18.4 g, 87.9 mmol) in methanol (350 mL) was added Pd/C (10 wt %, 1.84 g) under N_2. The atmosphere was changed to H_2, and the reaction mixture was stirred for 19 h. The Pd/C catalyst was removed by filtration, and the filtrate was concentrated to give **2-2** (16 g), which was used in the next step without more purification.

*(6S,7R)-2-Amino-7-hydroxy-6-(propylamino)-4,5,6,7-tetrahydrobenzothiazole (**2**).* To a mixture of **2-2** (593 mg, 3.2 mmol) and methanol (10 mL) was added propionaldeyde (467 μL, 6.5 mmol) at −15 °C, and the reaction mixture was stirred for 3 h, after which $NaBH_4$ (688 mg, 18.2 mmol) was added in portions. The reaction mixture was maintained at −15 °C for 3 h. Then the reaction was continued for 5 h after the temperature was increased slowly to room temperature. The mixture was concentrated to give the crude material, which was purified by column chromatography to obtain **2-1** (260 mg). **2** was obtained from **2-1** by chiral resolution. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.70 (s, 2H), 5.25 (s, 1H), 4.24 (d, J = 5.9 Hz, 1H), 2.56−2.66 (m, 2H), 2.50−2.53 (m, 1H), 2.45−2.49 (m, 1H), 2.28−2.43 (m, 2H), 1.92−2.00 (m, 1H), 1.46−1.53 (m, 1H), 1.42 (dd, J = 7.3 Hz, 14.6 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): 167.36, 146.02, 119.20, 68.24, 61.20, 48.91, 25.00, 24.18, 22.85, 11.78. MS (ESI, ev): m/z = 228.06 $[M + H]^+$.

*(S)-tert-Butyl (2-((tert-Butoxycarbonyl)amino)-4,5,6,7-tetrahydrobenzothiazol-6-yl)(propyl)carbamate (**4**).* Pramipexole (13.5 g, 64.0 mmol) and NEt_3 (11.0 mL, 78.9 mmol) were suspended in DCM (100 mL), and then $(Boc)_2O$ (16.2 mL, 70.4 mmol) was added dropwise at 0 °C. When TLC indicated that the aliphatic amine was consumed totally, NEt_3 (11.0 mL, 78.9 mmol) and $(Boc)_2O$ (16.2 mL, 70.4 mmol) were added again, and the mixture was stirred at 35 °C. When TLC indicated that the aromatic amine was converted completely, the solvent was removed to obtain the crude material, which was purified by column chromatography to give **4** (15.8 g). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.02 (s, 1H), 4.21 (brs, 1H), 3.02−3.16 (m, 2H), 2.70−2.88 (m, 4H), 1.90−2.04 (m, 2H), 1.58−1.60 (m, 2H), 1.53 (s, 9H), 1.46 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H). MS (ESI, ev): m/z = 412.41 $[M + H]^+$.

*2,6-Diamino-7-hydroxy-4,5,6,7-tetrahydrobenzothiazole (**3-7**).* To a suspension of **2-3** (21.6 g, 103 mmol) in methanol (216 mL), cooled to 0 °C, was added $NaBH_4$ (3.13g, 83 mmol) in portions. The reaction mixture was stirred for 90 min at 20−23 °C. When the starting material had disappeared, Pd/C (10 wt %, 2.16 g) was added after the atmosphere was changed to N_2. Then the mixture was subjected to H_2. The Pd/C catalyst was removed by filtration, and the filtrate was concentrated to afford a solid. The solid was washed with cold methanol to give **3-7**. The structural data for **3-7** were identical to those reported in the literature.[17]

*(6S,7S)-2,6-Diamino-7-hydroxy-4,5,6,7-tetrahydrobenzothiazole D-Tartrate Salt (**3-6**).* To a solution of D-tartaric acid (7.51 g, 50 mmol) in water (10 mL) was added a solution of **3-7** (9.24 g, 50 mmol) in water (50 mL). The reaction mixture was stirred at 0 °C for 3 h. Then the precipitate was filtered and washed with water to give **3-6** (8.3 g). The structural data for **3-6** were identical to those reported in the literature.[17]

*(6S,7S)-2,6-Diamino-7-hydroxy-4,5,6,7-tetrahydrobenzothiazole (**3-5**).* A suspension of **3-6** (8.3 g) in water (25 mL) was alkalized by the addition of 5 N NaOH solution. After **3-6** was dissolved completely, a white solid precipitated, and the reaction mixture was stirred for an additional 30 min. The precipitate was filtered and washed with water to yield **3-5** (1.8 g). The structural data for **3-5** were identical to those reported in the literature.[17]

*(6S,7S)-2-Amino-7-hydroxy-6-(propylamino)-4,5,6,7-tetrahydrobenzothiazole (**3-4**).* To a mixture of **3-5** (3.0 g, 16.2 mmol) and methanol (50.0 mL) was added propionaldeyde (2.5 mL, 34.4 mmol) at −20 °C. The reaction mixture was stirred for 45 min, and $NaBH_4$ (850 mg, 22.5 mmol) was added in small portions during 15 min. The mixture was maintained at that temperature for 30 min, and then the reaction was continued for 4 h after the temperature was slowly increased to room temperature. The mixture was concentrated to give the crude material, which was purified by column chromatography to obtain **3-4** (4.3 g). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.78 (s, 2H), 4.46 (d, J = 3.3 Hz, 1H), 4.12 (s, 1H), 3.36 (d, J = 17.5 Hz, 1H), 2.54−2.68 (m, 2H), 2.40−2.48 (m, 2H), 2.28−2.38 (m, 1H), 1.58−1.69 (m, 2H), 1.34−1.44 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). MS (ESI, ev): m/z = 228.04 $[M + H]^+$. HPLC: t_R = 10.35 min, 96% purity.

***3-4** Monosulfate.* To a solution of **3-4** in methanol was added concentrated H_2SO_4 at 0 °C. The mixture was stirred for 15 min and then filtered, and the filter cake was washed with methanol to obtain the monosulfate of **3-4**.

*N-((6S,7S)-2-Acetamido-7-hydroxy-4,5,6,7-tetrahydrobenzothiazol-6-yl)-N-propylacetamide (**3-3**).* **3-4** (4.2 g, 18.5 mmol) and triethylamine (5.6 mL, 40.2 mmol) were suspended in DCM (100 mL), and then acetyl chloride (3.2 mL, 33.3 mmol) was added at 0 °C. When TLC indicated that the reaction was finished, the reaction mixture was quenched with methanol. The resulting mixture was concentrated to obtain the crude material, which was purified by column chromatography to give **3-3** (3.2 g). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.00 (s, 1H), 5.34 (d, J = 6.4 Hz, 1H), 4.63 (brs, 1H), 4.41 (d, J = 13.3 Hz, 1H), 3.26 (d, J = 11.2 Hz, 1H), 3.15 (m, 1H), 2.75 (d, J = 15.4 Hz, 1H), 2.65 (d, J = 16.2 Hz, 1H), 2.11 (s, 3H), 2.04 (d, J = 6.6 Hz, 3H), 1.44−1.88 (m, 4H), 0.81 (dt, J = 7.2 Hz, 24.8 Hz, 3H). MS (ESI, ev): m/z = 312.40 $[M + H]^+$.

*tert-Butyl ((6S,7R)-2-Acetamido-6-(N-propylacetamido)-4,5,6,7-tetrahydrobenzothiazol-7-yl)((S)-6-((tert-butoxycarbonyl)(propyl)amino)-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbamate (**3-2**).* To a solution of **3-3** (20.0 g, 64.3 mmol) in THF (50 mL) were added PPh_3 (35.3 g, 134.7 mmol) and **4** (26.0 g, 63.2 mmol). The solution was cooled to 0 °C, and DIAD (26.7 mL, 134.7 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. When TLC showed the consumption of **4**, the reaction mixture was concentrated under vacuum and purified by column chromatography to give **3-2** (16.7 g). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.56 (brs, 1H), 5.44−5.56 (m, 1H), 4.80−4.95 (m, 2H), 3.07 (m, 4H), 2.50−2.90 (m, 6H), 2.16−2.30 (m, 4H), 1.92−2.10 (m, 6H), 1.53−1.66 (m, 4H), 1.31 (dd, J = 8.6 Hz, 14.2 Hz, 9H), 1.24

DOI: 10.1021/acs.oprd.6b00182
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(dt, J = 6.8 Hz, 12.4 Hz, 9H), 0.81−0.97 (m, 6H). MS (ESI, ev): m/z = 705.93 $[M + H]^+$.

*N-((6S,7R)-2-Amino-7-(((S)-6-(propylamino)-4,5,6,7-tetrahydrobenzothiazole-2-yl)amino)-4,5,6,7-tetrahydrobenzothiazol-6-yl)-N-propylacetamide (**3-1**).* To a solution of **3-2** (500 mg, 1.15 mmol) in methanol was added concentrated HCl (4 mL), and the reaction mixture was refluxed at 95 °C. The reaction was stopped when TLC indicated disappearance of the starting material. The reaction mixture was concentrated to obtain the crude material, which was purified by column chraomatography to give **3-1**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.56 (dd, J = 9.4 Hz, 71.2 Hz, 1H), 6.75 (d, J = 22.1 Hz, 2H), 4.87 (d, J = 71.2 Hz, 1H), 3.85 (d, J = 9.9 Hz, 1H), 2.94−3.14 (m, 3H), 2.86 (d, J = 11.1 Hz, 1H), 2.69 (t, J = 7.3 Hz, 2H), 2.58 (d, 16.5 Hz, 1H), 2.30−2.49 (m, 4H), 2.06 (brs, 4H), 1.82−1.94 (m, 2H), 1.60−1.76 (m, 2H), 1.52 (dt, 7.0 Hz, 13.9 Hz, 4H), 0.90 (t, J = 7.4 Hz, 3H), 0.81 (dt, J = 7.3 Hz, 22.5 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): 170.25, 167.93, 146.75, 144.87, 144.73, 117.87, 117.44, 60.23, 55.39, 54.08, 52.40, 47.96, 29.48, 28.29, 25.28, 23.26, 22.81, 22.66, 22.27, 21.90, 12.04. MS (ESI, ev): m/z = 463.06 $[M + H]^+$. HRMS (ESI^+): calcd for $C_{22}H_{25}ON_6S_2$ $[M + H]^+$ m/z = 463.2308; found 463.2296.

*N,N′-((6S,7S)-7-Hydroxy-4,5,6,7-tetrahydrobenzothiazol-2,6-diyl)dipropionamide (**3-11**).* **3-11** was prepared from **3-5** with propionyl chloride following the procedure described for the synthesis of **3-3**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.97 (s, 1H), 9.82 (brs, 1H), 6.35 (d, J = 8.5 Hz, 1H), 4.83 (d, J = 3.4 Hz, 1H), 4.22−4.29 (m, 1H), 2.64−2.77 (m, 2H), 2.51 (q, J = 7.5 Hz, 2H), 2.28 (q, J = 7.5 Hz, 2H), 1.90−2.02 (m, 2H), 1.24 (t, J = 7.5 Hz, 3H), 1.18 (t, J = 7.6 Hz, 3H). MS (ESI, ev): m/z = 298.26 $[M + H]^+$.

*tert-Butyl ((S)-6-((tert-Butoxycarbonyl)(propyl)amino)-4,5,6,7-tetrahydrobenzothiazol-2-yl)((6S,7R)-2,6-dipropionamido-4,5,6,7-tetrahydrobenzothiazol-7-yl)carbamate (**3-10**).* **3-10** was prepared from **3-11** following the procedure described for the synthesis of **3-2**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.80 (brs, 1H), 7.75 (d, J = 55.1 Hz, 1H), 5.44 (brs, 1H), 4.96 (brs, 1H), 4.59 (brs, 1H), 2.57−2.90 (m, 3H), 2.49 (q, J = 7.6 Hz, 2H), 2.18−2.34 (m, 3H), 2.01 (d, J = 4.7 Hz, 2H), 1.83 (brs, 2H), 1.64 (brs, 4H), 1.42 (d, J = 5.0 Hz, 2H), 1.28 (dd, J = 7.5 Hz, 15.1 Hz, 18H), 1.22 (t, J = 7.6 Hz, 3H), 1.19 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 6.4 Hz, 3H). MS (ESI, ev): m/z = 691.83 $[M + H]^+$.

*(6S,7R)-N7-((S)-6-(Propylamino)-4,5,6,7-tetrahydrobenzothiazol-2-yl)-4,5,6,7-tetrahydrobenzothiazole-2,6,7-triamine (**3-8**).* **3-8** was prepared from **3-10** following the procedure described for the synthesis of **3-1**. ^{1}H NMR (CD_3OD, 300 MHz): δ 5.29−5.38 (m, 1H), 3.56−3.64 (m, 1H), 3.05−3.16 (m, 1H), 2.55−2.86 (m, 3H), 2.16−2.35 (m, 2H), 1.95−2.15 (m, 3H), 1.66−1.90 (m, 2H), 1.51−1.65 (m, 2H), 1.41 (t, J = 9.3 Hz, 2H), 0.89 (t, J = 6.9 Hz, 3H). MS (ESI, ev): m/z = 379.56 $[M + H]^+$.

*(6S,7R)-N6-Propyl-N7-((S)-6-(propylamino)-4,5,6,7-tetrahydrobenzothiazol-2-yl)-4,5,6,7-tetrahydrobenzothiazole-2,6,7-triamine (**3**).* **3** was prepared from **3-8** following the procedure described for the synthesis of **3-4**. ^{1}H NMR (CD_3OD, 400 MHz): δ 4.75 (d, J = 5.9 Hz, 1H), 3.16 (brs, 1H), 2.92−3.03 (m, 2H), 2.75−2.86 (m, 3H), 2.44−2.69 (m, 6H), 2.17 (d, J = 5.4 Hz, 2H), 1.72−1.91 (m, 2H), 1.64 (dd, J = 7.6 Hz, 15.1 Hz, 2H), 1.56 (dd, J = 8.1 Hz, 14.3 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 169.54, 167.29, 146.36, 144.04, 116.10, 113.37, 58.70, 54.06, 53.81, 48.70, 48.37, 28.26, 28.17, 24.97, 24.61, 23.33, 22.24, 22.06, 10.62, 10.58. MS (ESI, ev): m/z = 420.87 $[M + H]^+$. HRMS (ESI^+): calcd for $C_{20}H_{33}N_6S_2$ $[M + H]^+$ m/z = 421.2203; found 421.2192. HPLC for **3**: t_R = 13.85 min, 94.6% purity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00182.

Spectra and data for the compounds listed in the Experimental Section (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +86-21-20231000-2407. Telephone: +86-21-2023100-2407. E-mail: jiangxiangrui@simm.ac.cn.

Author Contributions

‖T.H. and F.Y. contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the Science and Technology Commission of Shanghai Municipality (14431905500) and the National Natural Science Foundation of China (81273366).

■ ABBREVIATIONS

DIAD, diisopropyl azodicarboxylate; DCM, dichloromethane

■ REFERENCES

(1) Perez-Lloret, S.; Rey, M. V.; Ratti, L.; Rascol, O. *Expert Rev. Neurother.* **2011**, *11*, 925−935.

(2) Liyanage, S. H. *Aging Health* **2010**, *6*, 155−157.

(3) Ishibashi, K.; Ishii, K.; Oda, K.; Mizusawa, H.; Ishiwata, K. *PLoS One* **2011**, *6*, e17723.

(4) Koffarnus, M. N.; Collins, G. T.; Rice, K. C.; Chen, J.; Woods, J. H.; Winger, G. *Behav. Pharmacol.* **2012**, *23*, 331−338.

(5) Kano, O.; Ikeda, K.; Kiyozuka, T.; Iwamoto, K.; Ito, H.; Kawase, Y.; Sato, R.; Fujioka, T.; Araki, Y.; Baba, S.; Iwasaki, Y. *Neuropsychiatr. Dis. Treat.* **2008**, *2008*, 707−710.

(6) Sprenger, F.; Poewe, W. *CNS Drugs* **2013**, *27*, 259−272.

(7) Schattschneider, J.; Bode, A.; Wasner, G.; Binder, A.; Deuschl, G.; Baron, R. *J. Neurol.* **2004**, *251*, 977−982.

(8) Brindani, F.; Vitetta, F.; Gemignani, F. *Clin. Interventions Aging* **2009**, *4*, 305−313.

(9) Oertel, W. H.; Stiasny-Kolster, K.; Bergtholdt, B.; Hallström, Y.; Albo, J.; Leissner, L.; Schindler, T.; Koester, J.; Reess, J. *Mov. Disord.* **2007**, *22*, 213−219.

(10) Ferinistrambi, L. *Sleep. Med.* **2002**, *3*, S23−S25.

(11) Jama, L.; Hirvonen, K.; Partinen, M.; Alakuijala, A.; Hublin, C.; Tamminen, I.; Koester, J.; Reess, J. *Sleep Med.* **2009**, *10*, 630−636.

(12) Lin, S. C.; Kaplan, J.; Burger, C. D.; Fredrickson, P. A. *Mayo Clin. Proc.* **1998**, *73*, 497−500.

(13) Živec, M.; Anzic, B.; Gobec, S. *Org. Process Res. Dev.* **2010**, *14*, 1125−1129.

(14) Griss, G.; Schneider, C.; Hurnaus, R.; Kobinger, W.; Pichler, L.; Bauer, R.; Mierau, J.; Hinzen, D.; Schingnitz, G. Tetrahydro-

DOI: 10.1021/acs.oprd.6b00182
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

benzothiazoles, their production and their use as intermediates or drugs. European Patent 0186087, 1985.
(15) Vemic, A.; Malenovic, A.; Rakic, T.; Kostic, N.; Jancicstojanovic, B.; Ivanovic, D.; Medenica, M. *J. Braz. Chem. Soc.* **2012**, *23*, 2084−2092.
(16) Nishimura, E.; Kugimiya, A.; Naoki, H.; Hamanaka, N. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2951−2953.
(17) Schneider, C. S.; Mierau, J. *J. Med. Chem.* **1987**, *30*, 494−498.
(18) Gegö, C.; Fejes, I.; Garaczi, S.; Kovács, I.; Lukács, F.; Majercsik, O.; Schneider, G. Process for producing pramipexole. European Patent 1878731, 2008.
(19) Jia, G.; Li, Z.; Li, J.; Zou, J.; Yang, Y. Method for preparing *N*-(aminothiomethyl)-5-oxo-1-propyl-2-pyrrolidineacetamide. Chinese Patent 103012233, 2013.
(20) Wu, S.; Tong, Y.; Yang, Q.; Deng, Y.; Wang, C.; Ge, J.; Jiang, X.; Zhao, T.; Zhao, D.; Hu, S. Synthesis method for pramipexole dihydrochloride related substance B. Chinese Patent 103724291, 2014.
(21) Shin, I.; Lee, M. R.; Lee, J.; Jung, M.; Lee, W.; Yoon, J. *J. Org. Chem.* **2000**, *65*, 7667−7675.
(22) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235−4238.

DOI: 10.1021/acs.oprd.6b00182
Org. Process Res. Dev. XXXX, XXX, XXX−XXX