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EFFICIENT SYNTHESIS OF SUBSTANCES RELATED TO CINACALCET HYDROCHLORIDE VIA HECK COUPLING

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GRAPHICAL ABSTRACT



Abstract Efficient synthetic methods to process substances related to cinacalcet hydrochloride **1**, generated during the preparation, were described. The compounds were identified as [1-(7,8-dihydro-naphthalen-1-yl)-ethyl]-[3-(3-trifluoromethyl-phenyl)-propyl]-amine hydrochloride **2**, [1-(5,6,7,8-tetrahydro-naphthalen-1-yl)-ethyl]-[3-(3-trifluoromethyl-phenyl)propyl]-amine hydrochloride **3** and [1-(naphthalen-2-yl)-ethyl]-[3-(3-trifluoromethylphenyl)-propyl]-amine hydrochloride **4**. All were prepared from commercially available materials in several linear steps and characterized by their respective spectral data.

Keywords Cinacalcet hydrochloride; HPLC; process-related substances; synthesis

INTRODUCTION

(R)-*N*-(1-(Naphthalen-1-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)propan-1-amine hydrochloride, known as cinacalcet hydrochloride **1** (AMG 073, Sensipar, Mimpara), is a selective calcimimetic agent^[1] for the treatment of secondary hyperthyroidism in patients with chronic kidney disease on dialysis and for the treatment of elevated calcium levels in patients with parathyroid carcinoma.

Several methods have been reported in the literature for the preparation of cinacalcet hydrochloride 1 that rely on various reductive amination approaches^[2]

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Scheme 1. Reported synthetic route for cinacalcet hydrochloride 1 via reductive amination.



Scheme 2. Reported synthetic route for cinacalcet hydrochloride 1.

(Scheme 1). Thiel et al.^[3] reported a practically synthetic route via hydrogenation, amide coupling, reduction, and salification (Scheme 2). A similar route was also reported by Bijukumar et al.^[4]

During our development of cinacalcet hydrochloride **1**, high-performance liquid chromatographic (HPLC) analysis of crude product revealed other three impurities ranging from 0.05 to 0.20%, besides the starting materials and unreacted intermediates. The International Conference of Harmonization (ICH) has published guidelines on impurities in new drug substances, products, and residual solvents that state that the acceptable levels for known and unknown compounds in a final drug candidate must be less than 0.15% and 0.10%, respectively, and the impurities need to be extensively controlled and prepared for the quality controls of the main product.^[5] Hence, crude cinacalcet hydrochloride **1** was initially analyzed by liquid chromatography–mass spectrometry (LC-MS) to provide these three impurities. To confirm their proposed structures and complete their characterization, all three substances were individually synthesized and characterized by their respective spectral data, and retention time was checked in HPLC. We confirmed their structural assignment as shown in Fig. 1.



Figure 1. Structures of the three substances related to cinacalcet hydrochloride 1.

Herein, to meet the strict requirement of the ICH, we report the efficient synthesis of all the three substances related to cinacalcet hydrochloride 1.

RESULTS AND DISCUSSION

Thiel and coworkers reported that the dihydronaphthalene related substance 2, recognized as congeners by Wang et al.^[6] before, was formed when the amide was reduced by NaBH₄ in the presence of Lewis acid.^[3] Initially, we planned to synthesize the substance 2 shown in Scheme 3, but during our preparation the substance 2 was obtained with the purity of 87.49% by HPLC. It showed an impurity of 9.21% in the product, which could not be purified by normal recrystallization or column chromatography. Afterward, the impurity was identified as the tetrahydronaphthalene related substance 3 by LC-MS and HPLC. We speculated that it formed in the process of reductive amination. On one hand, because of the inductive effects in the formation of the imine, it decreased the dihydronaphthalene ring electron density and the offset of the π electron cloud, so as to result the polarization in the molecule and the reduction of the imine, Lewis acid Ti(O-*i*-Pr)₄ was added as solvent and the reactivity of NaBH₄ could be greatly enhanced in the presence of Lewis acid^[7] (Fig. 2).

For obtaining the substance 2 with satisfactory purity (>95%), it is necessary to avoid the reductive amination process. Through retrosynthetic analysis the substance 2 was decided to be synthesized by nucleophilic substitution in strategy 2 (Scheme 4).

Our approach utilized 5-hydroxytetralone **6** as starting material, which was first reduced by NaBH₄ to get the alcohol **7** in 93% yield (Scheme 5). Formation of the bis-triflate and the elimination step were carried out in one pot using 2.4 equiv of triflic anhydride and Et_3N in anhydrous dichloromethane to give the triflate **8** in overall 46% yield. The reaction conversions were nearly quantitative, but the poor isolated yield was attributed to partial decomposition of the triflate **8** during silica-gel chromatographic purification. The triflate **8** was converted to enol vinyl



Scheme 3. Original route of the related substance 2.



Figure 2. Formation and polarization of the imine intermediate.



Scheme 4. Retrosynthetic analysis of the related substance 2.

ethers via Heck coupling^[8] and hydrolyzed in 3 N hydrochloride to obtain the pure key intermediate **9** by silica-gel chromatography. The ketone **9** was reduced to the alcohol **10** by NaBH₄ in 94% yield. The alcohol **10** was chlorinated using 5 equiv of thionyl chloride in anhydrous dichloromethane to give the compound **11** in 72% yield, which was further reacted with 3-(3-(trifluoromethyl)phenyl) propan-1-amine **5**^[6] in the presence of potassium carbonate and a catalytic amount of potassium iodide. The crude product was salified and purified by recrystallization in acetonitrile to get **2** with satisfactory purity of 95.26% by HPLC.

Tetrahydronaphthalene-related substance **3** was reported to be formed in the reduction process.^[9] In the preparation procedure of cinacalcet hydrochloride **1**, the amide was reduced by NaBH₄/BF₃-tetrahydrofuran (THF) and the HPLC analysis showed that there was 0.20% of the tetrahydronaphthalene substance **3** in the crude product. The substance **3** was designed and synthesized (Scheme 6). We also took advantage of 5-hydroxytetralone **6** as starting material. The key intermediate **12** was obtained by Kishner–Wolff–Huang reduction in quantitative yield and treated with triflic anhydride and Et₃N in anhydrous dichloromethane



Scheme 5. Synthesis of the related substance 2. Reagents and conditions: (i) NaBH₄, MeOH, 0°C-rt, overnight, 93%; (ii) Tf₂O, TEA, DCM, -10° C, 2h, 46%; (iii) (a) n-butyl vinyl ether, Pd(OAc)₂, 1,3-dppp, TEA, DMF, 65 °C, 8h; (b) 3 N HCl, acetone, rt, 1h, 61% over two steps; (iv) NaBH₄, MeOH, 0°C-rt, 2h, 94%; (v) SOCl₂, DCM, 0°C-rt, 10h, 72%; (vi) (a) 5, K₂CO₃, KI, MeCN, reflux, overnight; (b) conc. HCl, *i*-PrOH reflux, 15 min, 78% over two steps.



Scheme 6. Synthesis of the related substance 3. Reagents and conditions: (i) (a) $(NH_{2})_2$ -H₂O, diglycol, 80 °C, 1.5 h; (b) KOH, 180 °C, 7 h, 97% over two steps; (ii) Tf₂O, TEA, DCM, -10 °C, 2 h, 67%; (iii) (a) n-butyl vinyl ether, Pd(OAc)₂, 1,3-dppp, TEA, DMF, 65 °C, 8 h; (b) 3 N HCl, acetone, rt, 1 h, 56% over two steps; (iv) (a) 5, Ti(O-*i*-Pr)₄, rt, overnight; (b) NaBH₄, MeOH, 0 °C–rt, 1 h; (c) conc. HCl, *i*-PrOH, reflux, 15 min, 81% over three steps.

to give the triflate 13 in overall 67% yield. The ketone 14 was also obtained via Heck coupling and hydrolization, directly reacted with the amine 5 in $Ti(O-i-Pr)_4$, and reduced by NaBH₄ in methanol to get the crude 3, which was further salified and recrystallized in acetonitrile to get 3 with the purity of 97.88% by HPLC.

The naphthalen-2-yl related substance **4** is a structural isomer of cinacalcet hydrochloride **1** and generated due to presence of 1-(2-naphthyl)ethylamine as an impurity in the key raw material 1-(1-naphthyl)ethylamine. In the HPLC analytic result it showed 0.08% in the crude cinacalcet hydrochloride **1**. Thus, we reported the synthesis of the naphthalen-2-yl substance **4** here (Scheme 7). 2-acetylnaphthalene **15** was treated with **5** in the presence of Ti(O-*i*-Pr)₄, and then reduced by NaBH₄ in methanol. The crude product was salified and recrystallized in acetonitrile to get **4** with the purity of 99.79% by HPLC.

In conclusion, we have synthesized and characterized the potential processrelated substance 2, 3, and 4 of cinacalcet hydrochloride 1 with satisfactory purity, which made us better understand the synthetic pathway of an active pharmaceutical ingredient (API). Meanwhile, this study provided us an access to the reference standard of this impurity for regulatory authorities and established the related substances profile.

EXPERIMENTAL

All reactions were carried out under an argon atmosphere. Most chemicals and solvents were analytical grade and used without further purification. Thin-layer



Scheme 7. Synthesis of the related substance 4. Reagents and conditions: (i) (a) 5, $Ti(O-i-Pr)_4$, rt, overnight; (b) NaBH₄, MeOH, 0°C–rt, 1 h; (c) conc. HCl, *i*-PrOH, reflux, 15 min, 84% over three steps.

chromatography (TLC) was performed using precoated silica gel GF254 (0.2 mm), while column chromatography was performed using silica gel (100–200 mesh). The melting point was measured on a YRT-3 melting-point apparatus (Shantou Keyi Instrument & Equipment Co. Ltd, Shantou, China). ¹H NMR spectra was taken on a Varian Inova 400 (Varian, Palo Alto, CA, USA) using CDCl₃, dimethylsulfoxide (DMSO- d_0), and D₂O as solvent. Chemical shifts were expressed in δ (ppm), with tetramethylsilane (TMS) functioning as the internal reference, and coupling constants (J) were expressed in Hz. The high-resolution mass (HRMS) spectra were recorded on a Bruker Maxis Impact Q-TOF instrument (Bruker, Billerica, MA, USA) coupled with a Dionex Ultimate 3000 spectrometer (Dionex, Sunnyvale, CA, USA). The purity was determined by HPLC-UV obtained on an Agilent 1946B electrospray ionization-mass spectrometry (ESI-MS) instrument (Agilent, Palo Alto, CA, USA). The HPLC parameters were as follows: column, Topsil C18 4.6 \times 150 mm, 5 μ m; wavelength, 210 nm for substance 2, 223 nm for substance 3 and 4; mobile phase, MeCN / 0.02 M NaH₂PO_{4(aq)}(0.20% TEA, pH was adjusted to 6.0 by H_3PO_4) 50/50; column temperature, 35 °C; flow rate, 1.0 ml/min.

General Procedure for the Preparation of the Dihydro- and Tetrahydro-naphthalen-1-ethanone (9) or (14) via Heck Coupling

TEA (2 eq) and *n*-butyl vinyl ether (4 eq) were added to a solution of trifluoro-methanesulfonic acid ester **8** or **13** (1 eq) in DMF at room temperature. The solution was bubbled with argon for 10 min and added to the mixture of palladium acetate (0.1eq) and 1,3-dppp (0.1 eq) in a flask purged by argon. The reaction was heated to $65 \,^{\circ}$ C and stirred for 8 h. The reaction was cooled to room temperature. Ethyl ether was added, and the solution was washed with saturated Na₂CO₃ solution and brine and then dried over Na₂SO₄. After the solvent was evaporated in vacuum brown oil was obtained, which was hydrolyzed directly in acetone and 3 N HCl ($1/1 \, v/v$) for 1 h at room temperature. When most acetone was evaporated in vacuum, DCM was added, followed by saturated Na₂CO₃ solution. The organic layer was separated, washed by brine, and dried over Na₂SO₄. After the solvent was evaporated in vacuum, a light-brown oil was obtained, which was purified by flash chromatography on silica gel to get colorless oil.

1-(7,8-Dihydronaphthalen-1-yl)ethanone (9)

Yield 61%. ¹H NMR (400 MHz, CDCl₃): δ 2.21–2.31 (m, 2H), 2.57 (s, 3H), 3.02 (t, J = 8.0 Hz, 2H), 6.08–6.12 (m, 1H), 6.47 (dt, J = 1.6 Hz, 9.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.45 (dd, J = 1.2 Hz, 7.6 Hz, 1H); ESI-HRMS calcd. for C₁₂H₁₃O⁺ [M + H]⁺ 173.0966; found: 173.0968.

1-(5,6,7,8-Tetrahydronaphthalen-1-yl)ethanone (14)

Yield 56%. ¹H NMR (400 MHz, CDCl₃): δ 1.78–1.83 (m, 4H), 2.55 (s, 3H), 2.80 (t, J = 5.6 Hz, 2H), 2.95 (t, J = 5.6 Hz, 2H), 7.14 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.43 (d, J = 7.2 Hz, 1H); ESI-HRMS calcd. for C₁₂H₁₅O⁺ [M + H]⁺ 175.1123; found: 175.1131.

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SUPPORTING INFORMATION

Full experimental details and ¹H and ¹³C NMR spectra are available. Supplemental data for this article can be accessed on the publisher's website.

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