Supporting Information

Efficient synthesis of the related substances of Cinacalcet hydrochloride via Heck Coupling

Fan Lei^{a*}, Boyi Qu^{a*}, Xiaolong Li^a, Li Guo^a, Mei Guan^b, Li Hai^a, Hui Jin^{a**}, Yong Wu^{a**}

^aKey Laboratory of Drug Targeting and Drug Delivery Systems, West China School of Pharmacy, Sichuan University, Chengdu 610041, P.R. China

^bWest China Hospital, Sichuan University, Chengdu, Sichuan 610041, P.R. China

EXPERIMENTAL

All reactions were carried out under an argon atmosphere. Most chemicals and solvents were analytical grade and used without further purification. TLC was performed using precoated silica gel GF254 (0.2mm), while column chromatography was performed using silica gel (100-200 mesh). The melting point was measured on YRT-3 melting point apparatus (Shantou Keyi instrument & Equipment Co. Ltd, Shantou, China). ¹H-NMR spectra was taken on a Varian INOVA400 (Varian, Palo Alto, CA, USA) using CDCl₃, DMSO-*d*₆ 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 ESI-MS instrument (Agilent, Palo Alto, CA, USA). HPLC method of the process-related substances: column: TopsisilTM C18 4.6*150mm 5 μ m; wavelength: 210nm for substance **2**, 223nm for substance **3** and **4**; mobile phase: MeCN/0.02M NaH₂PO_{4(aq)}(0.20% TEA, pH was adjusted to 6.0 by H₃PO₄) 50/50; column temperature: 35°C; flow rate: 1.0ml/min.

Preparation of **1, 2, 3, 4-tetrahydronaphthalene-1, 5-diol (7)**.

To a solution of 5-hydroxy-1-tetralone **6** (1.64g, 10mmol, 1eq) in MeOH in an ice bath was added NaBH₄ (454mg, 12mmol, 1.2eq) slowly in portions. After addition the solution was warmed to room temperature and stirred overnight. The reaction suspension was acidified by 6N HCl to destroy unreacted NaBH₄ and basified by Na₂CO₃. When most MeOH was evaporated the solution was added H₂O and extracted with DCM three times. The organic layer was put together, washed by brine and dried over Na₂SO₄. After the solvent was evaporated in vacuum a light-brown solid was obtained. For further purification the solid was recrystallized in ethyl acetate/petroleum ether to obtain an off-white solid 1.53g, yield 93%. ¹H NMR(400 MHz, CDCl₃): δ 1.75-2.08 (m, 4H),

*These authors contributed equally.

**Corresponding author. Tel: +86 02885503235; fax: +86 02885503666.

E-mail address: jinhui_1974@126.com (H. Jin), wyong@scu.edu.cn (Y. Wu).

2.50-2.63 (m, 1H), 2.65-2.80 (m, 1H), 4.79(t, J = 4.8 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H); ESI-HRMS calcd for $C_{10}H_{13}O_2^+$ $[M+H]^+$ 165.0916; found: 165.0914.

Preparation of trifluoro-methanesulfonic acid 7, 8-dihydro-naphthalen-1-yl ester (8).

To a mixture of 1, 2, 3, 4-tetrahydronaphthalene-1, 5-diol **7** (1.53g, 9.32mmol, 1eq) and TEA (2.26g, 22.37mmol, 2.4eq) in anhydrous DCM was colded to $-10^{\circ}C$ and added a solution of traflate anhydride (6.31g, 22.37mmol, 2.4eq) in anhydrous DCM dropwise. After addition, the reaction was stirred at $0^{\circ}C$ for 2h, and then quenched by saturated sodium bicarbonate solution at $0^{\circ}C$. DCM was added and the organic layer was separated. Washed by brine and dried over Na_2SO_4 , the organic layer was evaporated to dryness to give brownish oil, which was purified by flash chromatography on silica gel to get colorless oil 1.19g, yield 46%. 1H NMR(400 MHz, $CDCl_3$): δ 2.30-2.40 (m, 2H), 2.88 (t, J = 8.0 Hz, 2H), 6.14 (m, 1H), 6.49 (dt, J = 1.6 Hz, 9.6 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H); ESI-HRMS calcd for $C_{11}H_{10}F_3O_3S^+$ $[M+H]^+$ 279.0303; found: 279.0308.

Preparation of 5, 6, 7, 8-tetrahydronaphthalen-1-ol (12).

To a solution of 5-hydroxy-1-tetralone **6** (1.64g, 10mmol, 1eq) and hydrazine hydrate (1.5g, 30mmol, 3eq) in triethylene glycol was heated to $80^{\circ}C$ and stirred for 1.5h until TLC showed the starting material was disappeared. Then KOH (1.68g, 30mmol, 3eq) was added and the temperature was raised to $180^{\circ}C$ and stirred for another 7h. The solution was colded to room temperature and added H_2O . 3N HCl was added dropwise to the solution until pH was about 8, which was extracted with ethyl acetate three times. The organic layer was combined and washed by brine and dried over Na_2SO_4 . After the solvent was evaporated in vacuum an off-white solid was obtained, 1.44g, yield 97%, which was pure enough for further use. 1H NMR(400 MHz, $CDCl_3$): δ 1.72-1.90 (m, 4H), 2.64 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 4.69 (s, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H); ESI-HRMS calcd for $C_{10}H_{13}O^+$ $[M+H]^+$ 149.0966; found: 149.0962.

Preparation of trifluoro-methanesulfonic acid 5, 6, 7, 8-tetrahydro-naphthalen-1-yl ester (13).

To a mixture of 5, 6, 7, 8-tetrahydronaphthalene-1-ol **12** (1.44g, 9.72mmol, 1eq) and TEA (1.18g, 11.66mmol, 1.2eq) in anhydrous DCM was colded to $-10^{\circ}C$ and added a solution of traflate anhydride (3.29g, 11.66mmol, 1.2eq) in anhydrous DCM dropwise. After addition, the reaction was stirred at $0^{\circ}C$ for 2h, and then quenched by saturated sodium bicarbonate solution at $0^{\circ}C$. DCM was added and the organic layer was separated. Washed by brine and dried over Na_2SO_4 , the organic layer was evaporated to dryness to give brownish oil, which was purified by flash chromatography on silica gel to get colorless oil 1.83g, yield 67%. 1H NMR(400 MHz, $CDCl_3$): δ 1.74-1.94 (m, 4H), 2.67 (t, J = 6.8 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H), 6.90 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H); ESI-HRMS calcd for $C_{11}H_{12}F_3O_3S^+$ $[M+H]^+$ 281.0459; found: 281.0461.

Preparation of 1-(7, 8-dihydronaphthalen-1-yl)ethanol (10).

To a solution of 1-(7, 8-dihydronaphthalen-1-yl)ethanone **9** (450mg, 2.61mmol, 1eq) in

MeOH in an ice bath was added NaBH₄ (119mg, 3.13mmol, 1.2eq) slowly in portions. After addition the solution was warmed to room temperature and stirred for 2h. The reaction suspension was acidified by 6N HCl to destroy unreacted NaBH₄ and basified by Na₂CO₃. When most MeOH was evaporated in vacuum the solution was added H₂O and extracted with DCM three times. The organic layer was put together, washed by brine and dried over Na₂SO₄. After the solvent was evaporated in vacuum colorless oil was obtained, which was pure enough for further use, 427mg, yield 94%. ¹H NMR(400 MHz, CDCl₃): δ 1.46 (d, *J*= 6.8 Hz, 3H), 1.95 (brs, 1H), 2.24-2.36 (m, 2H), 2.68-2.83 (m, 1H), 2.78-2.92 (m, 1H), 5.12-5.24 (m, 1H), 6.00-6.10 (m, 1H), 6.48 (dt, *J*= 1.6 Hz, 9.6 Hz, 1H), 6.96(d, *J*= 7.6 Hz, 1H), 7.19 (t, *J*= 7.6 Hz, 1H) , 7.39 (d, *J*= 7.6 Hz, 1H); ESI-HRMS calcd for C₁₂H₁₅O⁺ [M+H]⁺ 175.1123; found: 175.1129.

Preparation of 8-(1-chloroethyl)-1, 2-dihydronaphthalene (11).

To a solution of 1-(7, 8-dihydronaphthalen-1-yl)ethanol **10** (427mg, 2.45mmol, 1eq) in anhydrous DCM in an ice bath was added a solution of SOCl₂ (1.46g ,12.25mmol , 5eq) in anhydrous DCM dropwise and stirred for another 10h. The solution turned light-blue and TLC showed the reaction finished. Then the mixture was quenched by saturated sodium bicarbonate solution. DCM was added and the organic layer was separated. Washed by brine and dried over Na₂SO₄, the organic layer was evaporated to dryness to give light yellow oil, which was used directly without purification, 340mg, yield 72%. ¹H NMR(400 MHz, CDCl₃): δ 1.84 (d, *J*= 6.8 Hz, 3H), 2.26-2.37 (m, 2H), 2.72-2.94 (m, 2H), 5.37-5.59 (m, 1H), 6.12-6.23 (m, 1H), 6.54 (dt, *J*= 1.6 Hz, 9.6 Hz, 1H), 7.05(d, *J*= 7.6 Hz, 1H), 7.26 (t, *J*= 7.6 Hz, 1H) , 7.46 (d, *J*= 7.6 Hz, 1H); ESI-HRMS calcd for C₁₂H₁₄Cl⁺ [M+H]⁺ 193.0784; found: 193.0789.

Preparation of [1-(7, 8-dihydro-naphthalen-1-yl)-ethyl]-[3-(3-trifluoromethyl-phenyl)-propyl]-amine hydrochloride (2).

To a mixture of 8-(1-chloroethyl)-1, 2-dihydronaphthalene **11** (340mg, 1.76mmol, 1eq), 3-(3-(trifluoromethyl)phenyl)propanamine **5** (429mg, 2.11mmol, 1.2eq), K₂CO₃ (730mg, 5.28mmol, 3eq) and KI (29mg, 0.176mmol, 0.1eq) in MeCN was refluxed overnight and TLC showed the reaction completed. When most MeCN was evaporated in vacuum the solution was added H₂O and extracted with EA three times. The organic layer was put together, washed by brine and dried over Na₂SO₄. After the solvent was evaporated in vacuum colorless oil was obtained, which was pure enough for further use. The oil was dissolved in *i*-PrOH and refluxed while conc. HCl was added dropwise. After addition the solution was refluxed for another 20 min and cooled to room temperature, and then poured into water slowly. The precipitation was collected and dried in vacuum to obtain an off-white solid, which was further purified by recrystallization in MeCN to get the final product **2** as a white crystal, 543mg with the purity of 95.26% by HPLC, yield 78%. melting point: 176-178°C; IR (KBr) cm⁻¹: 3458, 3421, 3037, 2969, 2797, 2747, 2641, 2511, 2429, 1589, 1452, 1329, 1169, 1129, 1072, 808, 703; ¹H NMR(400 MHz, CDCl₃): δ 1.77 (d, *J*= 6.8 Hz, 3H), 2.14-2.36 (m, 4H), 2.52-2.64 (m, 2H), 2.68-2.76 (m, 4H), 4.59 (m, 1H), 6.04-6.12 (m, 1H), 6.47 (d, *J*= 9.6 Hz, 1H), 7.03 (d, *J*= 7.2 Hz, 1H), 7.22-7.34 (m, 4H), 7.38 (d, *J*= 6.8 Hz, 1H), 7.78 (d, *J*= 8.0 Hz, 1H), 9.68 (s, 1H), 10.31 (s, 1H); ¹³C NMR(100 MHz, CDCl₃): δ 20.5, 22.7, 23.0, 27.1, 32.5, 45.1, 53.6, 123.0, 124.8, 125.0, 126.8, 127.7, 127.9, 128.7, 128.8, 130.4, 130.8, 131.6, 132.8, 133.0, 134.7, 140.8; ESI-HRMS calcd for C₂₂H₂₅F₃N⁺ [M+H]⁺ 360.1939; found: 360.1945.

General procedure for the preparation of the related compounds 3 or 4 by reductive amination in Ti(O-*i*-Pr)₄ and NaBH₄/MeOH.

To a solution of the proper naphthalenylethanone **14** or **15** and 3-(3-(trifluoromethyl)phenyl)propanamine **5** (1.05eq) in Ti(O-*i*-Pr)₄ was stirred overnight. When MeOH was added and the mixture was cooled to 0°C, NaBH₄ (1.2eq) was added slowly in portions. After addition the solution was warmed to room temperature and stirred for 1h. The reaction suspension was acidified by 6N HCl to destroy unreacted NaBH₄ and basified by Na₂CO₃. After filtration to remove titanium salt most MeOH was evaporated in vacuum and the solution was added H₂O and extracted with ethyl acetate three times. The organic layer was put together, washed by brine and dried over Na₂SO₄. After the solvent was evaporated in vacuum colorless oil was obtained, which was pure enough for further use. The oil was dissolved in *i*-PrOH and refluxed while conc. HCl was added dropwise. After addition the solution was refluxed for another 20min and cooled to room temperature, and then poured into water slowly and the precipitation was collected and dried in vacuum to obtain an off-white solid, which was further purified by recrystallization in MeCN to get the final product as a white crystal.

[1-(5, 6, 7, 8-tetrahydro-naphthalen-1-yl)-ethyl]-[3-(3-trifluoromethyl-phenyl)-propyl]-amine hydrochloride (3), 475mg with the purity of 97.88% by HPLC, yield 81%. melting point: 187-189°C; IR (KBr) cm⁻¹: 3420, 2939, 2701, 2638, 2510, 1637, 1452, 1399, 1329, 1167, 1131, 1072, 800, 704, 663; ¹H NMR(400 MHz, CDCl₃): δ 1.73 (d, *J*= 6.4 Hz, 3H), 1.68-1.92 (m, 4H), 2.12-2.34 (m, 2H), 2.52-2.74 (m, 6H), 2.79 (t, *J*= 6.0 Hz, 2H), 4.52 (m, 1H), 7.07 (d, *J*= 7.6 Hz, 1H), 7.20-7.34 (m, 4H), 7.38 (d, *J*= 6.8 Hz, 1H), 7.75 (d, *J*= 8.0 Hz, 1H), 9.68 (s, 1H), 10.31 (s, 1H); ¹³C NMR(100 MHz, CDCl₃): δ 20.7, 22.2, 23.0, 26.0, 27.2, 30.1, 32.5, 45.1, 53.7, 123.0, 123.5, 124.8, 126.8, 128.8, 129.9, 130.4, 130.7, 131.6, 134.1, 134.5, 138.2, 140.8; ESI-HRMS calcd for C₂₂H₂₇F₃N⁺ [M+H]⁺ 362.2096; found: 362.2087.

[1-(naphthalen-2-yl)-ethyl]-[3-(3-trifluoromethyl-phenyl)-propyl]-amine hydrochloride (4), 452mg with the purity of 99.79% by HPLC, yield 84%. melting point: 117-120°C; IR (KBr) cm⁻¹: 3450, 2951, 2795, 2749, 2643, 2511, 2422, 1631, 1584, 1455, 1391, 1331, 1162, 1115, 1074, 822, 800, 749, 701, 662, 478; ¹H NMR(400 MHz, CDCl₃): δ 1.92 (d, *J*= 6.8 Hz, 3H), 2.18-2.32 (m, 2H), 2.48-2.62 (m, 2H), 2.62-2.80 (m, 2H), 4.35 (m, 1H), 7.15-7.23 (m, 2H), 7.27-7.35 (m, 2H), 7.52-7.58 (m, 2H), 7.82-7.92 (m, 3H), 7.92-7.98 (m, 2H), 10.01 (s, 1H), 10.39 (s, 1H); ¹³C NMR(100 MHz, CDCl₃): δ 20.4, 27.0, 32.3, 45.1, 59.3, 122.9, 124.2, 124.8, 126.7, 126.9, 127.6, 127.7, 128.1, 128.7, 129.7, 130.4, 130.7, 131.5, 133.0, 133.1, 133.4, 140.7; ESI-HRMS calcd for C₂₂H₂₃F₃N⁺ [M+H]⁺ 358.1783; found: 358.1791.

SPECTRA OF THE TARGET COMPOUNDS

IR of the related substance 2

¹H-NMR of the related substance 3

¹³C-NMR of the related substance 3

IR of the related substance 3

IR of the related substance 4