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COMMUNICATION

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Industrial Application of the Forster Reaction: Novel One-Pot Synthesis of Cinacalcet Hydrochloride, a Calcimimetic Agent

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ABSTRACT: Described is a new, practical, and one-pot process, based on the Forster reaction, for the synthesis of cinacalcet hydrochloride (**1**), a calcimimetic agent and calcium-sensing receptor antagonist. The synthesis comprises the condensation of (1*R*)-(+)-1-naphthylethyl amine (**2**) with benzaldehyde (**3**) followed by reaction of obtained Schiff's base **4** with 1-(3-halopropyl)-3-(trifluoromethyl)-benzene (**5**) to provide highly unstable iminium salt **6**. Subsequent hydrolysis of **6** with water in the same pot yielded cinacalcet. The treatment of cinacalcet with hydrochloric acid during the workup process furnished **1** with an overall yield of around 60%. Our synthetic approach for **1**, discussed in this report demonstrates industrial application of the century-old, unexplored name reaction, "Forster's Reaction" or Forster−Decker synthesis.

INTRODUCTION

Synthetic route selection is the critical starting point for Process Research and Development, especially in generic pharmaceutical industries due to cost pressure and to overcome possible infringement issues in order to enter the regulated markets.[1] Exploration of new and efficient chemical routes designed empirically by retrosynthetic approaches, new intermediates, reaction conditions, reagents, catalysts, and polymorphs with superior bioavailability and efficacy etc., are the key success factors to get rid of entry barriers. While doing so, a chemist, working under stringent conditions and led by instinct and experience, identifies and unearths new ways of doing chemistry with the competitive advantages that helps companies to generate intellectual wealth.[2] This article reports a novel, one-pot process for making the cinacalcet hydrochloride (**1**), a selective calcimimetic agent, by using Forster's reaction. This reaction is used for the formation of secondary amine derivatives by condensing the primary amines with an aldehyde followed by addition of alkyl halide to the obtained Schiff's base and subsequent hydrolysis of the iminium salt.[3] Cinacalcet hydrochloride (**1**) is a first novel drug in the class of calcimimetics, approved by United States Food and Drug Administrative as Sensipar, and Mimpara. Calcimimetics belong to a class of orally active, small molecules that decrease the secretion of parathyroid harmone (PTH) by activating calcium receptors. This class of compounds is used to treat hyperparathyroidism (HPT), a condition characterized by oversecretion of PTH, the result of the failure of calcium receptors on parathyroid glands to respond properly to calcium in the bloodstream. Elevated levels of parathyroid hormone (PTH), an indicator of secondary hyperparathyroidism (SHPT), are associated with altered metabolism of calcium and phosphorus, bone pain, fractures, and increased risk for cardiovascular death. The secretion of PTH is normally regulated by the calcium-sensing receptor. Calcimimetic agents increase the sensitivity of this receptor to calcium, which inhibits the release of parathyroid hormone, and lowers PTH levels within few hours.[4]

Original synthetic methods were developed on the basis of reductive amination approaches that involve the use of reagents such as titanium isopropoxide (which is highly hygroscopic, expensive, and pyrophoric) and sodium cyanoborohydride, and DIBAL (which are toxic and flammable). These reported methods as depicted in Scheme 1 also employed chiral chromatographic techniques, which are not feasible on industrial scale. In recent years, extensive efforts have been made towards the development of efficient synthetic methods for **1**; few of them are superior, improved, and scalable over the first-generation syntheses.[5]

Our approach for the development of **1** is based on the Forster reaction which can be performed in one pot without the isolation of intermediates, minimizing waste and exposure and increasing throughput. A new process for the preparation of **1** in high chemical and optical purity has been developed and scaled up successfully in what is believed to be the first industrial application of Forster's reaction.

RESULTS AND DISCUSSION

Most of the synthetic endeavors published recently for synthesis of cinacalcet involves the use of (1*R*)-(+)-1-naphthylethyl amine (**2**) as one of the key starting material; recently, an improved process for synthesis of **2** has been reported by our laboratory.[6] Another intermediate, 1-(3-bromopropyl)-3-(trifluoromethyl)benzene (**5**) required for the synthesis was prepared according to literature process[5d,g] with minor modifications.[7] The preparation of cinacalcet was studied using Forster reaction by reacting the (1*R*)-1-naphthyl ethylamine (**2**) with benzaldehyde (**3**) at room temperature to furnish Schiff's base (1*R*)-1-(2-naphthyl)-*N*-[1-phenylmethylene]ethanamine (**4**), which is then reacted with 1-(3-bromopropyl)-3-(trifluoromethyl)-benzene (**5**) in *N*-methyl-2-pyrrolidone at 130−135 °C to obtain

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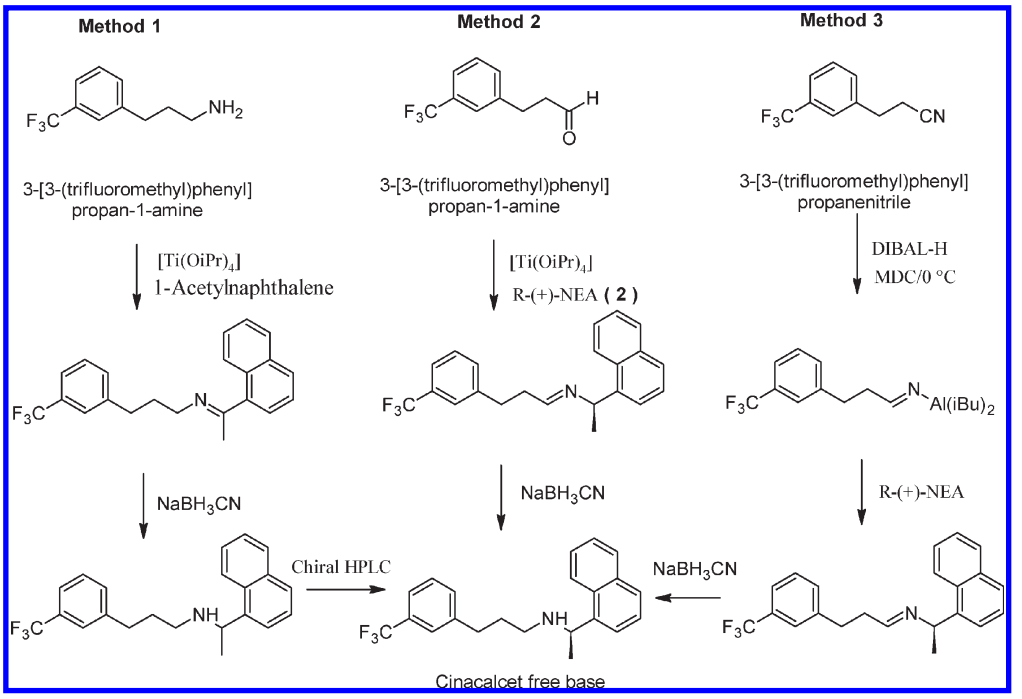
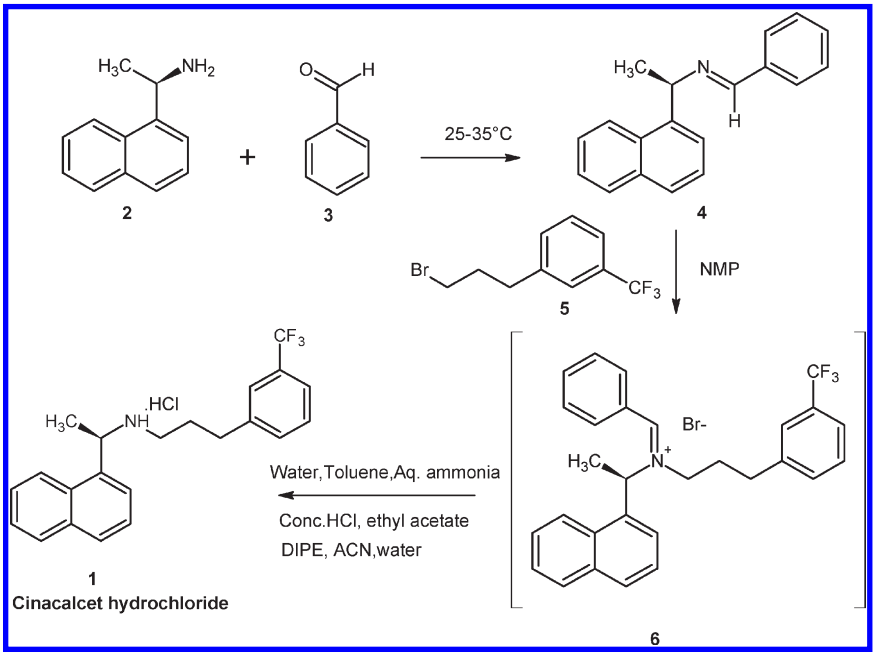
Scheme 1



Scheme 2. One-pot synthesis of cinacalcet hydrochloride (1)



an iminium salt **6**. Hydrolysis of iminium salt **6** with water and/or an acid furnished the cinacalcet hydrochloride (**1**).[8] Syntheses of Schiff's base **4** and cinacalcet hydrochloride (**1**) were run separately, that is consecutively during feasibility in order to establish the reaction parameters and understand the impurity profile at each stage. Subsequently both the steps were telescoped and conveniently performed in one pot once the critical process parameters are established (Scheme 2). Reaction of **2** with **3** was initially conducted in ethanol at 70−80 °C for 5−6 h. The Schiff base **4** precipitated out in the reaction mass and was isolated as white crystalline solid by filtering the reaction mass. The solid product **4** obtained was directly used in the next step without further purification. **4** was found unstable upon storage for a longer period in the presence of moisture. However, the dried sample of **4**, stored under inert atmosphere, was found to remain stable for a longer period. The structure of **4** was characterized by different spectroscopic methods.

The reaction of **4** with 1-(3-bromopropyl)-3-(trifluoromethyl)-benzene (**5**) in *N*-methyl-2-pyrrolidone at 130−135 °C provided iminium salt **6**, which on treatment with water or an aqueous acid

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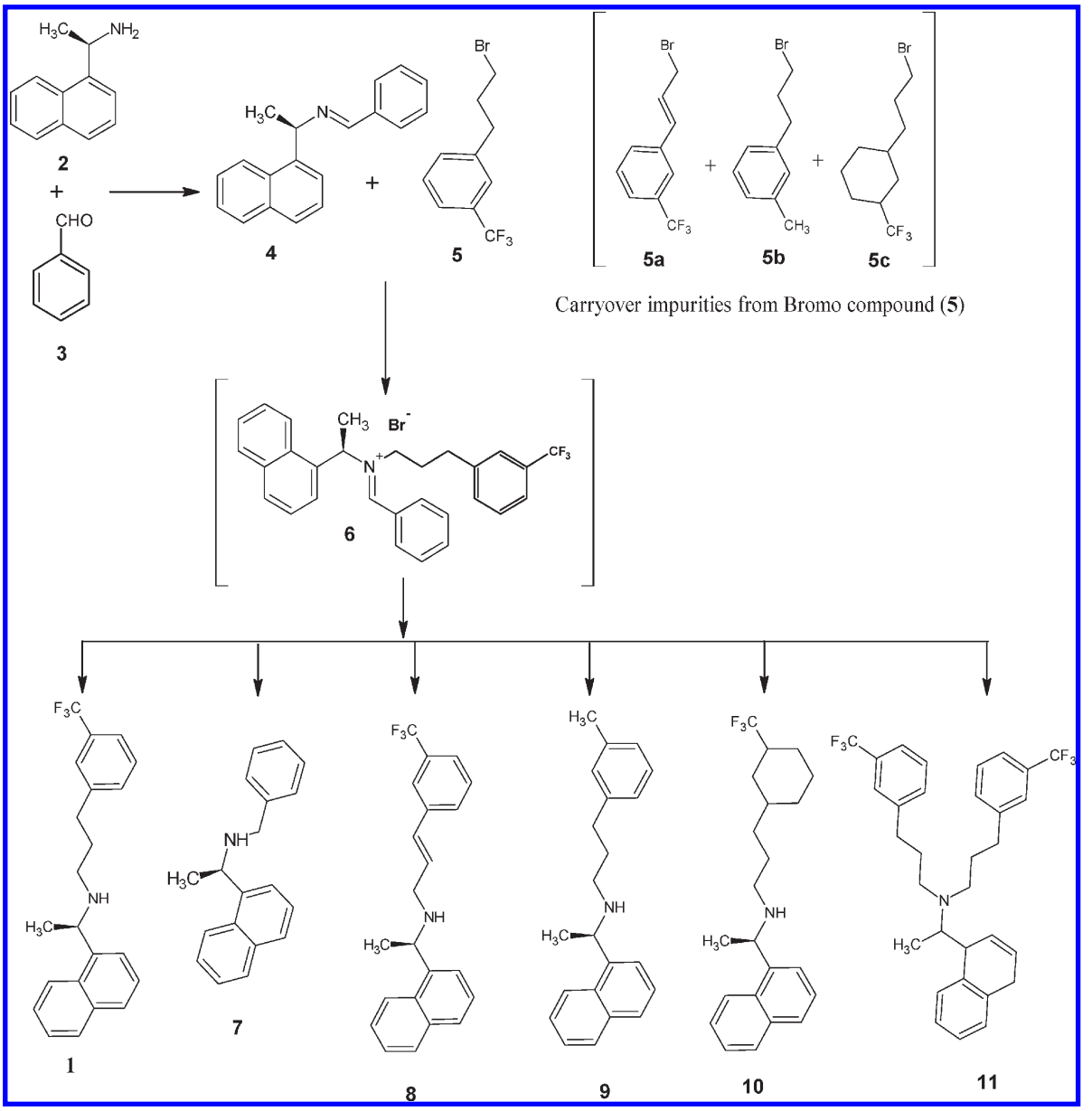
Scheme 3. Formation of impurities in cinacalcet hydrochloride (1)



at 25−35 °C followed by usual workup procedure furnished cinacalcet hydrochloride (**1**). After completion of reaction (by TLC) the reaction mass was quenched with water, and the pH of the mass was adjusted to 8−9 using aqueous ammonia. The reaction mass was extracted in toluene, the toluene layer was washed with water followed by 10% sodium metabisulphite solution to remove traces of aldehyde **3** from the product layer. Water was then added to the toluene layer, and the pH of the solution was adjusted to 0.5−1.5 using concentrated hydrochloric acid. The resulting reaction solution was stirred, and the layers were separated. The organic layer containing cinacalcet hydrochloride (**1**) was washed with water and concentrated under reduced pressure to obtain thick syrup. The syrup was dissolved in heptane or diisopropylether and stirred for 2 h, and the solid obtained was filtered. This solid was suspended in ethyl acetate, heated at 55−60 °C for 30 min, and cooled to 15−20 °C; the resultant solid was filtered, washed with ethyl acetate, dried, and recrystallized with acetonitrile and water (2:10 v/v) to afford cinacalcet hydrochloride (**1**) as a white crystalline solid with 99.9% purity by HPLC with an overall yield of 58−60%. Of the several reaction conditions, including catalysts such as potassium iodide and/or phase transfer catalyst such as tetrabutyl ammonium bromide, in solvents such as acetonitrile, *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylacetamide, tetrahydrofuran (THF), toluene, dimethylformamide (DMF), or dimethylsulfoxide (DMSO), *N*-methyl-2-pyrrolidone (NMP) was proved to be the superior solvent for this reaction. The use of catalyst or phase transfer catalyst added no advantages to the established process. The original Forster reaction does not use any solvent for the formation of iminium salt, but in our case, many impurities were formed when the reaction was performed without solvent.

After establishing both reactions independently, a one-pot process was established by telescoping both the reactions. While

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telescoping and establishing the one-pot process, the formation of **4** was achieved without using the solvent at 25−30 °C within 1−2 h. *N*-Methyl-2-pyrrolidone was added to the reaction mass containing **4**, followed by 1-(3-bromopropyl)-3-(trifluoromethyl)benzene (**5**), and rest of the operations were performed in the same manner as described above to obtain the cinacalcet hydrochloride (**1**) in one pot.

EVALUATION OF IMPURITIES

Evaluation (identification, characterization, and synthesis) of impurities (by products, starting materials, intermediates, carryover impurities from starting materials, etc.) formed in the reaction mass and their control in the product at the end to meet the regulatory norms (ICH quality) is another critical objective during the process development.[9] Analysis of the reaction mass and crude cinacalcet hydrochloride (**1**) by HPLC helped to identify the impurity peaks, which are subsequently identified by LC−MS. The proposed impurities were synthesized, characterized, and confirmed by spiking studies using HPLC. By understanding the structures, their control and removal strategy have been designed for preparing chemically and enantiomerically pure **1**. Five potential impurities viz., **7**, **8**, **9**, **10**, and **11** were identified, synthesized, and characterized by LC−MS (Scheme 3).

Alkylation of Schiff's base **4** with **5** is a very slow reaction and does not go to completion even after prolonged heating. Unreacted **4** was converted into **2** during the workup and was selectively removed by washing the organic layer with dilute hydrochloric acid. Benzaldehyde (**3**) was removed by metabisulfite wash. Dimer impurity **11**, formed by the alkylation of **1**, was eliminated by purification using ethylacetate. However, **7** that was present in at 1−2% level in the crude product was not removed. Crystallization from acetonitrile−water was established specifically to remove **7**. While a set of three impurities **8**, **9**, and **10** that are formed due to the presence of carryover impurities **in 5**(**5a**, **5b**, and **5c**) were eliminated in **5**. Removal of **8**, **9**, and **10** by recrystallization was difficult without significant yield loss. However, their formation during the preparation of **1** was eliminated by the purification of **5** by fractional distillation.[7] Though the reaction condition for alkylation was harsh (130−135 °C), racemization of the products was not observed as chiral purity of the crude product was 99.98% by chiral HPLC.

The contents of all six of these potential impurities (**2**, **7**, **8**, **9**, **10**, and **11**) and other unknown impurities were well below the ICH limits (NMT 0.15%). However, the absence of impurity **5** in **1** has been confirmed by gas chromatography (GC) studies.

CONCLUSION

In conclusion, an efficient, and environmentally friendly process to make cinacalcet hydrochloride in high chemical and chiral purity has been developed by employing the Forster reaction.

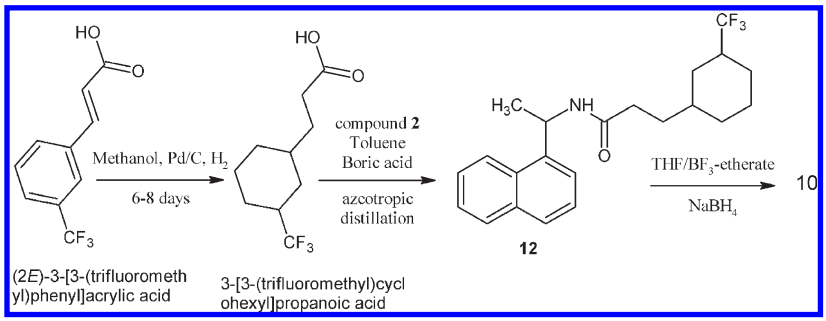
EXPERIMENTAL SECTION

General. Melting points were determined on Analab melting point apparatus, in open capillary tubes, and were uncorrected. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts were reported in parts per million using tetramethylsilane as the internal standard and are given in δ units. The solvents for NMR spectra were $CDCl_3$ and DMSO-d_6 unless otherwise stated. Infrared spectra were taken on Perkin-Elmer Spectrum 100 in potassium bromide pellets unless otherwise stated. A mass spectrum was recorded on Shimadzu GC−MS QP mass spectrometer with an ionization potential of 70 eV. Elemental analyses were performed on a Hosli CH-Analyzer and were within the theoretical percentage of ±0.3. Progress of all reactions was monitored by thin layer chromatography (TLC) and carried out on 0.2 nm silica gel 60 F_{254} (Merck) plates, using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals were either commercially available and were used without further purification or were prepared by standard literature procedures

One-Pot Process for the Preparation of Cinacalcet Hydrochloride (1). To a stirred solution of (1*R*)-1-naphthyl ethylamine (**2**, 1.0 kg, 5.85 mol) was added benzaldehyde (**3**, 0.62 kg, 5.85 mol), and the contents were stirred at 25−30 °C for 1−2 h. After completion of the reaction (by HPLC), *N*-methyl-2-pyrrolidinone (3.0 L) was added to the above mixture and stirred for 15−20 min, before the addition of 1-(3-bromopropyl)-3-(trifluoromethyl)benzene (**5**, 1.72 kg, 6.44 mol). The temperature of the reaction mass was slowly raised to 125−130 °C and maintained for 10−12 h. Reaction mass was cooled to 25−30 °C and quenched with water (10.0 L). The pH of the mass was adjusted to 8−9 using aqueous ammonia and extracted with toluene (10.0 L). The toluene layer was separated, washed with water (10.0 L) followed by 10% sodium metabisulphite (10.0 L × 2). Water (10.0 L) was added into the toluene layer, the pH of the solution was adjusted to 0.5−1.5 using concentrated hydrochloric acid, the resulting solution was stirred, and the layers were separated. The organic layer was washed with water (10.0 L × 2) and concentrated under reduced pressure to provide thick syrup. The syrup was dissolved in diisopropylether (6.0 L) and stirred for 2 h; the solid obtained was filtered. The obtained solid was suspended in ethyl acetate (5.0 L), heated at 55−60 °C for 30 min, cooled to 15−20 °C, filtered, washed with ethyl acetate (0.10 L), and dried. The dried solid was recrystallized with acetonitrile and water (3.0 L:15.0 L) to afford **1** as white crystalline solid. Yield: 1.334 kg (58.0%); HPLC purity: 99.95%; Chiral Purity: 99.98%; mp: 178−182 °C; IR (KBr) cm^{-1}: 3436, 2962, 2797, 1587, 1450, 1379, 1327, 1166, 1129, 797, 774, 746; MS: m/z = 358.79 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.67−1.69 (d, 3H), 1.97−2.02 (m, 2H), 2.67−2.69 (t, 4H), 5.27 (q, 1H), 7.44−7.46 (m, 4H), 7.54−7.61 (m, 3H), 7.93−7.99 (m, 2H), 8.026−8.08 (d, J = 7.2 Hz, 1H), 8.20−8.23 (d, J = 7.2 Hz, 1H), 9.46 (s, 1H), 10.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.49 (CH_3), 27.50 (CH_2), 32.02 (CH_2), 45.18 (CH_2), 52.60 (CH), 123.06, 123..23, 123.26, 124.94, 125.17, 125.21 (CF_3), 126.0, 126.60, 127.39, 129.35, 129.39, 129.82, 130.79, 132.88, 133.83, 134.58, 142.75; Anal. Calcd for $C_{22}H_{23}NF_3Cl$: C, 67.09; H, 5.84; N, 3.55; Found: C, 66.92; H, 5.68; N, 3.58.

Preparation of (1*R*)-1-(2-Naphthyl)-*N*-(phenylmethylene)-ethanamine (4). To a stirred solution of (1*R*)-1-naphthyl ethylamine (**2**, 5 g, 0.029 mol) in ethanol (25 mL), was added benzaldehyde (**3**, 3.71 g, 0.035 mol) at 25−30 °C, and the resultant mass was stirred at 55−60 °C for 5−6 h. Upon completion of reaction (by TLC), the reaction mass was gradually cooled to 5−10 °C and maintained for 30 min. The precipitated solid was filtered, washed with ethanol (10 mL), and dried under vacuum to yield **4** as a white crystalline solid. Yield: 7.1 g (94.67%); HPLC purity: 99.20%; mp: 90−92 °C; IR (KBr) cm^{-1}: 3446, 2975, 2926, 1641, 1445, 1392, 803, 781, 762; MS: m/z = 260.0

Scheme 4. Synthetic route for the preparation of compound 10



$[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74−1.76 (d, 3H), 5.34−5.39 (q, 1H), 7.41−7.42 (t, J = 6.0 Hz, 3H), 7.48−7.51 (m, 3H), 7.80−7.87 (m, 5H), 8.25−8.27 (d, J = 8.0 Hz, 1H), 8.44 (s, 1H).

Preparation of (1*R*)-*N*-Benzyl-1-(1-naphthyl)ethanamine (7). To a stirred solution of (1*R*)-1-(2-naphthyl)-*N*-(phenylmethylene)ethanamine (**4**, 10 g, 0.038 mol) in ethanol (200 mL) was added sodium cyanoborohydride (3.63 g, 0.057 mol) at 25−30 °C. The reaction mass was further stirred at 45−50 °C for 5−6 h. Upon completion of the reaction (by TLC), the reaction mass was cooled, quenched with water (100 mL), and extracted with *n*-heptane (100 mL). The organic layer was separated, washed with water (100 mL), and concentrated under reduced pressure to provide thick oil. The oil was dissolved in *n*-heptane (90 mL) and stirred, and the pH of the solution was adjusted to 1−2 using concentrated hydrochloric acid. The precipitated solid was filtered, washed with *n*-heptane (10 mL), and dried under vacuum to yield **7** as a white crystalline solid. Yield: 8.2 g, (81.42%); HPLC purity: 99.10%; IR (KBr) cm^{-1}: 3445, 2965, 2759, 2728, 2682, 1596, 1457, 1378, 801, 781, 779; MS: m/z = 262.07 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73−1.75 (d, J = 8.8 Hz, 3H), 3.95−3.99 (br dd, 1H), 4.16−4.19 (br dd, 1H), 5.24−5.26 (q, J = 8.8 Hz, 1H), 7.38−7.39 (m, 3H), 7.48−7.50 (t, 2H), 7.57−7.59 (m, 2H), 7.64−7.66 (d, 1H),7.98−8.03 (m, 3H), 8.08−8.11 (d, J = 9.2 Hz, 1H), 9.72 (bs, 1H), 10.48 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.15 (CH_3), 48.34 (CH_2), 51.48 (CH), 121.35, 125.04, 125.9, 126.69, 128.52, 129.0, 129.11, 129.61, 130.21, 130.76, 132.11, 133.60.

Preparation of (2*E*)-*N*-[(1*R*)-1-(1-Naphthyl) ethyl]-3-[3-(trifluoromethyl)phenyl]prop-2-en-1-amine (8). To a stirred solution of (1*R*)-1-naphthyl ethylamine (**2**, 10 g, 0.058 mol), was added benzaldehyde (**3**, 17.04 g, 0.064 mol) and maintained at 25−30 °C for 1−2 h. After the completion of reaction (by HPLC), *N*-methyl-2-pyrrolidinone(30 mL) was added followed by 1-[(1*E*)-3-bromopropyl-1en-1-yl]-3-(trifluoromethyl)benzene[10] (**5a**, 17.04 g, 0.064 mol), and the temperature of the reaction mass was raised to 125−130 °C and maintained for 12 h. After completion of the reaction (by HPLC), the reaction mass was quenched with water (100 mL); the pH was adjusted to 8−9 using aqueous ammonia, and the solution was extracted with toluene (100 mL). The toluene layer was separated, washed with water (100 mL) followed by an aqueous solution of 10% sodium metabisulphite (100 mL × 2). Water (100 mL) was added to the toluene layer, and the pH of the solution was adjusted to 0.5−1.5 using concentrated hydrochloric acid, and the resulting reaction solution was stirred for 10−15 min. Organic layer was separated, washed with water (100 mL × 2), and concentrated under reduced pressure to provide a thick syrup. The syrup was then dissolved in *n*-heptane (60 mL) and stirred for 2−3 h; the obtained solid was filtered. This solid was suspended in ethyl acetate (50 mL); the suspension was heated at 55−60 °C for 30 min and cooled to 15−20 °C; the obtained solid was filtered, washed with ethyl acetate, and dried to afford compound **8** as a white crystalline solid. Yield: 13.80 g (60%); HPLC purity: 90.20%; Chiral Purity: 99.9%; IR (KBr) cm^{-1}: 2961, 2925, 2853, 1734, 1595, 1448, 1331, 1164, 1124, 1072, 799, 778, 696 ; MS: m/z = 356.1 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.46−1.48 (d, 3H), 3.32−3.35 (d, J = 7.6 Hz, 2H), 4.82 (q, 1H), 6.47−6.52 (dt, J = 18.0 and 7.6 Hz, 1H), 6.57−6.61 (d, J = 16.0 Hz, 1H), 7.49−7.54 (m, 6H), 7.68−7.70 (d, J = 8.0 Hz, 1H), 7.77−7.79 (d, J = 8.0 Hz, 1H), 7.83−7.85 (d, J = 8 Hz, 1H), 7.93−7.95 (dd, J = 8.0 Hz, 1H) 8.23−8.25 (dd, J = 8.0 and 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.19 (CH_3), 46.61 (CH_2), 51.44 (CH), 122.62 (CH), 122.72 (CH), 122.93, 124.69, 125.48 (CF_3), 125.63, 126.15, 126.87, 128.97, 129.37, 129.69, 129.90, 130.25, 130.36, 133.41, 134.03, 134.61.

Preparation of 3-(3-Methylphenyl)-*N*-[(1*R*)-1-(1-naphthyl)ethyl]propan-1-amine (9). To a stirred solution of (1*R*)-1-naphthyl ethylamine (**2**, 10 g, 0.058 mol) was added the benzaldehyde (**3**, 17.04 g, 0.058 mol) and stirred at 25−30 °C for 1−2 h. After completion of the reaction (by HPLC) *N*-methyl-2-pyrrolidinone (30 mL) was added to the mixture and stirred for 15−20 min followed by addition of 1-(3-bromopropyl)-3-methylbenzene (18.68 g, 0.087 mol). The temperature of reaction mass was raised to 125−130 °C and maintained until completion of the reaction (by HPLC). The reaction mass was quenched with water (100 mL), pH of the resulting solution was adjusted to 8−9 using aqueous ammonia, and the solution was extracted with toluene (100 mL). The toluene layer was separated, washed with water (100 mL) followed by 10% sodium metabisulphite (100 mL × 2). Water (100 mL) was added into toluene layer, and the pH of the solution was adjusted to 0.5−1.5 using concentrated hydrochloric acid. The resulting solution was stirred, and the layers were separated. The organic layer was washed with water (100 mL × 2) and concentrated under reduced pressure to provide thick syrup. Syrup was dissolved in *n*-heptane (60 mL) and stirred for 2 h, and the solid obtained was filtered. The wet solid was suspended in ethyl acetate (50 mL); the solution was heated at 55−60 °C for 30 min, cooled to 15−20 °C, filtered, washed with ethyl acetate, and dried to afford des(trifluorocinacalcet) (**9**) as a white crystalline solid. Yield: 11.0 g (55.92%); HPLC purity: 99.60%; Chiral Purity: 99.90%; IR (KBr) cm^{-1}: 3435, 3006, 2962, 2945, 2798, 1588, 1455, 799, 771, 702; MS: m/z = 304.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.66−1.68 (d, 3H),

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1.93−1.96 (m, 2H), 2.22 (s, 3H), 2.52−2.54 (m, 2H), 2.71−2.74 (dt, 1H), 2.90−2.94 (dt, 1H), 5.29−5.31 (q, 1H), 6.89−6.97 (dd, J = 8.0 Hz and 3.0 Hz, 3H), 7.11−7.13 (t, J = 8.0 Hz, 1H), 7.59−7.63 (dd, J = 8.0 Hz and 3.0 Hz, 3H), 7.97−8.02 (m, 3H), 8.23−8.25 (d, J = 8.0 Hz, 1H), 9.24 (bs, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.13 (CH_3), 21.02 (CH3), 27.16 (CH_2), 31.92 (CH_2), 44.88 (CH_2), 52.07 (CH), 122.68, 124.51, 125.25, 125.62, 126.19, 126.64, 126.98, 128.64, 128.89, 130.36, 133.39, 134.22, 137.36, 140.59.

Preparation of 3-(3-(Trifluoromethyl)cyclohexyl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)propan-1-amine (10). (2*E*)-3-[3-(Trifluoromethyl)phenyl]acrylic acid (100 g, 0.462 mol), methanol (1000 mL), and 10% Pd/C (25.0 g, 50% wet) were added into an autoclave, and hydrogen pressure of 5 kg/cm^2 was applied; the reaction was maintained at 50−55 °C for 8 days. The catalyst was filtered, and solvent was removed under reduced pressure to obtain 3-[3-(trifluoromethyl)cyclohexyl]propanoic acid (98.0 g) as an oil. The oil was then treated with **2** (67.68 g, 0.395 mol) in toluene (670 mL) at 110 °C for 16−18 h in the presence of boric acid (1.4 g, 0.022 mol) under azeotropic conditions. After completion of the reaction (by TLC), the reaction mass was cooled to 25−30 °C, and washed with 2 N hydrochloric acid solution (670 mL) followed by 10% aqueous solution of sodium bicarbonate (670 mL) and water (500 mL). The organic layer was separated and concentrated under reduced pressure to yield 114.0 g of amide compound **12** (Scheme 4). To a cooled solution of amide **12** in tetrahydrofuran (1700 mL) was added $NaBH_4$ (89.62 g, 3.258 mol) lotwise at −5 to 0 °C, followed by slow addition of BF_3-etherate (349.55 g, 5.14 mol). Reaction mass was heated to 50−55 °C, maintained for 5−6 h, and quenched over 2 N hydrochloric acid solution (456 mL). The resulting reaction mass was distilled out atmospherically below 70 °C to remove THF and cooled to 25−30 °C; the pH of the reaction mass was adjusted to 8−9 using aqueous ammonia. The reaction mass was extracted with toluene (1140 mL), the toluene layer was washed with water (500 mL) and concentrated to get crude **10** as oil. The obtained crude oil was purified by column chromatography on silica gel (70 mm ×60 cm column) using neat chloroform as the elution solvent to afford compound **10** as a white solid.

Yield: 13.0 g ; HPLC purity: 86.3%; Chiral Purity: 99.9%; IR (KBr): cm^{-1} 3434, 2938, 2859, 2736, 1587, 1453, 1256, 1170, 1096, 800, 778; MS: m/z = 364.10 [M + H] $^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.82−0.88 (m, 2H), 1.14−1.22 (m, 4H), 1.48−1.52 (t, 4H), 1.49 −1.52 (d, 3H), 1.72−1.86 (m, 4H), 2.50−2.56 (t, 2H), 4.63−4.64 (q, 1H), 7.45−7.48 (m, J = 8.0 and 3.0 Hz, 3H), 7.62−7.64 (d, J = 8.0 Hz, 1H), 7.73−7.75 (d, J = 8.0 Hz, 1H), 7.86−7.88 (d, J = 8.0 Hz, 1H), 8.16−8.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.03 (CH_3), 22.70, 23.59, 24.46, 28.79, 30.94, 31.32, 33.22, 34.91, 45.42, 52.01, 122.65, 124.41, 125.60, 126.18, 126.96, 128.92 (CF_3), 130.31, 133.38, 134.27.

Preparation of (1-Naphthalen-1-yl-ethyl)-*N*,*N*-bis-[3-(3-trifluoromethylphenyl)-propyl]amine (11). To a stirred solution of cinacalcet hydrochloride (**1**, 10 g, 0.028 mol) in toluene (150 mL) was added potassium carbonate (7.74 g, 0.056 mol) followed by 1-(3-bromopropyl)-3-(trifluoromethyl)benzene (**5**, 14.95 g, 0.056 mol) under stirring at 25−30 °C. The reaction mass was heated and stirred at 110−111 °C for 48 h. Upon completion of the reaction (by TLC), the reaction mass was cooled and quenched with water (100 mL). The organic layer was separated, washed with water (100 mL), and concentrated under reduced pressure to obtain thick oil. The crude oil was then purified by column chromatography on silica gel (70 mm × 60 cm column) by eluting with chloroform to afford compound **11** as a thick transparent oil. Yield: 10.50 g (69.03%); HPLC purity: 91.22%; IR (NaCl) cm^{-1}: 3441, 3049, 2940, 2861, 1596, 1492, 1449, 1331, 900, 702, 661; MS: m/z = 544.0 [M + H] $^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35−1.37 (d, 3H), 1.57−1.63 (m, 4H), 2.42−2.46 (t, 4H), 2.52−2.55 (t, 4H), 4.60−4.62 (m, 1H), 7.23−7.25 (d, J = 8.0 Hz, 1H), 7.32(s, 2H), 7.37−7.41 (t, 3H), 7.47−7.51 (m, 6H), 7.76−7.78 (d, J = 8.0 Hz, 1H), 7.87−7.89 (dd, 1H), 8.42−8.44 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.46 (CH_3), 29.38 (CH_2), 32.99 (CH_2), 50.03 (CH_2), 56.90 (CH), 122.68, 122.72, 122.76, 123.37, 124.78, 124.83, 124.86, 124.91, 125.58, 125.68, 125.72 (CF_3), 128.88, 129.28, 129.33, 129.40, 129.49, 129.58, 129.60, 129.91, 132.06, 132.63, 134.04, 140.62, 144.01.

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(7) Preparation of 1-(3-bromopropyl)-3-(trifluoromethyl)benzene (**5**): To a stirred solution of 3-[3-(trifluoromethyl)phenyl]propan-1-ol (10 g, 49 mmol) was added concentrated sulphuric acid (14.4 g, 114 mmol) under stirring at 25−30 °C followed by aqueous hydrobromic acid (86.3 g, 107.8). The reaction mass was heated and stirred at 50−55 °C for 3−4 h. Upon completion of the reaction by thin layer chromatography (TLC), the reaction mass was cooled, quenched with water (100 mL), and extracted with methylene dichloride (100 mL). The organic layer was separated, washed with 10% sodium bicarbonate (100 mL) followed by 5% brine solution, and concentrated under

reduced pressure to yield the crude **5** as an oil. Obtained crude oil was purified by fractional distillation to afford highly pure compound **5**. Yield: 11.0 g (76.45%); GC purity: 99.85%; IR (NaCl): 3017 w, 2940 s, 292863 w, 1597 w, 1492 w, 1451 s, 1165 s, 1125 s, 799 s, 702 s; MS: $m/z = 272.80\ [M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.14-2.23$ (m, 2H), 2.82−2.87 (t, 2H), 3.38−3.42 (t, 2H), 7.40−7.48 (dd, 4H).

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(10) 1-[(1*E*)-3-Bromopropyl-1en-1-yl]-3-(trifluoromethyl)benzene (**5a**) was recovered by repeated distillation of residue obtained after fractional distillation of crude **5**, and its structure was identified by GC−MS.