

(containing product) was separated into dedicated containers. The aqueous layer was collected in dedicated containers and kept aside.

The organic layer obtained from second extraction to fifth extraction was combined and dried over anhydrous sodium sulfate (13.5 Kg). The supernatant, clean, dry organic layer was taken in the reactor, containing the crude product obtained from first extraction, and solvent was removed by distillation under reduced pressure (>500 mm Hg or > 66 kPa) maintaining mass temperature below $50\text{ }^{\circ}\text{C}$. The residual mass was cooled to $25\text{-}30\text{ }^{\circ}\text{C}$ and collected the technical product (14.36 Kg).

Yield: 98.49 %;

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.55 - 1.69 (5H, m), 1.83 - 2.02 (8H, m), 2.65 - 2.69 (3H, m), 3.66 - 3.70 (1H, m);

Mass (m/z): 156.2 ($\text{M}+\text{H}$) $^+$.

Step (ii): Preparation of 4-(1-cyclobutylpiperidin-4-yloxy)-1-nitrobenzene

Tetrahydrofuran (THF) (43.2 L) was charged into a Stainless steel reactor (SS reactor) at $25\text{-}30\text{ }^{\circ}\text{C}$ under nitrogen atmosphere followed by addition of sodium hydride (5.22 Kg) maintaining mass temperature at $25\text{-}30\text{ }^{\circ}\text{C}$ under nitrogen atmosphere. The contents were stirred for 15 minutes at $25\text{-}30\text{ }^{\circ}\text{C}$. The temperature of the reaction mass was raised to $35\text{-}40\text{ }^{\circ}\text{C}$.

THF (56.7 L) was charged into another SS reactor at $25\text{-}30\text{ }^{\circ}\text{C}$ under nitrogen atmosphere by the addition of above obtained step (i) material (13.5 Kg, 86.96 M). The mass was stirred for 15 minutes at $25\text{-}30\text{ }^{\circ}\text{C}$ to obtain a clear solution. The resulting solution was added to the above reactor containing sodium hydride in THF, maintaining the mass temperature of the main reactor at $35\text{-}40\text{ }^{\circ}\text{C}$ over a period of ~ 45 minutes under nitrogen atmosphere. The resulting mass was further stirred for 90 minutes at $35\text{-}40\text{ }^{\circ}\text{C}$.

In the meanwhile THF (35.8 L) was charged into another SS reactor at $25\text{-}30\text{ }^{\circ}\text{C}$ under nitrogen atmosphere, followed by the addition of 4-fluoro-1-nitrobenzene (14.72 Kg, 104.32 M). The contents of the reactor were stirred for 15 minutes at $25\text{-}30\text{ }^{\circ}\text{C}$ to obtain a clear solution. The clear solution, thus obtained,

charged into a clean SS reactor at 25-30 °C. All the volatiles are distilled off under reduced pressure (> 500 mm Hg or > 66kPa) maintaining the mass temperature below 55 °C. The residual mass was cooled to 25-30 °C and charged DM water (32.18 L). The pH of the reaction mass was adjusted to 9.0 - 10.0 with 91 L of sodium carbonate solution (prepared by dissolving 21.5 Kg of sodium carbonate in 80 L of DM water), while maintaining the mass temperature at 25-30 °C. Final pH is 9.14. The solid mass, separated in the reactor, was centrifuged and collected the filtrate in dedicated containers. The product was spin dried (20.34 Kg).

Ethylacetate (EtOAc) (80 L) was charged into a clean SS reactor at 25-30 °C followed by the wet cake (20.34 Kg) obtained above. The mass was stirred for 15 minutes at 25-30 °C. Then added DM water (32 L) and further stirred the mass for 15 minutes and settled for 15 minutes. The aqueous layer was separated and collected in dedicated containers.

The organic layer containing the product was filtered through nutsche filter through hyflow bed (formed with 5.15 Kg hyflow and 26 L water) and filtrate was collected in dedicated containers. The bed was washed with EtOAc (13 L). The combined organic layer and EtOAc washings were charged into a clean SS reactor. Charged 20 L DM water, stirred for 15 minutes and settled for 15 minutes at 25-30 °C. The aqueous layer is separated and the organic layer was dried over anhydrous sodium sulfate (20 Kg).

The clean, dried organic layer was charged into a reactor at 25-30 °C. Solvent was distilled off under reduced pressure (> 500 mm Hg or > 66kPa) below 50 °C (Solvent recovered: 70 L). The residual product was cooled to 25-30 °C and unloaded into dedicated containers (12.30 Kg) and sent for complete analysis.

Weight of the product: 12.3 Kg (wet with solvent EtOAc: 9.1 %),

Yield (on dry basis): 97.5 %;

Purity: 97.79 %;

IR (cm⁻¹): 3424, 3345, 2943, 1627, 1509, 1229, 1168, 1044, 821;

¹H-NMR (δ ppm, DMSO): 1.49 - 1.61 (4H, m), 1.71 - 1.83 (4H, m), 1.92 - 1.97 (5H, m), 2.52 - 2.53 (2H, m), 3.99 - 4.04 (1H, m), 4.59 (2H, bs), 6.46 - 6.48 (2H, d, J = 8.60 Hz), 6.61 - 6.63 (2H, d, J = 8.66 Hz);

aqueous layer was separated and collected in dedicated containers. The organic product layer was dried over anhydrous sodium sulfate (22.4 Kg). The volume of the organic layer was 360 L. The organic layer obtained as above was charged into a clean GLR at 25-30 °C. Solvent was distilled off under reduced pressure (> 500 mm Hg or > 66kPa) maintaining mass temperature below 55 °C (volume of recovered solvent; 178 L). The mass was cooled to 25-30 °C. Solid mass separated in the reactor.

Recrystallization

Isopropanol (72.8 L) was charged into the reactor containing the solids (~ 13.5 Kg) at 25-30 °C, followed by methanol (~ 58.2 L) at 25-30 °C. Stirred the reaction mass at 25-30 °C for 30 minutes. The mass temperature was raised slowly to reflux temperature and maintained at reflux till a clear solution is obtained (~ 30 minutes). Then the mass was cooled to 25-30 °C and stirred the mass for 60 minutes. The mass was further cooled to ~12 -15 °C, stirred for 30 minutes and centrifuged the material. The cake on the centrifuge was washed with 2 x 7 L isopropanol (25-30 °C) and spin dried thoroughly.

The wet cake (11.2 Kg) was dried in a vacuum tray drier (VTD) for ~ 4 hours at 40-50 °C to obtain crystallized product (9.7 Kg).

Yield: 66.12 %;

Purity (by HPLC): 99.56 %;

IR (cm⁻¹): 3307, 3278, 2951, 1670.43, 1612, 1554.69, 1508.4, 1240.28, 1171.81, 1047.39, 953.84, 832.32;

¹H-NMR (δ ppm, DMSO): 1.53 - 1.61 (4H, m), 1.72 - 1.74 (2H, m), 1.87 - 1.99 (6H, m), 2.49 - 2.53 (2H, m), 2.64 - 2.68 (1H, m), 4.19 (2H, s), 4.24 - 4.29 (1H, m), 6.88 - 6.90 (2H, d, J = 8.96 Hz), 7.44 - 7.46 (2H, d, J = 8.96 Hz), 10.12 (1H, s);

Mass (m/z): 323.3, 325.2 (M+H)⁺.

Mother liquor obtained, after recrystallization and centrifuging the product, was processed for isolating second crop.

2nd extraction: Charged the above obtained aqueous layer into the reactor followed by EtOAc (47 L). The mass was stirred 15 minutes and settled for 15 minutes and layers separated. The organic layer containing the product was collected in dedicated containers.

5 **3rd extraction:** Charged the above obtained aqueous layer into the reactor followed by EtOAc (40 L). The mass was stirred 15 minutes and settled for 15 minutes and layers separated. The organic layer containing the product was collected in dedicated containers.

10 The combined organic layer was dried over sodium sulfate (9.4 Kg) and the clean organic layer was taken for distillation under reduced pressure (> 500 mm Hg or > 66kPa) at 50-55 °C. The mass was cooled to 25-30 °C. Added 23.5 L of acetonitrile and stirred well.

15 Part of the reaction mass (65 L of acetonitrile solution) from GLR was unloaded and charged into the above reaction mass at 25-30 °C and stirred 30 minutes, whereby a clear solution was obtained. The mass was transferred to the main reactor. Washing was given to this reactor with 20 L fresh acetonitrile at 40-45 °C and again transferred to the main reactor and stirred 15 minutes before sampling.

20 The final, uniformly mixed reaction mass was sampled from the main GLR and analyzed. HPLC: 99.09 % product and 0.31 % SM. So charged morpholine (510 grams) and K₂CO₃ (825 grams) and the mass was heated to reflux and further maintained the mass at reflux temperature for 2 hours. A sample was analyzed after 2 hours reflux. Starting material was absent (product purity: 99.24 %).

25 The reflux was further continued for another 2 hours and then cooled the mass temperature to 30-35 °C. Solvent was distilled off under reduced pressure (> 500 mm Hg or > 66kPa), maintaining mass temperature below 55 °C.

1st Extraction: Charged DM water (23.5 L) to the residual mass at 25-30 °C. Stirred the mass for 15 minutes and charged ethyl acetate (80 L). A clear solution was obtained. Stirred the mass for 15 minutes and settled the mass for 15 minutes. Layers separated and the product organic layer collected in dedicated containers.

5 **2nd Extraction:** The aqueous layer obtained as above (pH was found to be 9.9 on meter) was charged into the reactor followed by ethyl acetate (40 L). Stirred the mass for 15 minutes and settled the mass for 15 minutes. Layers separated and the product organic layer collected in dedicated containers.

10 **3rd Extraction:** The aqueous layer obtained as above was once again charged into the reactor followed by ethyl acetate (40 L). Stirred the mass for 15 minutes and settled the mass for 15 minutes. Layers separated and the product organic layer collected in dedicated containers.

15 **Brine washing:** The combined organic layer was taken in the reactor and charged ~ 35 L brine solution (prepared by dissolving 9.4 Kg sodium chloride in 28.2 L DM water). The mass was stirred for 15 minutes and settled for 30 minutes. Layers separated and collected aqueous layer in dedicated containers.

20 The organic product layer was dried over anhydrous sodium sulfate (18.8 Kg). Total volume of the organic layer was 185 L. The solvent was distilled off under reduced pressure (> 500 mm Hg, or > 66kPa) maintaining mass temperature below 55 °C. Solid mass (Step-5 material) separated in reactor.

Yield: Quantitative;

Purity: 99.51 %;

25 ¹H-NMR (CDCl₃, δ ppm): 1.65 - 2.04 (12H, m), 2.61 - 2.63 (6H, m), 2.69 - 2.77 (1H, m), 3.12 (2H, s), 3.76 - 3.78 (4H, m), 4.26 - 4.27 (1H, m), 6.87 - 6.89 (2H, d, J = 8.82 Hz), 7.43 - 7.45 (2H, d, J = 8.80 Hz), 8.91 (1H, s);

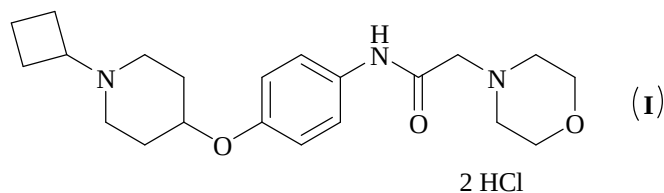
Mass (m/z): 374.4 (M+H)⁺.

Step (vi): Preparation of N-[4-(1-Cyclobutyl piperidin-4-yloxy) phenyl]-2-(morpholin-4-yl) acetamide dihydrochloride

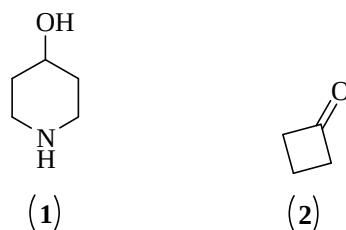
30 Charged isopropyl alcohol (75 L) into the reactor containing step (v) product. The reaction mass temperature was raised to 50-55 °C and stirred for 30

We claim:

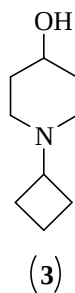
1. A process for production of N-[4-(1-cyclobutyl piperidin-4-yloxy) phenyl]-2-(morpholin-4-yl) acetamide dihydrochloride of formula (I),
5 which comprises:



Step (i): reaction of 4-hydroxy piperidine of formula (1) with cyclobutanone of formula (2)



10 in presence of sodium triacetoxy borohydride in ethylene dichloride at a temperature in the range of 20 °C to 30 °C for a period of 12 hours to 14 hours to obtain 1-cyclobutylpiperidin-4-ol of formula (3);



Step (ii): reaction of 1-cyclobutylpiperidin-4-ol of formula (3) with 4-fluoro-1-nitrobenzene of formula (4)

