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Abstract

This protocol outlines the synthesis of the Gut-restricted LXR Agonist WUSTL0717 for the treatment of Short bowel syndrome (SBS), including structural characterization using nuclear magnetic resonance (NMR) and mass spectrometry (LC-MS).

Synthesis of WUSTL0717

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2 **Abstract**

This protocol outlines the synthesis of the Gut-restricted LXR Agonist WUSTL0717 for the treatment of Short bowel syndrome (SBS), including structural characterization using nuclear magnetic resonance (NMR) and mass spectrometry (LC-MS).

N-(2-Chloro-3-(trifluoromethyl)benzyl)-2,2-diphenylethan-1-amine[a]

3 1. Combine 3.0 g of 2,2-diphenylethan-1-amine (15.20 mmol, 1.0 equiv.) and 3.17 g of 2-chloro-3-(trifluoromethyl)benzaldehyde (15.20 mmol, 1.0 equiv.) in 20.0 mL of 1,2-dichloroethane.

2. Add 4.89 g of $NaBH(OAc)_3$ (23.11 mmol, 1.5 equiv.) and a few drops of acetic acid to the mixture.

3. Stir the reaction at room temperature under a nitrogen atmosphere for 16 hours.

4. Monitor the reaction progress using LC-MS and TLC.

5. Quench the reaction mixture with saturated aqueous $NaHCO_3$.

6. Extract the product with 1,2-dichloroethane (2 × 100.0 mL).

7. Dry the combined organic layers over anhydrous Na_2SO_4.

8. Filter the solution and concentrate it by evaporating the solvent.

9. Collect the crude product as a colorless oil.

10. Yield: 5.8 g (98%).

11. **Characterization:**
LC-MS (ESI) *m/z*: 390.90 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, J = 7.9, 1.7 Hz, 1H), 7.56 (dd, J = 7.7, 1.6 Hz, 1H), 7.38 – 7.28 (m, 6H), 7.30 –7.18 (m, 8H), 4.25 (t, J = 7.7 Hz, 1H), 3.99 (s, 2H), 3.27 (d, J = 7.7 Hz, 2H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 142.50, 139.91, 133.15, 131.55, 128.93, 128.74, 128.70, 128.65, 128.25, 128.00, 127.95, 126.84, 126.65, 126.42, 126.21 (q, $J_{C,F}$ = 6.0 Hz), 124.30, 121.58, 53.78, 51.15, 51.01.

3-Bromo-N-(2-chloro-3-(trifluoromethyl)benzyl)-N-(2,2-diphenylethyl)propan-1-amine

4 1. Dissolve 1.0 g of N-(2-Chloro-3-(trifluoromethyl)benzyl)-2,2-diphenylethan-1-amine (2.56 mmol) and 2.61 mL of 1,3-dibromopropane (25.65 mmol) in 5.0 mL of acetonitrile.

2. Add 531.0 mg of K_2CO_3 (3.84 mmol, 1.5 equiv.) to the reaction mixture.
3. Heat the mixture to reflux at 90°C and stir for 15 hours.

4. Cool the reaction mixture to room temperature.

5. Filter the mixture through a pad of Celite and wash with ethyl acetate (EtOAc).

6. Concentrate the filtrate in vacuo to remove EtOAc.

7. Remove excess 1,3-dibromopropane under reduced pressure.

8. Collect the titled product as a nearly pure colorless oil.

9. Yield: 1.18 g (90%).

10. **Characterization:**
LC-MS (ESI) *m/z*: 511.95 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, J = 7.6, 1.8 Hz, 1H), 7.31 (t, J = 7.2 Hz, 6H), 7.28 – 7.19 (m, 8H), 7.17 (t, J = 7.6 Hz, 2H), 4.21 (t, J = 7.7 Hz, 1H), 3.82 (s, 2H), 3.26 (t, J = 6.4 Hz, 2H), 3.18 (d, J = 7.7 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H), 1.98 (p, J = 6.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.24, 139.45, 133.87, 131.50, 128.74, 128.60, 128.37, 128.25, 128.17, 128.11, 128.00, 126.84, 126.38, 126.18, 125.95 (q, $J_{C,F}$ = 5.0 Hz), 124.44, 121.66, 60.48, 56.21, 52.68, 49.74, 31.90, 30.39.

Ethyl 2-(3-(3-((2-chloro-3-(trifluoromethyl)benzyl)(2,2-diphenylethyl)amino)propoxy)phenyl)acetate

5 1. Dissolve 1.65 g of (3-Bromo-propyl)-(2-chloro-3-trifluoromethyl-benzyl)-diphenylethyl-amine (3.23 mmol) and 640.0 mg of ethyl 2-(3-hydroxyphenyl)acetate (3.55 mmol) in 10.0 mL of acetonitrile.

2. Add 680.0 mg of K_2CO_3 (4.90 mmol, 1.5 equiv.) to the solution.

3. Heat the reaction mixture to reflux at 90°C and stir for 20 hours.

4. Cool the reaction mixture to room temperature.

5. Filter through a pad of Celite and wash with ethyl acetate (EtOAc).

6. Concentrate the filtrate in vacuo to remove the solvent.

7. Purify the crude product by silica gel column chromatography using EtOAc/hexane (1:4) as the eluent.

8. Collect the title compound as a colorless oil.

9. Yield: 1.54 g (78%).

10.**Characterization:**
LC-MS (ESI) *m/z*: 611.20 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, J = 7.9, 1.6 Hz, 1H), 7.30 – 7.12 (m, 12H), 6.95 – 6.83 (m, 2H), 6.68 (t, J = 2.1 Hz, 1H), 6.64 (dd, J = 8.1, 2.5 Hz, 1H), 4.25 – 4.05 (m, 3H), 3.80 (s, 2H), 3.68 (t, J = 5.9 Hz, 2H), 3.58 (s, 2H), 3.15 (d, J = 7.7 Hz, 2H), 2.71 (t, J = 6.5 Hz, 2H), 1.85 (p, J = 6.3 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.48, 158.94, 143.39, 139.65, 135.41, 133.76, 129.40, 128.33, 128.20, 126.31, 126.12, 125.71 (q, $J_{C,F}$ = 6.0 Hz), 121.38, 115.35, 112.98, 64.87, 60.84, 60.28, 56.00, 50.76, 49.72, 41.45, 26.81, 14.18.

2-(3-(3-((2-Chloro-3-(trifluoromethyl)benzyl)(2,2-diphenylethyl)amino)propoxy)phenyl)acetic acid (GW3965):

6 1. Dissolve 1.2 g of Ethyl 2-(3-(3-((2-chloro-3-(trifluoromethyl)benzyl)(2,2-diphenylethyl)amino)propoxy)phenyl)acetate (1.96 mmol) in a 1:1 mixture of THF and H_2O.

2. Add 490.0 mg of $LiOH·H_2O$ (11.80 mmol) at room temperature.

3. Stir the reaction mixture at room temperature for 20 hours, monitoring progress by LC-MS and TLC analysis.

4. Dilute the reaction mixture with 10.0 mL of ethyl acetate (EtOAc).

5. Carefully neutralize with 1N aqueous HCl.

6. Extract the mixture with EtOAc (3 × 20.0 mL).

7. Wash the combined organic layers with water and brine.

8. Dry over anhydrous Na_2SO_4, filter, and concentrate under reduced pressure.

9. Collect the crude product **GW3965** as a colorless oil.

10. Yield: 1.0 g (90%), with >99% purity confirmed by HPLC area percentage.

11. **Characterization:**
LC-MS(ESI) ***m/z*** = 583.10 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.8 Hz, 1H), 7.31 – 7.07 (m, 13H), 6.86 (d, J = 7.4 Hz, 2H), 6.65 (dd, J = 9.1, 1.8 Hz, 2H), 4.22 – 4.05 (m, 1H), 3.79 (s, 2H), 3.64 (d, J = 12.5 Hz, 4H), 3.15 (d, J = 7.7 Hz, 2H), 2.77 – 2.62 (m, 2H), 1.84 (d, J = 6.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.24, 158.97, 143.36, 139.60, 136.10, 134.47, 133.73, 129.52, 128.34, 128.18,
126.32, 126.12, 125.76, 125.70, 121.47, 115.44, 113.23, 64.81, 60.20, 55.96, 50.66, 49.67, 40.99, 26.75

2-(3-(3-((2-Chloro-3-(trifluoromethyl)benzyl)(2,2-diphenylethyl)amino)propoxy)phenyl)acetamide (WUSTL0717)[b]

7 1. Dissolve GW3965 (0.55 g, 0.945 mmol) in 10.0 mL of acetonitrile (CH_3CN) under a nitrogen atmosphere.

2. Add triethylamine (Et_3N, 0.221 g, 0.3 mL, 2.192 mmol, 2.32 equiv.) to the solution.

3. Add Py.BOP (0.57 g, 1.096 mmol, 1.16 equiv.) at room temperature.

4. Stir the reaction mixture for 10 minutes at room temperature.

5. Add NH_3 in dioxane (0.4 M, 2.83 mL, 1.2 equiv.) to the reaction mixture.

6. Stir the reaction mixture at room temperature for 4 hours.

7. Concentrate the mixture under reduced pressure.

8. Partition the residue between EtOAc (20.0 mL) and 5% aqueous $NaHCO_3$ solution.

9. Separate the organic layer, dry over anhydrous Na_2SO_4, and concentrate.

10.Purify the crude product by flash column chromatography using EtOAc/Hexane (1:1).

11. Collect the titled product as a colorless oil.

12. Yield: 428.3 mg (78%).

13. **Characterization:**
LC-MS(ESI) ***m/z*** = 582.08 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.48 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.29 – 7.09 (m, 13H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.73 – 6.60 (m, 2H), 5.55 (s, 1H), 5.39 (s, 1H), 4.13 (q, *J* = 7.8 Hz, 1H), 3.79 (s, 2H), 3.70 (t, *J* = 6.0 Hz, 2H), 3.55 (s, 2H), 3.15 (d, *J* = 7.7 Hz, 2H), 2.72 (t, *J* = 6.5 Hz, 2H), 1.87 (dd, *J* = 12.8, 6.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 173.24, 159.33, 143.33, 139.62, 136.15, 133.81, 131.36, 130.03, 128.73, 128.33,
128.18, 128.00, 126.83, 126.33, 126.05, 127.78 (d, $J_{C,F}$ = 6.0 Hz), 121.43, 115.39, 113.36, 65.05, 60.26, 56.07, 50.72, 49.69, 43.39, 26.77

WUSTL0717. HCl:

8 1. Dissolve 500.0 mg (0.86 mmol) of 2-(3-(3-((2-chloro-3-(trifluoromethyl)benzyl)(2,2-diphenylethyl)amino)propoxy)phenyl)acetamide in ether.

2. Add 0.86 mL of 2M HCl in ether to the solution at room temperature.

3. Stir the mixture at room temperature for 1 hour.

4. Evaporate the solvent under reduced pressure.

5. Collect the HCl salt as a colorless solid.

6. Yield: 510.0 mg (96%).

Protocol references

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