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Improved Synthesis of RO4858542, a 5-HT_6 Receptor Antagonist

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Abstract:

An improved synthesis of a 5-HT_6 antagonist is described. A problematic amide reduction step was avoided by a reductive amination. Overall, 2.9 kg was produced over 6 steps with an overall yield of 56%.

Introduction

RO4858542 (**1**) is a 5-HT_6 antagonist developed at Roche Palo Alto for central nervous system (CNS) indications including Parkinson's disease.[1] This compound was first synthesized by our medicinal chemists using the route shown in Scheme 1. Displacement of one of the nitro groups of 2,6-dinitrobenzonitrile provided a piperazine derivative **2**. Reduction of the nitro group and acylation provided amide **3**. The nitrile group and the amide group were simultaneously reduced. Cyclic urea formation followed by deprotection of the *t*-Boc group and HCl salt formation afforded compound **1**. There were several issues that needed to be addressed prior to further scale-up: The starting material, 2,6-dinitrobenzonitrile, had limited commercial availability; the double reduction of compound **3** was low yielding and produced significant amounts of impurities resulting from the amide bond cleavage, and triphosgene utilized for the urea formation is toxic and odorous. These issues have been successfully addressed and are described below.

Results and Discussion

2-Chloro-6-nitrobenzonitrile was tested and abandoned as a new substrate because displacement of the nitro group was favored over the chloride (Scheme 2). Instead, we turned our attention to 2-amino-6-fluorobenzonitrile (**6**). This compound is readily available in bulk quantities. The amino group was acylated to provide amide **7** (Scheme 3), which was isolated by crystallization upon the addition of water.

Attention then turned toward the displacement of the fluoride by BOC protected piperazine. Various conditions were tested before the suitable reaction conditions were found. The results from the screening studies are shown in Table 1. The use of DIEA as a base in DMSO yielded the best results. The reaction did not proceed when TEA was used as a base, probably due to the lower temperature. The reaction using DBU generated a complex mixture, with 20−30% of the mixture being the desired product. KF/Al_2O_3 was successfully used in the past for the aromatic displacement of fluorides;[2] however, the conditions were ineffective for this particular transformation.

In order to produce the initial batch for toxicity studies, we followed the route shown in the scheme 1 for the remainder of the synthesis. We replaced borane−DMS with borane−THF for the double reduction because borane−DMS has unpleasant odor. For the urea formation, we replaced triphosgene with the safer reagent 1,1′-carbonyldiimidazole (CDI). The cyclization was carried out in acetonitrile, and the product crystallized from the reaction mixture and allowed for removal of a significant amount of the impurities generated in the double reduction step. Removal of the *t*-BOC group and the HCl salt formation was achieved using aqueous HCl/methanol. Overall, 400 g of **1** were produced in 20% yield over 6 steps.

After delivering material for the initial toxicity studies, we returned to further improving the scalability of the synthesis. We decided to prepare benzylamine **8** as it lacks the amide bond that could be cleaved during the reduction of the nitrile group. Reductive amination of **6** was carried out using sodium triacetoxyborohydride (Scheme 4).[3] We found that the aromatic displacement could be cleanly carried out using 5 equiv of piperazine instead of *N*-Boc-piperazine if run in hot (80 °C) DMSO. DIEA was needed when 5 equiv of piperazine was used. After water quench, the product was extracted into ethyl acetate and reacted with di-*tert*-butyl dicarbonate. Upon crystallization from isopropanol, amine **10** was obtained in 93% yield over two steps. The subsequent nitrile reduction was carried out using $NaBH_4/BF_3-Et_2O$. This reagent offered an advantage over borane−THF by reducing the reaction volume. The amine was not isolated but instead was directly converted to urea **5** by reaction with 1,1′-carbonyldiimidazole. Boc deprotection was carried out as before to provide compound **1**. Overall, 2.9 kg of RO4858542 were produced in 56% yield over 6 steps.

Conclusions

In conclusion, we developed a new, efficient synthetic route for a 5-HT_6 receptor antagonist. Key improved steps in the process are the reductive amination of 2-amino-6-fluorobenzonitrile and aromatic displacement of the fluorine using piperazine. The use of 2-amino-6-fluorobenzonitrile instead of 2,6-dinitrobenzonitrile addressed the issue of starting material availability. Introduction of benzyl group onto an amine via the reductive amination avoided a low-yielding amide reduction.

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(1) (a) Berger, J.; Flippin, L. A.; Greenhouse, R.; Jaime-Figueroa, S.; Liu, Y.; Miller, A. K.; Putman, D. G.; Weimhardt, K. K.; Zhao, S. H. U. S. Patent 1999/005958934, 1999. (b) Maag, H.; Sui, M.; Zhao, S. H. U. S. Patent 2004/0092512, 2004. (c) Bonhaus, S. W.; Martin, R. S. U. S. Patent 2006/0069094, 2006. (d) Sui, M.; Zhao, S. H. WO/2005/067933, 2005.

(2) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J., III. *J. Org. Chem.* **1998**, *63*, 6338.

(3) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595.

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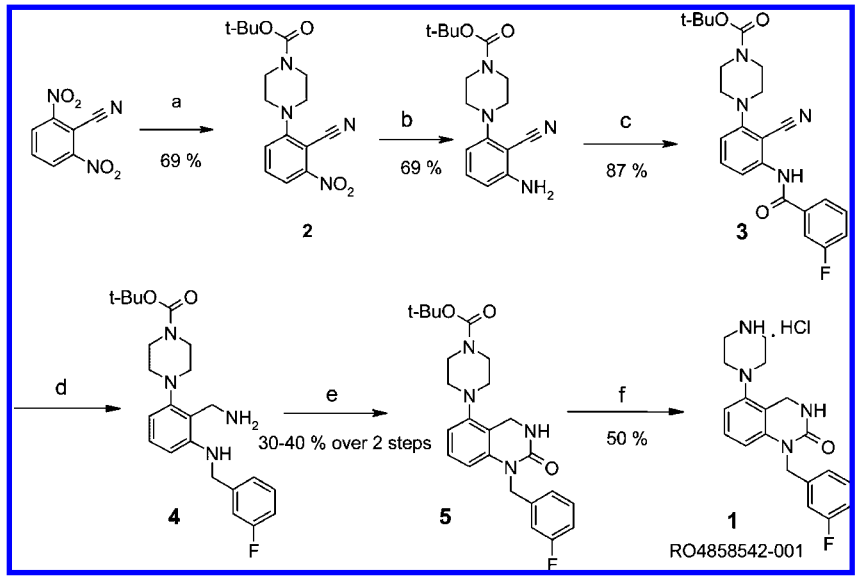
Scheme 1. **Original synthesis of RO4858542**[a]



[a] Reagents and conditions: a) *N*-Boc-piperazine, DMF, 50 °C. b) H_2, Pd/C. c) 3-Fluorobenzoyl chloride, THF, triethylamine. d) BH_3-Me_2S, THF, reflux. e) triphosgene, CH_2Cl_2, triethylamine. f) HCl, EtOH.

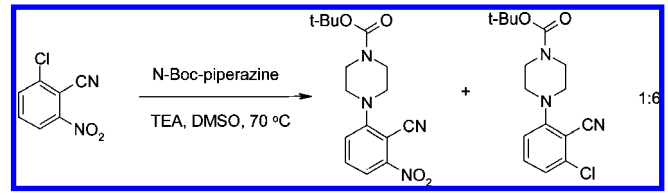
Experimental Section

The NMR spectra were obtained at 300 and 75 MHz, for ^1H and ^{13}C, respectively. Drying of products and rotary evaporations were carried out under 25−28 inHg house vacuum.

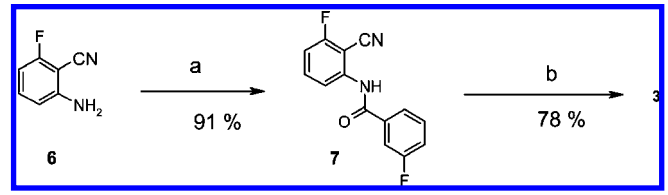
***N*-(2-Cyano-3-fluorophenyl)-3-fluorobenzamide (7).** A solution of 2-amino-6-fluorobenzonitrile (167 g,1.23 mol) and pyridine (7 L) was cooled to 0−5 °C and a solution of 3-fluorobenzoyl chloride (195 g, 1.23 mol) in THF (167 mL) was added at ≤10 °C. The reaction mixture was stirred for 3 h while allowing it warm to ambient temperature. Water (8 L) was added over 1 h. The white slurry was filtered and washed with water (2 × 1.5 L). Drying overnight at 50 °C in a vacuum oven provided *N*-(2-cyano-3-fluorophenyl)-3-fluorobenzamide (**7**) (289 g, 91%). ^1H NMR [DMSO-d_6] δ 7.39−7.48 (m, 2 H), 7.52 (m, 1.0 Hz, 1 H), 7.63 (m, 1 H), 7.76−7.89 (m, 3 H), 10.89 (s, 1 H). Anal. Calcd for $C_{14}H_8F_2N_2O$: C, 65.11; H, 3.12; N, 10.85. Found: C, 65.01; H, 3.19; N, 10.91.

4-[2-Cyano-3-(3-fluorobenzoylamino)phenyl]piperazine-1-carboxylic Acid *tert*-Butyl Ester (3). *N*-(2-Cyano-3-fluorophenyl)-3-fluorobenzamide (**7**) (163 g, 0.63 mmol), *N*-Boc-piperazine (163 g, 1.27 mmol), diisopropylethylamine (163 g, 1.26 mmol), and DMSO (650 mL) were heated at 120 °C for 60 h. The mixture was cooled to 30 °C and diluted with water (400 mL). The mixture was extracted with EtOAc (5 × 200 mL) in a wash vessel. The organic layer was washed with water (300 mL) and brine (300 mL). The organic layer was evaporated. The residue was dissolved in isopropanol (500 mL) at reflux. The solution was cooled to 45 °C, diluted with water (450 mL), and seeded. After cooling to 18−22 °C, the mixture was stirred for 15 h. The product was collected by filtration. The cake was washed with water (2 × 200 mL) and hexanes (2 × 150 mL). Drying in a vacuum oven at 55−60 °C provided 4-[2-cyano-3-(3-fluorobenzoylamino)phenyl]piperazine-1-carboxylic acid *tert*-butyl ester (**3**) as a white solid (210 g, 78%). ^1H NMR [$CDCl_3$] δ 1.49 (s, 9 H), 3.16 (m, 4 H), 3.65 (m, 4 H), 6.78 (dd, J = 8.3, 0.8 Hz, 1 H), 7.30 (m, 1 H), 7.52 (m, 2 H), 7.67 (m, 2 H), 8.18 (dd, J = 8.4, 0.7 Hz, 1 H), 8.36 (br s, 1 H). Anal. Calcd for $C_{23}H_{25}FN_4O_3$/0.2 M H_2O: C, 64.53; H, 5.98; N, 13.09; Found: C, 64.55; H, 6.10; N, 13.02.

Scheme 2. **Reaction of 2-chloro-6-nitrobenzonitrile and *N*-Boc-piperazine**



Scheme 3. **Improved synthesis of amide 3**[a]



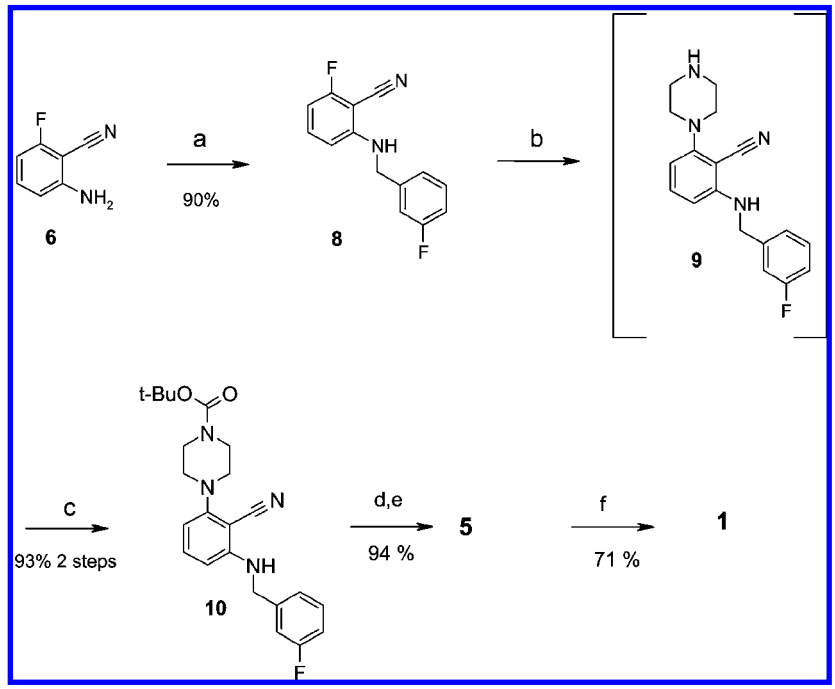
[a] Reagents and conditions: a) 3-Fluorobenzoyl chloride. b) *N*-Boc-piperazine, DIEA, DMSO, 120 °C.

4-[1-(3-Fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-5-yl]piperazine-1-carboxylic Acid *tert*-Butyl Ester (5). Synthesis from 3. 4-[2-Cyano-3-(3-fluorobenzoylamino)phenyl]piperazine-1-carboxylic acid *tert*-butyl ester (**3**) (863 g, 2.04 mol) was chilled in an ice bath while borane−THF (1 M solution in THF, 8 L) was added over 1 h while keeping the internal temperature below 50 °C. The ice bath was removed, and the reaction mixture was heated to reflux. After 4 h, the solution was stirred overnight at room temperature. Methanol (420 mL) was added while keeping the temperature below 40 °C. The solution was evaporated, and the residue was dissolved in ethyl acetate (4.7 L). The solution was washed with water (4 × 2.8 L). The organic layer was evaporated to afford diamine **4** as an orange oil (804 g). The diamine (804 g) in acetonitrile (3.8 L) was added to 1,1′-carbonyldiimidazole (289 g, 1.78 mol). The solution was stirred for 16 h at room temperature. The slurry was filtered and washed with acetonitrile (4 × 400 mL). The

Table 1. **Reaction of fluoride 7 with *N*-Boc-piperazine**

base	solvent	temp (°C)	time (h)	conversion (%)	notes
K_2CO_3	DMSO	140	24	11	
KF-Al_2O_3/18-C-6	DMSO	120	24	0	
KO^{t}Bu	DMSO	120	20		displacement of the fluoride by *tert*-butoxide
Cs_2CO_3	DMF	120	20	0	
KO^{t}Bu	NMP	120	20		displacement of the fluoride by *tert*-butoxide
TEA	DMSO	110	20	0	
DBU	DMSO	120	45		complex mixture
DIEA	DMSO	120	45	94	

Scheme 4. **Improved synthesis of RO4858542**[a]



[a] Reagents and conditions: a) 3-Fluorobenzaldehyde, $NaB(OAc)_3H$, AcOH. b) DMSO, piperazine. c) $(Boc)_2O$. d) $NaBH_4$, BF_3-Et_2O. e) 1,1′-Carbonyldiimidazole, CH_3CN, rt. f) HCl, EtOH.

solid was dried for 14 h at 60 °C under vacuum to provide 4-[1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-5-yl]piperazine-1-carboxylic acid *tert*-butyl ester (**5**). (527 g, 59% over 2 steps).

2-Fluoro-6-(3-fluorobenzylamino)benzonitrile (8). 2-Amino-6-fluorobenzonitrile (2.27 kg, 1.00 equiv), acetic acid (21.4 kg), trifluoroacetic acid (2.04 kg, 1.05 equiv), and 3-fluorobenzaldehyde (2.35 kg; 1.10 equiv) were heated at 35−40 °C for 1.5 h. The mixture was slowly added to a slurry of sodium triacetoxyborohydride (95%, 5.95 kg, 1.60 equiv) in 2.4 kg acetic acid while keeping the internal temperature <36 °C. After ∼30 min, additional sodium triacetoxyborohydride (0.96 kg) in acetic acid (5.3 kg) was added. After an additional 30 min, water (36.5 kg) was added while keeping the internal temperature below 40 °C. The slurry was cooled to 6 °C, filtered, and washed with water (3 × 11.4 kg). The filter cake was vacuum dried at 60 °C, providing 2-fluoro-6-(3-fluorobenzylamino)benzonitrile (**8**) (3.675 kg, 90.3%). ^{1}H NMR [DMSO-d_6] δ 4.46 (d, J = 6 0.2 Hz, 2 H), 6.44 (d, J = 8.6 Hz, 1 H), 6.53 (m, 1 H), 7.06 (m, 1 H), 7.20 (m, 1 H), 7.26−7.41 (m, 3 H). Anal. Calcd for $C_{14}H_{10}F_2N_2$: C, 68.85; H, 4.13; N, 11.47; Found: C, 68.68; H, 4.00; N, 11.54.

4-[2-Cyano-3-(3-fluorobenzoylamino)phenyl]piperazine-1-carboxylic Acid *tert*-Butyl Ester (10). 2-Fluoro-6-(3-fluorobenzylamino)benzonitrile (3.65 kg, 14.1 mol), piperazine (5.01 kg, 58.2 mol), and DMSO (12.8 L) were heated at 80 °C for 5 h. The mixture was cooled to room temperature, and water (18 L) was added. The mixture was extracted in the reactor with EtOAc (20 L, then 10 L). The combined organic layers were vacuum distilled to ∼19 L. The solution was transferred to di-*tert*-butyl dicarbonate (3.59 kg, 16.1 mol). The mixture was stirred overnight at room temperature. The solution was vacuum distilled (25−28 inHg) at 20−50 °C to ∼15 L. The vacuum distillation continued while adding 30 L of isopropanol and keeping the volume at ∼15 L. The slurry was cooled for 3 h at 5−10 °C. The product was isolated by filtration and washed with cold isopropanol (10 L). Drying in a vacuum oven at 60 °C provided 4-[2-cyano-3-(3-fluorobenzylamino)phenyl]piperazine-1-carboxylic acid *tert*-butyl ester (**10**) (5.62 kg, 91.6%). ^{1}H NMR [DMSO-d_6] δ 1.42 (s, 9 H), 3.00 (t, J = 5.0 Hz, 4 H), 3.47 (t, J = 4.4 Hz, 4 H), 4.42 (d, J = 6.2 Hz, 2 H), 6.22 (d, J = 8.4 Hz, 1 H), 6.28 (d, J = 7.7 Hz, 1 H), 6.75 (m, 1 H), 7.04 (m, 1 H), 7.13−7.22 (m, 2 H), 7.36 (m, 1 H). Anal. Calcd for $C_{23}H_{27}FN_4O_2$ H_2O: C, 67.29; H, 6.63; N, 13.65; Found: C, 67.41; H, 6.60; N, 13.80.

4-[1-(3-Fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-5-yl]piperazine-1-carboxylic Acid *tert*-Butyl Ester (5). Synthesis from 10. 4-[2-Cyano-3-(3-fluorobenzylamino)phenyl]piperazine-1-carboxylic acid *tert*-butyl ester (**10**) (6.20 kg, 14.6 mol), sodium borohydride (705 g, 18.7 mol), and THF (35 kg) were cooled to −5 °C. BF_3-etherate (3.5 kg, 24.6 mol) and THF (2 kg) were added while keeping the reactor temperature below 10 °C. The solution was heated at 40−45 °C for 19 h and cooled to 15−20 °C. Methanol (8.0 kg) was added over 1 h. The mixture was stirred for 1 h at 15−20 °C and concentrated to 17 L under vacuum. The concentration continued while acetonitrile (3 × 21 kg) was added, keeping the volume constant. Acetonitrile (23 kg) was added, and the mixture was cooled to 15−20 °C. The solution was added to 1,1′-carbonyldiimidazole (1.98 kg, 12.2 mmol) and acetonitrile (36.8 kg). The mixture was stirred for 20 h at 15−20 °C. The product was isolated by filtration and washed with acetonitrile (2 × 18 L). Drying for 15 h at 50 °C under vacuum afforded 4-[1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-5-yl]piperazine-1-carboxylic acid *tert*-butyl ester (**5**). (5.01 kg, 94%). ^{1}H NMR [$CDCl_3$] δ 1.49 (s, 9 H), 2.79 (t, J = 5.0 Hz, 4 H), 3.55 (br s, 4 H), 4.54 (d, J = 1.7 Hz, 2 H), 5.10 (s, 2 H), 5.19 (s, 1 H), 6.48 (d, J = 7.7 Hz, 1 H), 6.74 (d, J = 7.4 Hz, 1 H), 6.93 (m, 2 H), 7.08 (m, 2 H), 7.28 (m, 1 H). Anal. Calcd for $C_{24}H_{29}FN_4O_3$: C, 65.44; H, 6.64; N, 12.72. Found: C, 65.42; H, 6.57; N, 12.83.

1-(3-Fluorobenzyl)-5-piperazin-1-yl-3,4-dihydro-1H-quinazolin-2-one Hydrochloric Acid Salt (1). 4-[1-(3-Fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-5-yl]piperazine-1-carboxylic acid *tert*-butyl ester (**5**) (4.75 kg, 10.8 mol), methanol (40 kg), and concd HCl (3.1 kg) were refluxed for 3 h and cooled to 15−20 °C. The slurry was filtered and washed with methanol (2 × 8 kg). Drying at 60 °C under vacuum afforded 1-(3-fluorobenzyl)-5-piperazin-1-yl-3,4-dihydro-1H-quinazolin-2-one hydrochloric acid salt (**1**) (3.03 kg). The solid was dissolved in isopropanol (55 kg) and water (28 kg) at 70 °C. The solution was filtered through a 5 μm filter and washed with isopropanol (11 kg). The filtrate was concentrated under vacuum to 45 L. Concentration continued while adding isopropanol (3−77 kg) and keeping the volume constant. At the end of the distillation, the mixture was cooled to 15−20 °C and stirred for 16 h. The slurry was filtered and washed with isopropanol (2−11 kg). 1-(3-Fluorobenzyl)-5-piperazin-1-yl-3,4-dihydro-1H-quinazolin-2-one hydrochloric acid salt (**1**) was obtained as a white solid (2.89 kg, 71%). ^{1}H NMR [DMSO-d_6] δ 3.00 (m, 4 H), 3.19 (m, 4 H), 4.35 (d, J = 1.2 Hz, 2 H), 5.05 (s, 2 H), 6.53 (d, J = 8.1 Hz, 1 H), 6.72 (d, J = 7.9 Hz, 1 H), 7.01−7.16 (m, 4 H), 7.30−7.42 (m, 2 H), 9.39 (s, 2 H). Anal. Calcd for $C_{19}H_2FN_4OCl$ (adjusted for 0.35 equiv of H_2O): C, 59.56; H, 5.97; N, 14.62; Cl, 9.41. Found: C, 59.56; H, 5.65; N, 14.62; Cl, 9.26.

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