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Scale-Up Synthesis of the Dopamine Uptake Inhibitor GBR-12909

Michael D. Ironside,* Priyantha M. Sugathapala, Jerod Robertson, Mark C. P. Darey, and Jianzhong Zhang

Chemical Development Department, Albany Molecular Research Inc., 21 Corporate Circle, PO Box 15098, Albany, New York 12212, U.S.A.

Abstract:

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR-12909) is a dopamine uptake inhibitor. The development of a robust process for the preparation of this compound in kilogram quantities is described. The primary aims of the development work were to eliminate chromatographic purifications, to minimize the use of environmentally unacceptable reagents, and to improve the overall yield of the three-step convergent process. These objectives were met, with significant improvements obtained in the key coupling reaction of *N*-(3-phenylpropyl)piperazine dihydrochloride salt with 1-[bis(4-fluorophenyl)methoxy]-2-chloroethane, which was previously low-yielding and lacking in reproducibility.

Introduction

Cocaine, a powerful drug of abuse, is known to bind to all three monoamine transporter systems in the brain which mediate the neuronal uptake of dopamine (dopamine transporter, DAT), serotonin (SERT), and norepinephrine (NET).[1−3] The reinforcing effect of cocaine is believed to be initiated by binding to, and thus causing inhibition of, DAT.[4−6] As a result, this protein has become one target for the development of the medications for treating cocaine addiction. Development targeting the DAT has resulted in the generation of some very potent and selective molecules of diverse structure.[7−9] In 1980, Van der Zee and co-workers developed the GBR series of compounds in which the tropine moiety of benztropine was replaced by a substituted piperazine.[9] Some well-known GBR compounds, GBR-12935 and its bisfluorinated analogue GBR 12909 (vanoxerine), were shown to have high potency for the DAT (Figure 1).[10,11] Structure−activity relationship (SAR) studies in this class of compounds have revealed that different cyclic and acyclic diamine moieties can be introduced instead of piperazine, and it has been demonstrated that the unsubstituted phenyl ring can be replaced with a thiophene, furan, or pyridine ring without compromising the affinity and selectivity in many of these analogues.[12,13]

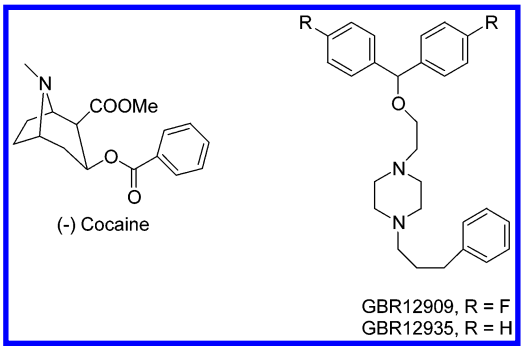

Figure 1.

To support planned clinical trials, kilogram quantities of GBR-12909 were required. The existing synthesis, supplied by the National Institute on Drug Abuse (Scheme 1), which had been used to deliver initial small quantities, was evaluated critically and was deemed suitable for scale-up. However, it was clear that a number of major process issues needed to be resolved to allow successful manufacture of kilogram batches.

The dihydrochloride salt formation of both intermediate **2** and GBR-12909 employed undesirable reagents and produced difficult-to-filter solids, which required vacuum-drying prior to proceeding. A further obstacle to scale-up was the necessity for column chromatographic purification of intermediate **4**. Finally, the key synthetic step, namely the coupling of intermediates **2** and **4**, was low-yielding and not reproducible.

Results and Discussion

Preparation of *N*-(3-Phenylpropyl)piperazine Dihydrochloride Salt (2). In the original process, *N*-(3-phenylpropyl)piperazine free base was formed by reacting 1-bromo-3-phenylpropane **1** with an excess of piperazine (10 equiv) in refluxing acetonitrile for 2 h. The large excess of piperazine was required to minimize competing polyalkylation side reactions. It was found that the reaction temperature needed to be carefully maintained at 75−80 °C to

* Corresponding author. E-mail: michaeli@albmolecular.com. Telephone: (518) 464-0279. Fax: (518) 464-0289.

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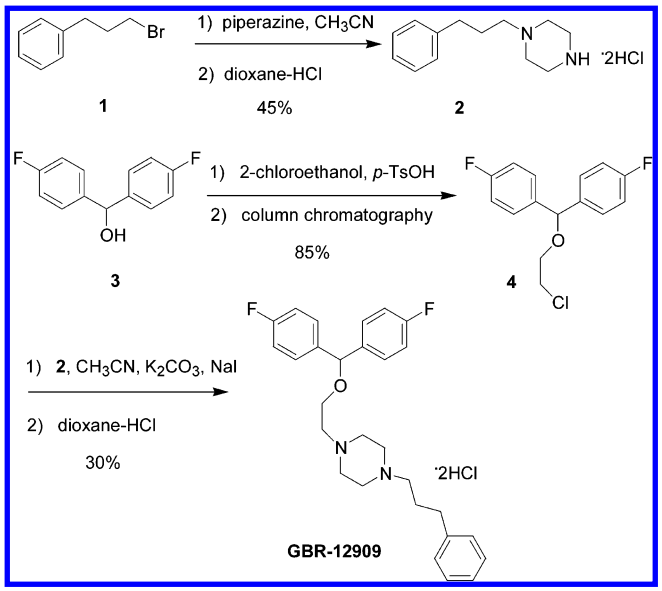
Scheme 1



minimize the sublimation of piperazine, which was observed at higher reaction temperatures. Upon complete consumption of **1**, the reaction was worked up by adding ethyl acetate and water (21 vols) to the reaction mixture at 50 °C. Attempts to improve throughput by reducing this large volume of water in the workup were unsuccessful since lesser volumes failed to completely dissolve the unreacted piperazine. The free base was extracted into ethyl acetate, and the extracts were then concentrated under vacuum to afford the product as an oil. Dissolving the free base in 1,4-dioxane and then adding 4 M hydrochloric acid in 1,4-dioxane subsequently formed the dihydrochloride salt **2**, which was isolated by filtration, although the brown-colored solid proved to have very poor filtration characteristics and only 80−85% purity by HPLC analysis. Crude **2** was subsequently purified by reslurrying in heptane followed by vacuum-drying the heptane-wet filter cake. Finally, a recrystallization from methanol−acetone and subsequent vacuum-drying afforded dihydrochloride salt **2** of acceptable quality (>95% purity by HPLC) in 45% yield.

Initial development work focused on eliminating the solvent 1,4-dioxane, a suspected carcinogen,[14] from the process and finding a safer, more cost-efficient alternative to 4 M hydrochloric acid in 1,4-dioxane. It was demonstrated that the dihydrochloride salt **2** could be efficiently formed by dissolving the *N*-(3-phenylpropyl)piperazine free base in ethanol and treating the resultant solution with 2.2 equiv of concentrated hydrochloric acid at 20−30 °C. Addition of acetone as an antisolvent and chilling the resultant suspension to 0−5 °C afforded crude **2** as an easily filterable white solid in >95% purity by HPLC analysis. The crude wet cake could be further purified by recrystallization from methanol−acetone to furnish **2** in 65% overall yield and >97% purity by HPLC analysis.

The improved process was scaled up, and 1740 g of **2** was isolated (52% yield). The lower than anticipated yield was due to product losses incurred during both the dihydrochloride salt formation and recrystallization steps, as confirmed by HPLC analysis of filtrates. No optimization of solvent volumes to improve product recovery was attempted. Nonetheless, sufficient material was in hand, and time constraints did not permit a full study at that point.

Although the process had been demonstrated to scale-up smoothly, efforts were made to further improve the yield and throughput. Initial development focused on identification of the major process impurities. HPLC analysis of the reaction mixture showed a 3:1 ratio of desired product to a single major impurity, subsequently identified as the dialkylated piperazine. Formation of this byproduct clearly had a deleterious effect on the final yield but was otherwise not a major issue since it was efficiently removed in the filtrate during dihydrochloride salt formation. It was shown that levels of this impurity could be reduced somewhat by employing an extended addition time for the 1-bromo-3-phenylpropane. As a result of this simple change, the isolated yield could be increased to 72%.

Further development work centered on investigating alternative solvents that could serve for both the coupling reaction between **1** and piperazine and for the subsequent dihydrochloride salt formation. This strategy was attractive since it would eliminate a solvent exchange. It was discovered that both methyl ethyl ketone and *n*-butyl acetate were satisfactory solvents for both conversions. However, neither approach was scaled up beyond a 100-g batch size since the isolated yields obtained in the dihydrochloride salt formation were lower than those observed with acetonitrile as the coupling reaction solvent.

In an attempt to improve volume efficiency, alternative means of removing the unreacted piperazine were investigated. It was discovered that by cooling the reaction mixture to 30 °C, a mobile slurry formed and the bulk of the excess piperazine could be easily removed by filtration. HPLC analysis confirmed that no product was lost in this filter cake. This approach dramatically reduced the volume of water necessary in the subsequent workup, thereby improving volume efficiency.

Preparation of 1-[Bis(4-fluorophenyl)methoxy]-2-chloroethane (4). In the original process, compound **4** was prepared by heating 4,4′-difluorobenzhydrol in 2-chloroethanol at 90 °C in the presence of molecular sieves and *p*-toluenesulfonic acid. The reaction was quenched by adding ethyl acetate, cooling to 0−5 °C, and then adding aqueous sodium bicarbonate solution. The product was extracted into ethyl acetate and concentrated under reduced pressure to remove the solvent and residual 2-chloroethanol. The crude product was purified by column chromatography to >85% purity by HPLC analysis. A major issue with this procedure was the formation of interfacial solids and emulsions upon extraction with ethyl acetate; therefore the replacement of this solvent prior to scale-up was essential. In addition, the distillation to remove excess 2-chloroethanol was not trivial, and subsequent chromatographic purification was tedious and impractical at a large scale.

Development work revealed that heptane could be utilized instead of ethyl acetate to simplify the extraction step. The modified procedure involved diluting the reaction mixture

(14) *Ninth Report on Carcinogens* (**PB2000−107509, 2000**) III-122.

with heptane, filtering to remove molecular sieves, and then quenching with sodium bicarbonate at 30−40 °C. The subsequent separations were clean, and the 2-chloroethanol, which has low affinity for heptane, remained in the aqueous layer. Removal of heptane under reduced pressure afforded **4** in >95% purity by HPLC analysis, which was suitable for use in the following step without further purification. This obviated any requirement for column chromatography, which was previously a serious bottleneck. The improved process was immediately scaled up to afford 2511 g of **4** in 93% yield.

Further development work aimed at eliminating 2-chloroethanol as solvent was carried out on this reaction. A procedure was developed in which compound **4** was synthesized in almost quantitative yield by heating a solution of 4,4′difluorobenzhydrol **3** and one equivalent of 2-chloroethanol in toluene, with concentrated sulfuric acid as a catalyst. This resulted in a 98% yield of the desired compound and a facile workup since removal of excess 2-chloroethanol was not an issue. Heptane was also demonstrated to be a suitable reaction solvent, which conferred the added advantage that the batch did not need to be concentrated to an oil, since residual heptane can be removed azeotropically using methyl ethyl ketone (MEK), the reaction solvent for the final step.

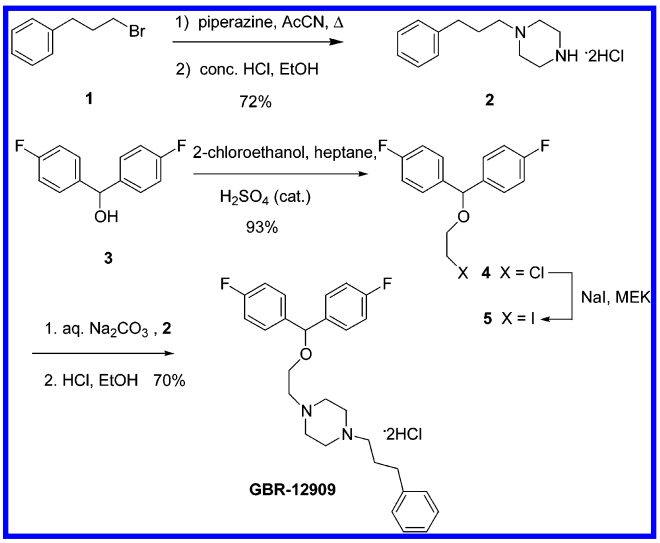
Preparation of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR-12909). The original process was a one-pot coupling reaction between compounds **2** and **4** in refluxing acetonitrile, catalyzed by sodium iodide, to afford GBR-12909 free base. Formation of GBR-12909 dihydrochloride salt was subsequently achieved by treatment of a solution of the free base in 1,4-dioxane with 4 M hydrochloric acid in 1,4-dioxane in 25−30% overall yield. Consequently, this reaction also suffered from the same drawbacks as the previous hydrochloride salt formation (vide supra).

Investigative work showed that chloroether **4** reacted extremely slowly in the absence of sodium iodide. It was also demonstrated that the conversion of chloroether **4** to the more reactive iodoether **5** was inefficient in acetonitrile, thereby contributing to the slow reaction rate. Consequently, it was envisioned that by cleanly preforming the iodo derivative and then coupling with compound **2**, a quicker reaction should result. Acetone and acetonitrile proved to be poor solvents for the conversion of chloroether **4** to its corresponding iodoether **5** (Scheme 2), whereas MEK proved to be an excellent solvent for this transformation.

With a procedure to cleanly generate the reactive iodoether **5** in hand, the coupling reaction was carried out using potassium carbonate, the base utilized in the original process. Unfortunately, the coupling still proved to be extremely slow, presumably due to the heterogeneous nature of the reaction mixture. Typically, the reaction required at least 72 h at 80 °C to reach completion.

After aqueous workup, the GBR-12909 free base was converted to its dihydrochloride salt. As per intermediate **2**, it was discovered that crude dihydrochloride salt could be formed more efficiently by treating the organic extracts with

Scheme 2

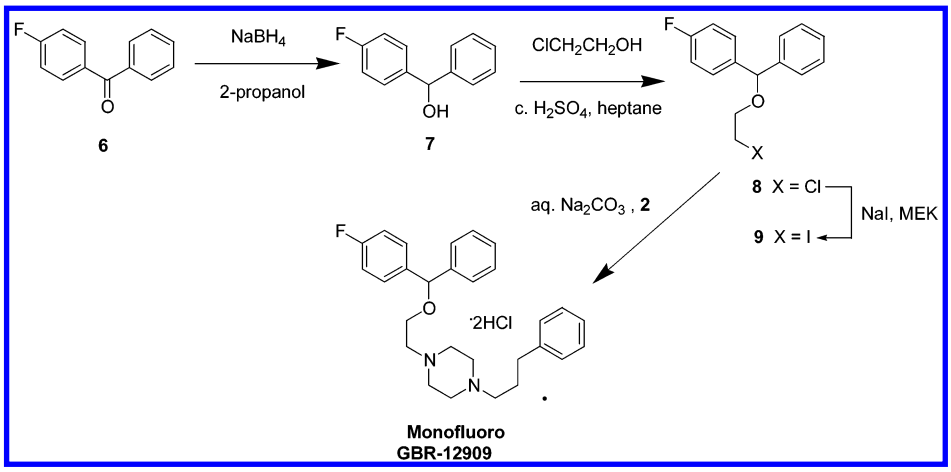


2.2 equiv of concentrated hydrochloric acid at 20−30 °C and then cooling to 0−5 °C. The salt was conveniently isolated as a white solid by filtration. This new procedure eliminated 1,4-dioxane from the process and simplified product isolation by eliminating a solvent-exchange step. The crude product was further purified by recrystallization from aqueous ethanol to afford the target molecule. The improved process was scaled up to afford 1470 g of GBR-12909 in 45% yield. The yield was lower than anticipated, due to product losses in the mother liquors incurred during the hydrochloride salt formation and recrystallization steps, as evidenced by HPLC analysis. No optimization of solvent volumes to improve product recovery was attempted, however, since an improved process was already in hand (Scheme 2).

Further process work revealed that a significant improvement in both reaction time and yield could be achieved utilizing homogeneous reaction conditions. Thus, a solution of the iodoether **5** in MEK was heated at 80 °C with a solution of salt **2**, dissolved in aqueous sodium carbonate. Typically the reaction was complete within 18 h. Workup was facile, involving a phase separation and subsequent back-extractions of the aqueous phase with MEK to isolate the desired free base. The resulting extracts could be treated directly with concentrated hydrochloric acid to furnish the crude dihydrochloride salt in 55−60% yield. Improved yields and better reproducibility could however be obtained by conducting the hydrochloride salt formation in ethanol as solvent, which necessitated a solvent swap after reaction completion. Using this procedure, crude GBR-12909 dihydrochloride was isolated in 70% yield on a 100-g scale.

Impurity Identification. HPLC analysis of the GBR-12909 batch indicated the presence of a single impurity at >0.1% (by area normalization). LC/MS analysis indicated an [M + 1] value of 451.5 for the main peak, corresponding to the molecular weight of GBR-12909 minus 2 mol of hydrochloric acid. The impurity peak yielded an [M + 1] value of 432.5, corresponding to the monofluoro analogue of GBR-12909 minus 2 mol of hydrochloric acid. Presumably this impurity emanated from the presence of 4-fluoroben-

Scheme 3



zhydrol **7** in the 4,4′-difluorobenzhydrol **3** starting material. To confirm the structural assignment of this impurity, the monofluoro analogue of GBR-12909 was prepared on a small-scale following a similar route used for the synthesis of GBR-12909 (Scheme 3). An HPLC spiking experiment using this independently synthesized monofluoro GBR-12909 confirmed that it was indeed the impurity detected in the batch of GBR-12909. Subsequently, a batch of monofluoro GBR-12909 was prepared for evaluation in clinical trials using the route outlined in Scheme 3. Many of the improvements developed for the original GBR-12909 process were incorporated. Gratifyingly, a marked improvement in yield for the final coupling step (70%) was recorded on a kilogram scale using an aqueous base.

Conclusions

In summary, the original synthetic strategy was employed although several significant improvements were incorporated to allow smooth scale-up and give higher yields for all steps. The undesirable solvent 1,4-dioxane and the reagent 4 M hydrochloric acid in 1,4-dioxane were replaced with ethanol or MEK and concentrated hydrochloric acid, respectively, in the hydrochloride salt formation reactions. The hydrochloride salts formed via the new process displayed improved filtration characteristics and were of higher purity than those produced via the original route. The introduction of heptane as the extraction solvent in the ether formation step eliminated a problematic phase separation and a chromatographic purification step. Preformation of the iodoether **5** prior to the last coupling step facilitated the formation of GBR-12909. In the coupling step, MEK proved to be a superior solvent than acetonitrile for the reaction, providing a cleaner reaction profile by HPLC analysis. The use of an aqueous base in the key final coupling step was key to achieving an improved reaction rate and yield versus the original heterogeneous conditions.

Experimental Section

Reagents and solvents were obtained from commercial sources and used as received. Proton magnetic resonance spectra were obtained on a Bruker AC-300 spectrometer at 300 MHz using either dimethyl sulfoxide-d_6 or chloroform-*d* as the solvent. Infrared spectra were obtained as KBr pellets on a Perkin-Elmer Spectrum 1000 infrared spectrophotometer. Mass spectra analyses were performed on a Shimadzu QP-5000 GC/MS (CI mass spectrometry). Melting points were obtained on a Mettler Toledo Star DSC. Elemental analyses were obtained from Quantitative Technologies, Inc., Whitehouse Junction, NJ. Silica gel for flash chromatography was purchased from E-M Scientific (mesh 230−400). Thin-layer chromatography (TLC) was performed using 2.5 × 10 cm Analtech silica gel GF plates (25-μm thick). Visualization of TLC plates was performed using ultraviolet light.

Initial Scale-Up of *N*-(3-Phenylpropyl)piperazine Dihydrochloride Salt (2). A solution of piperazine (9804 g, 113.80 mol) in acetonitrile (12 L) was heated to 75−80 °C. To this solution was added 1-bromo-3-phenylpropane (1820 mL, 11.97 mol) dropwise over a period of 4 h. Upon completion of the addition, no residual 1-bromo-3-phenylpropane was detected by HPLC analysis. The reaction was quenched with water (50 L), followed by extraction into ethyl acetate (20 L). The aqueous layer was separated and back-extracted with ethyl acetate (2 × 10 L). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 L), dried over anhydrous sodium sulfate (1 kg), filtered, and concentrated under reduced pressure at 40−45 °C to afford 2678 g of the free base as a thick oil. The free base was dissolved in ethanol (7.2 L), treated with concentrated hydrochloric acid (2.4 L) at 20−30 °C, and stirred for 1 h. The batch was diluted with acetone (22 L) at 20−30 °C and the resultant slurry was stirred for 2 h prior to cooling to 0−5 °C. The crude dihydrochloride salt was filtered and found to be 95% pure by HPLC (AUC). The filter cake was dissolved in refluxing methanol (9 L), and the resultant solution was cooled to 50−55 °C and diluted with acetone (20 L). The slurry was cooled to 0−5 °C, then filtered, and the filter cake was washed with acetone (3 L), then dried under vacuum at 40 °C to constant weight to afford 1739 g (52% yield) of compound **2** in 97% purity by HPLC (AUC). ^{1}H NMR (300 MHz, CD_3OD) δ 7.30−7.16 (m, 5H), 3.69−3.51 (b, 5H), 3.30−3.21 (m, 3H), 2.79−2.69 (m, 3H), and 2.20−2.08 ppm (m, 3H). HPLC method: Waters Symmetry C18, 3.5 μm, 2.1 mm × 150 mm, 0.25 mL/min, 267 nm, 15% CH_3CN:85% water to 90% CH_3CN:10% water

over 30 min. MS *m*/*z* 205 [M + 1] (free base).

Final preparation of *N*-(3-Phenylpropyl)piperazine Dihydrochloride Salt (2). To a solution of piperazine (500.0 g, 5.5 mol) in acetonitrile (1 L) at 75−80 °C was added 1-bromo-3-phenylpropane (85 mL, 0.56 mol) over a period of 8 h. The mixture was then cooled to 15−25 °C and filtered to remove piperazine. The filter cake was washed with acetonitrile (250 mL), and the filtrate was concentrated under vacuum at <40 °C to furnish a thick, mobile slurry. The concentrate was diluted with ethyl acetate (500 mL) and water (500 mL). The organic phase was separated, and the aqueous layer was back-extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (250 mL) and then concentrated under vacuum at <40 °C to afford the free base as a thick oil. The concentrate was dissolved in ethanol (250 mL), treated with concentrated hydrochloric acid (110 mL), at 20−30 °C, and stirred for 1 h. The batch was diluted with acetone (700 mL) at 20−30 °C, and the resultant slurry was stirred for 2 h. The batch was cooled to 0−5 °C and then filtered; the filter cake was washed with acetone (150 mL) and then dried under vacuum at 40 °C to constant weight to afford 111.5 g (72% yield) of compound **2** in 98.4% purity by HPLC (AUC). ^{1}H NMR (300 MHz, CD_3OD) δ 7.30−7.16 (m, 5H), 3.69−3.51 (b, 5H), 3.30−3.21 (m, 3H), 2.79−2.69 (m, 3H), and 2.20−2.08 ppm (m, 3H). HPLC method: Waters Symmetry C18, 3.5 μm, 2.1 mm × 150 mm, 0.25 mL/min, 267 nm, 15% CH_3CN:85% water to 90% CH_3CN: 10% water over 30 min.

MS *m*/*z* 205 [M + 1] (free base).

Initial Scale-Up of 1-[Bis(4-fluorophenyl)methoxy]-2-chloroethane (4). A mixture of 4,4′-difluorobenzhydrol (2100 g, 9.5 mol), 2-chloroethanol (19 L), *p*-toluenesulfonic acid (1800 g), and molecular sieves (4 Å) (125 g) was heated at 85 °C for 10 h. At this point no 4,4′-difluorobenzhydrol was detected by TLC analysis in 80:20 heptane/ethyl acetate. The reaction mixture was cooled to 25 °C, diluted with heptane (12 L), and filtered through a Celite pad to remove solids. The resulting filtrate was washed with saturated aqueous sodium bicarbonate solution (3 L) and stirred for 30 min. The aqueous layer was separated and back-extracted with heptane (3 L). The combined organic extracts were washed with saturated aqueous sodium chloride solution (3 L), dried over sodium sulfate (500 g), filtered, and concentrated under reduced pressure to afford 2511 g (93% yield) of ether **4** as a yellow oil in 97% purity by HPLC (AUC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.21 (m, 4H), 7.05−6.97 (m, 4H), 5.36 (s, 1H), and 3.71−3.62 ppm (m, 4H). HPLC method: Waters Symmetry C8, 5 μm, 3.9 mm × 150 mm, 1.0 mL/min, 267 nm, 30% CH_3CN with 0.1% TFA: 70% water to 90% CH_3CN with 0.1% TFA:10% water over 30 min.

Final Preparation of 1-[Bis(4-fluorophenyl)methoxy]-2-chloroethane (4). A mixture of 2-chloroethanol (37.0 mL, 555 mmol), toluene (60 mL), and sulfuric acid (6.5 mL, 131.0 mmol) was gently heated to 40 °C and treated with a solution of 4,4′-difluorobenzhydrol (81.26 g, 369 mmol) in toluene (100 mL) over a period of 45 min. The resulting light-yellow solution was heated to 85 °C and stirred for 3 h until only trace amounts of 4,4′-difluorobenzhydrol were detected by TLC analysis in 80:20 heptane/ethyl acetate. The reaction mixture was cooled to 15−25 °C, diluted with toluene (100 mL), and neutralized with potassium bicarbonate (powder) to pH 6−7. The mixture was filtered, and the filtrate was washed with water (3 × 300 mL) and concentrated under reduced pressure at <40 °C to afford 102.3 g (98% yield) of compound **4** as a yellow oil in 99% purity by HPLC (AUC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.21 (m, 4H), 7.05−6.97 (m, 4H), 5.36 (s, 1H), and 3.71−3.62 ppm (m, 4H). HPLC method: Waters Symmetry C8, 5 μm, 3.9 mm × 150 mm, 1.0 mL/min, 267 nm, 30% CH_3CN with 0.1% TFA:70% water to 90% CH_3CN with 0.1% TFA:10% water over 30 min.

Initial Scale-Up of 1-[2-[Bis(4-fluorophenyl)methoxy]-ethyl]-4-(3-phenylpropyl) Piperazine Dihydrochloride (GBR-12909). A mixture of compound **4** (1948 g, 6.89 mol), sodium iodide (2782 g, 18.5 mol), and MEK (17 L) was heated at 80 °C for 24 h, at which point less than 5% residual chloroether **4** was detected by HPLC analysis. The reaction mixture was cooled to 25 °C and filtered through a Celite pad to remove the inorganic salts. To the filtrate was added potassium carbonate (5217 g) and salt **2** (1739 g, 6.27 mol). The batch was heated at 80 °C for 68 h, at which point there was <10% residual iodoether **5** by HPLC (AUC). The reaction mixture was cooled to <35 °C, quenched with water (3.5 L) and saturated aqueous sodium bicarbonate (7 L). The organic layer was separated, and the aqueous layer was back-extracted with MEK (3 × 3.5 L). The combined organic extracts were washed with saturated aqueous sodium chloride solution (5 L) and then treated with concentrated hydrochloric acid (1.5 L) and stirred at 20−30 °C for 2 h. The reaction mixture was then cooled to 0−5 °C and stirred for an additional 4 h to afford a thick slurry. The crude GBR-12909 was isolated by filtration in reasonable yield (2800 g wet) and purity 99.0% (AUC by HPLC analysis). The crude product was purified by dissolution in 5% aqueous ethanol (25 L) at 80 °C. The solution was cooled to 50−60 °C, clarified by filtration (to remove extraneous matter), and then diluted with acetone (34 L). The resultant slurry was cooled to 0−5 °C and filtered. The filter cake was dried at 45 °C until the residual ethanol and acetone levels were <0.5% by GC analysis, to afford 1470 g (45% yield) of GBR-12909 dihydrochloride as a white solid with 99.8% purity by HPLC (AUC): mp = 228−233 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.42−7.05 (m, 13H), 5.56 (s, 1H), 3.82−3.54 (m, 10H), 3.3−3.29 (m, 4H), 2.75−2.71 (m, 2H), and 2.11−2.09 (m, 2H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 163.4, 160.2, 140.9, 138.3, 138.2, 129.1, 129.0, 128.8, 128.6, 126.5, 115.7, 115.5, 81.9, 63.1, 55.6, 48.9, 48.3, 40.7, 40.4, 40.2, 39.9, 39.3, 39.0, 32.3, 25.1; IR (KBr) 3433, 2947, 2390, 1603, 1507, 1453, 1222, 1155, 1098, and 1014 cm^{-1}. Anal. Calcd for $C_{28}H_{34}Cl_2F_2N_2O$: C, 64.24; H, 6.55; N, 5.35. Found: C, 63.91; H, 6.47; N, 5.27. HPLC method: Waters Symmetry C8, 5 μm, 3.9 mm × 150 mm, 1.0 mL/min, 267 nm, 30% CH_3CN with 0.1% TFA:70% water to 90% CH_3-

CN with 0.1% TFA:10% water over 30 min. MS *m*/*z* 451 [M + 1] (free base).

Final Preparation of 1-[2-[Bis(4-fluorophenyl)methoxy]-ethyl]-4-(3-phenylpropyl) Piperazine Dihydrochloride (GBR-12909). A mixture of compound **4** (93.6 g, 331.1 mmol), sodium iodide (71.0 g, 473.4 mmol), and MEK (800 mL) was heated at 80 °C for 24 h, at which point less than 5% residual chloroether was detected by HPLC analysis. The reaction mixture was cooled to 25 °C and filtered through a pad of Celite to remove the inorganic salts. The filtrate was treated with a solution of sodium carbonate (53.3 g), salt **2** (82.0 g, 260.0 mmol), and water (400 mL). The reaction mixture was heated at 75−80 °C for 24 h until complete by HPLC (<10% iodoether **5**) and then cooled to <35 °C. The aqueous layer was separated and back-extracted with MEK (3 × 400 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (400 mL) and concentrated under vacuum at <40 °C to a volume of 100 mL. The concentrate was dissolved in ethanol (450 mL), clarified by filtration (to remove extraneous matter) and treated with concentrated hydrochloric acid (60 mL) at 15−25 °C. The batch was stirred at 15−25 °C for 2 h, treated with acetone (800 mL), cooled to 0−5 °C, and stirred for another 2 h. The product was collected by filtration, washed with chilled acetone (2 × 80 mL), and dried under vacuum at 45 °C until the residual ethanol and acetone levels were <0.5% by GC analysis. A total of 108.4 g (70% yield) of GBR-12909 dihydrochloride was isolated as a white solid in 99.2% purity by HPLC (AUC). A second crop [8.5 g (5.5% yield)] of GBR-12909 dihydrochloride was obtained upon vacuum concentration of the filtrate at <45 °C to a volume of 40 mL, although of slightly lower purity at 97.8% (AUC). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.42−7.05 (m, 13H), 5.56 (s, 1H), 3.82−3.54 (m, 10H), 3.3−3.29 (m, 4H), 2.75−2.71 (m, 2H), and 2.11−2.09 ppm (m, 2H); IR (KBr) 3433, 2947, 2390, 1603, 1507, 1453, 1222, 1155, 1098, and 1014 cm^{-1}. Anal. Calcd for $C_{28}H_{34}Cl_2F_2N_2O$: C, 64.24; H, 6.55; N, 5.35. Found: C, 63.91; H, 6.47; N, 5.27.

4-Fluorobenzhydrol (7). A solution of 4-fluorobenzophenone **6** (966 g, 4.83 mol) in 2-propanol (12 L) was treated with sodium borohydride (70 g, 1.85 mol). The reaction mixture was stirred for 16.5 h, whereupon TLC analysis in 80:20 heptane/ethyl acetate showed no starting material and a single product. The reaction mixture was concentrated under reduced pressure and the crude product partitioned between water (12 L) and ethyl acetate (6 L). The layers were separated, the aqueous layer was extracted with ethyl acetate (5 L), and the combined organic layers were washed with saturated aqueous sodium chloride (5 L), dried over sodium sulfate (200 g), filtered, and concentrated under reduced pressure to afford 4-fluorobenzhydrol **7** as a light orange solid (982 g, 98% theory) of 99% purity by HPLC (AUC). Analytical data was consistent with data published in the literature.[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 7.08−6.97 (m, 4H), 5.83 (s, 1H), and 2.22 ppm (s, 1H). HPLC method: Phenomenex Synergi Hydro RP, 4 μm, 4.6 mm × 250 mm, 1.0 mL/min, 220 nm, 15% CH_3CN with 0.05% TFA:85% water with 0.05% TFA to 100% CH_3CN with 0.1% TFA over 25 min. MS *m*/*z* 185 [M − OH].

1-[(4-Fluorophenyl)phenylmethoxy]-2-chloroethane (8). A solution of 4-fluorobenzhydrol 7 (970 g, 4.80 mol) in heptane (1810 mL) and dichloromethane (100 mL) at 40 °C was added over 1 h in 270-mL portions to a solution of 2-chloroethanol (440 mL, 528.4 g, 6.56 mol, 1.37 equiv) and concentrated sulphuric acid (73 mL, 1.3 mol, 0.27 equiv) in heptane (800 mL), keeping the temperature at 35−40 °C. After the addition was complete, the temperature was increased to 80−85 °C, and the batch was stirred at this temperature for 5 h. The reaction was complete as judged by TLC in 80:20 heptane/ethyl acetate. The batch was cooled to 15−25 °C, and washed with saturated sodium bicarbonate solution (2 × 6 L) and purified water (3 × 6 L). The batch was then concentrated under vacuum at 45 °C. The concentrate was dissolved in MEK (3 L) and the batch reconcentrated under vacuum to give 1-[(4-fluorophenyl)phenylmethoxy]-2-chloroethane (1254 g, 98.7%) as an oil in 95% purity by HPLC (AUC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.21 (m, 5H), 7.05−6.97 (m, 4H), 5.41 (s, 1H), and 3.74−3.62 ppm (m, 4H). HPLC method: Phenomenex Synergi Hydro RP, 4 μm, 4.6 mm × 250 mm, 1.0 mL/min, 220 nm, 15% CH_3CN with 0.05% TFA:85% water with 0.05% TFA to 100% CH_3CN with 0.1% TFA over 25 min. MS *m*/*z* 185 [M − OCH_2CH_2Cl].

1-[2-[(4-Fluorophenyl)phenylmethoxy]ethyl]-4-(3-phenylpropyl)piperazine Dihydrochloride (Monofluoro GBR-12909). 1-[(4-Fluorophenyl)phenylmethoxy]-2-chloroethane **8** (1227 g, 4.63 mol) was added to a mixture of MEK (10.5 L) and sodium iodide (1672 g, 11.15 mol) and heated at 80 °C for 24 h. After this time, the amount of residual chloroether **8** was 8.3% by HPLC analysis. The batch was cooled and filtered through a pad of Celite to remove the inorganic salts. Sodium carbonate (679 g, 6.4 mol) was dissolved in purified water (5.2 L), and *N*-(3-phenylpropyl)-piperazine dihydrochloride salt **2** (1045 g, 3.77 mol) was added carefully to this solution, avoiding excessive frothing. Once the *N*-(3-phenylpropyl)piperazine dihydrochloride salt had dissolved, the aqueous solution was added to the filtered batch, and the mixture was heated to 75−80 °C. The batch was stirred at this temperature for 22.5 h, after which time the amount of residual iodoether **9** was 9.6% by HPLC. The batch was cooled to below 40 °C, and the lower aqueous phase was separated. The aqueous phase was extracted with MEK (3 × 4 L), and the combined organic layers were washed with saturated sodium chloride solution (3 L). The batch was concentrated under vacuum at 45 °C and the concentrate dissolved in ethanol (5 L). Concentrated hydrochloric acid (731 mL, 7.3 mol) was added over 1 h, maintaining the batch temperature at 15−30 °C. The batch was then stirred at 10−25 °C for 2 h prior to addition of acetone (10.5 L), which induced crystallization of the dihydrochloride salt. The resultant slurry was cooled to 0−5 °C, stirred for 16 h in this temperature range, and then filtered. The filter cake was washed twice with chilled acetone (2 L). The purity of the wet cake was 93.3% by

(15) Sell, M. S.; Hanson, M. V.; Rieke, R. D. *Synth. Commun.* **1994**, *24*(16), 2379.

HPLC (AUC). The wet cake was dissolved in a mixture of ethanol (8 L) and purified water (1.4 L) at 80 °C. The hot solution was clarified by filtration, cooled to 40−45 °C, and stirred at this temperature for 30 min. Acetone (14 L) was added over 1 h, and the batch was cooled to 0−5 °C in an ice/ethanol bath and stirred for 30 min prior to filtration. The filter cake was washed twice with prefiltered acetone (5 L). The batch was dried under vacuum at 40 °C to afford 1-[2-[(4-fluorophenyl)phenylmethoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride (1334 g, 70%) as a white solid in >99.8% purity by HPLC (AUC). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52−7.10 (m, 14H), 5.58 (s, 1H), 3.92−3.35 (m, 10H), 3.3−3.05 (m, 4H), 2.75−2.63 (m, 2H), and 2.11−2.00 ppm (m, 2H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 163.6, 160.5, 141.9, 140.9, 138.4, 129.2, 129.0, 128.9, 128.8, 128.6, 127.9, 127.0, 126.5, 115.7, 115.4, 82.7, 49.0, 40.7, 40.4, 40.2, 39.9, 39.3, 39.0, 32.3, 25.1; IR (KBr) 2971, 2358, 1598, 1504, 1453, 1373, 1331, 1217, 1098, and 1017 cm^{-1}. Anal. Calcd for $C_{28}H_{35}Cl_2FN_2O$: C, 66.53; H, 6.98; N, 5.54. Found: C, 66.76; H, 6.95; N, 5.39. Mp 226−229 °C. HPLC method: Phenomenex Synergi Hydro RP, 4 μm, 4.6 mm × 250 mm, 1.0 mL/min, 220 nm, 15% CH_3CN with 0.05% TFA:85% water with 0.05% TFA to 100% CH_3CN with 0.1% TFA over 25 min. MS *m*/*z* 433 [M + 1] (free base).

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