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Identification and Comparison of Impurities in Fluoxetine Hydrochloride Synthesized by Seven Different Routes

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Abstract:

Fluoxetine HCl was prepared by seven different synthetic routes, all previously reported. The major impurities in each route were identified by GC/MS, HPLC/MS, and gradient HPLC analysis. Impurities were classified as being derived from impurities in 4-chlorobenzotrifluoride, those arising during the SNAr reaction of this compound and 3-methylamino-1-phenylpropanol, and those arising during the synthesis of this alcohol. Fifteen impurities belonging to the latter two categories were identified, and their structures were confirmed by synthesis of authentic material for most of the compounds. It was found that a variety of analytical tools was needed for complete characterization of the impurity profile of fluoxetine HCl and that purification of the intermediate and recrystallization of the drug itself are highly effective in minimizing the levels of the impurities.

Introduction

The examination of multiple synthetic routes to modern pharmaceutical active ingredients is a key function of the process chemist. Many factors, including the availability of the starting materials, yields, safety issues, and the quality of the product, are involved in the selection of the routes to be used, and these factors and thus the selected routes often change during the development of the product. Additionally, when multiple companies produce a generic product, it may be synthesized by many different routes. Process and analytical chemists and regulatory scientists all inherently recognize that the identity and amounts of impurities in pharmaceutical products may vary as a function of the route of synthesis as well as the degree of optimization within each process within a route. Indeed, identification and minimization of impurities is a key activity of the development laboratories, a process whose goals have been standardized somewhat by the recent adoption of guidelines from the International Conference on Harmonization.[1]

Although the relationship between synthetic route and impurity identity is often assumed and often investigated during development, the results are seldom made public. The purpose of this report is to examine this relationship with a simple but important drug, which can readily be synthesized by multiple routes from multiple commercially available precursors.

Fluoxetine hydrochloride, **1**, is a successful antidepressant which selectively inhibits the uptake of serotonin and is marketed in the United States as Prozac.[2] The synthesis of the oxalate salt of **1** as disclosed in the original patents is shown in Figure 1 and is designated as route A.[3] 3-Dimethylaminopropiophenone, readily available from the Mannich reaction of acetophenone and dimethylamine, was reduced with diborane and the resulting alcohol chlorinated with thionyl chloride. Displacement with 4-trifluoromethylphenol gave *N*-methylfluoxetine, **2**, which was demethylated with cyanogen bromide. Although appropriate for the early development of fluoxetine, this route had obvious safety liabilities for large-scale manufacture. Two key improvements have been the replacement of sodium borohydride for the diborane[4] and the use of ethyl chloroformate (or other chloroformates) instead of cyanogen bromide for the Von Braun de-alkylation.[5] The simplicity of these operations is supported by their use by undergraduates to produce *N*-methylfluoxetine as a teaching exercise.[6]

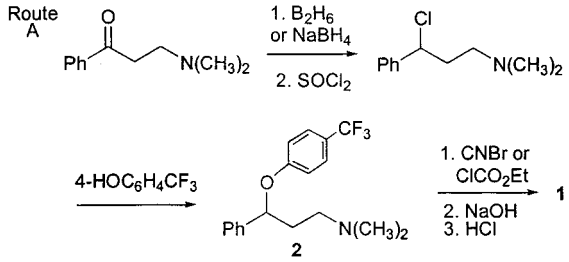
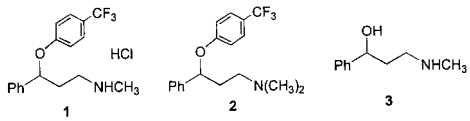


Figure 1. **Original reported synthesis of 1, Route A.**



In the nearly two decades since the discovery of fluoxetine, many synthetic routes to it or its enantiomers have been published. Most of these routes do not utilize the cresol as a starting material as does route A. Instead, they utilize the nucleophilic aromatic substitution reaction between 3-methylamino-1-phenylpropanol, **3**, and 4-chlorobenzotrifluoride, shown in Figure 2. The chief advantage of these routes is the reduced cost of the trifluoroaromatic compound.

The six routes to **3** that have been replicated, designated as B through G in Figure 3, begin from six different pre-

(1) Guideline for Industry, Impurities in New Drug Substances, ICH Q3A, January 4, 1996, 61 FR 371.

(2) Fuller, R. W.; Wong, D. T.; Robertson, D. W. *Med. Res. Rev.* **1991**, *11*, 17−34.

(3) Molloy, B. B.; Schmiegel, K. K. U.S. Patent 4,314,081, issued February 2, 1982.

(4) Jakobsen, P.; Drejer, J. U.S. Patent 5,019,592, issued May 28, 1991.

(5) Crnic, Z.; Kirin, S. I. U.S. Patent 5,618,968, issued April 8, 1997.

(6) Perrine, D. M.; Sabanayagam, N. R.; Reynolds, K. J. *J. Chem. Educ.* **1998**, *75*, 1266.

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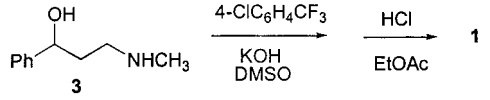


Figure 2. **SNAr method for the preparation of 1.**

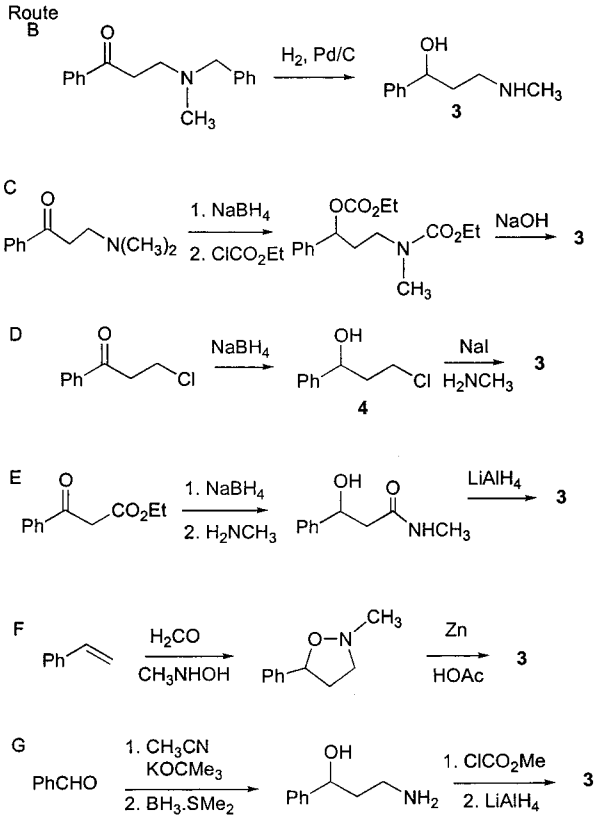


Figure 3. **Routes B−G for the preparation of 3.**

cursors. They vary in length and the choice of reagents but all are high yielding. Since the emphasis on this work is impurities, other attributes of the various routes such as expense and safety concerns are not addressed. The seven routes were executed as described in the literature and were not optimized. Thus, it is likely that the impurity profiles would improve with additional development work. The purpose of this examination is not to compare impurity profiles of the routes after optimization and implementation in a manufacturing facility but rather in their infancy and without purification of the drug substance, thus mimicking the state of knowledge in the early part of the development cycle.

Results and Discussion

Fluoxetine HCl was made by all seven methods without significant difficulty. It was crystallized by the addition of anhydrous HCl to a solution of the free base in ethyl acetate. Samples were analyzed by two main methods, a gradient HPLC method specifically developed to detect and identify unknown nonpolar compounds, and a GC method useful for impurities lacking good chromophores or unstable to the acidic conditions of the HPLC method.[7] Both methods can use a mass spectrometer for detection, greatly aiding in the identification of unknown impurities.

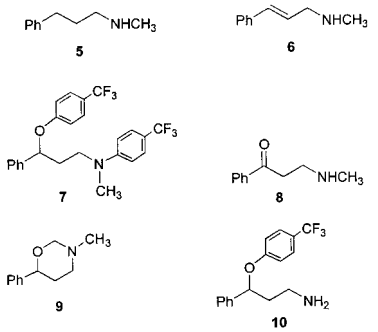
Table 1. **Route-specific impurities**

route	impurities[a]
A	2, 11, 12, 16
B	10, 15
C	10, 12, 17 (*m*/*e* 443)
D	11, 12
E	12
F	2, 9, 10, 11, 12, 13, 14, 18 (*m*/*e* 453)
G	2, 10, 12

[a] Underlining indicates a level over 0.1% by area at 260 nm.

Impurities observed have been classified into one of three categories. Those that arise from impurities in the 4-chlorobenzotrifluoride such as from positional isomers or dichlorinated benzotrifluoride are not treated here since they are largely a function of the quality of this starting material and its purity is derived from its purification by distillation. They may be identified and quantified by the referenced gradient and GC methods or, for the *meta* isomer of fluoxetine, by the isocratic HPLC method adopted by the USP.[8]

The second class of impurities are those common to routes B through G since they arise in the SNAr coupling step. These include unreacted **3**, its reduced analogue, **5**, *N*-methylcinnamylamine (**6**) a potential degradation product, and the aniline **7**. Additionally, ketone **8** is present in some of these products, apparently arising from Oppenauer oxidation of the anion of **3** by oxygen. Due to its enhanced chromophore, its quantity is exaggerated by the HPLC method.



Compound **7** was unexpected since amines are generally not regarded as substrates for arylation by haloaromatic compounds. Its structure was proven by synthesis using the more reactive 4-fluorobenzotrifluoride. It was produced at apparent levels of up to 2% in some samples. As a result of its reduced basicity, it elutes very late in the HPLC method and is relatively well rejected by recrystallization.

The third group of impurities are those that are a function of the routes shown in Figures 1 and 3. Impurities identified that are in this category are compounds **9** through **16** and the routes in which they were observed are summarized in Table 1. The underlined compound numbers are those present at levels near or over 0.1% in the fluoxetine HCl made via

(7) Wirth, D. D.; Olsen, B. A.; Hallenbeck, D. K.; Lake, M. E.; Gregg, S. M.; Perry F. M. *Chromatographia*, **1997**, *46*, 511−3.

(8) *U.S. Pharmacopeia* **1999**, *24*, 738−9.

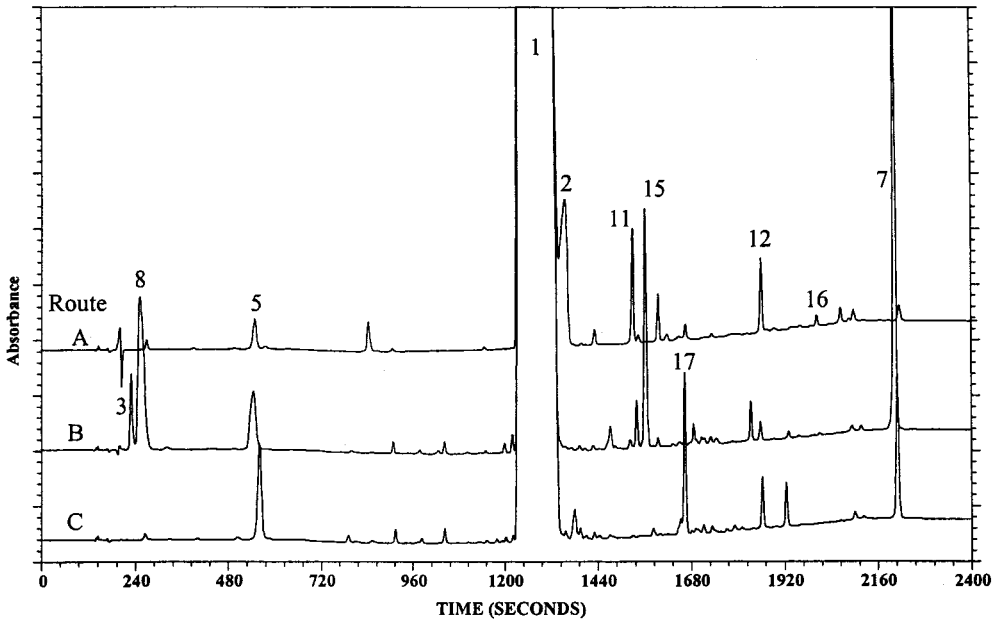
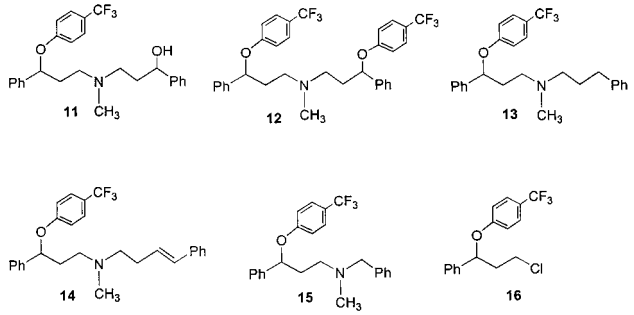


Figure 4. **Gradient HPLC chromatograms of 1 produced by Routes A−C.**

that route, a level chosen due to its importance in the harmonization guideline.[1]



The identities of these impurities were proven by comparison with authentic materials. Compounds **2**,[3] **3**, **5**,[9] **6**,[10] **8**,[16] and **10**[22] were available from procedures known in the literature. The remaining compounds were synthesized as reported in the Experimental Section. The identities of the impurities with mass spectral data only were not definitively proven. Figures 4 and 5 display the gradient HPLC chromatograms of the fluoxetine HCl produced by the seven methods with the impurity peaks labeled. These chromatograms reveal the presence of many additional unidentified peaks under the apparent level of 0.1%. Since absorption at 260 nm is quite dependent on the structures, their actual levels may vary considerably from their area % values.

The main impurities seen in route A are **2**, from incomplete demethylation, and **11** and **12**, which likely arise from the intermediacy of the alkylating agent **16**. The latter is an expected byproduct of the dealkylation procedure in which *N*,*N*-dimethyl ethylcarbamate is produced rather than methyl chloride. Under the forcing conditions of the SNAr reaction, **16** and fluoxetine react to form **12**.

Other than impurities common to the arylation, the only impurity in the material produced via route B over 0.1% is *N*-benzylfluoxetine, **15**, which arises from incomplete hydrogenation of the intermediate. It was previously shown to be present in several commercial samples of **1**.[7]

The major impurities seen in material produced via route C are **12**, an impurity seen in all routes with Von Braun demethylations, and unknown **17**. High-resolution mass spectrometry indicated the formula of this material to be $C_{26}H_{29}NO_2F_3$, an isomer of **11**. Since synthetic **11** was a mixture of diastereomers which coeluted, **17** must be a positional isomer of **11**, not just a diastereomer.

Fluoxetine HCl produced via route D contained a large amount, about 2%, of the 3° amine, **12**. Given the propensity of 1° amines to over-alkylate, this impurity is expected; it is the chief reason that this otherwise inexpensive route is not preferred from a quality viewpoint.

Although expected in routes A, C, and D, impurity **12** was also surprisingly found in **1** prepared via route E. Its origin in this process is unclear.

The interesting isoxazolidine route (F) produced an array of low-level impurities. Although not all were identified, the presence of **13** and **14** were proven and are clear evidence of the presence of both unreacted formaldehyde and styrene during the reduction of the isoxazolidine. Thus, reaction of **3** with formaldehyde to yield the iminium ion followed by trapping with styrene would lead to **13**. Compound **14** could arise by addition of an additional formaldehyde molecule before the styrene addition. Compound **18** (formula $C_{28}H_{31}NOF_3$ by LC/HRMS) appears to be a homologue of **14**. Reduction of the fluoxetine−formaldehyde iminium ion by zinc would produce **2**, which was in fact the largest impurity

(9) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* **1977**, *42*, 2082−7.
(10) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 21726.
(11) Although **10** can be detected by the GC method, it is not well-separated from **2**.
(12) Parli, C. J.; Hicks, J. *Fed. Proc.* **1974**, *33*, 560.
(13) Wirth, D. D.; Stephenson, B. A. *Org. Process Res. Dev.* **1997**, *1*, 55−6.
(14) Reiter, J.; Budai, Z.; Simig, G.; Blasko, B.; Mezei, T.; Imre, J.; Nagy, K.; Ladayni, L.; Tompe, P. PCT, WO 98/11054, published March 19, 1988.
(15) Againe Csongor, E.; Drexler, F.; Aracsne Trischler, Z.; Harsanyi, K.; Ujvari, B.; Vargane Gal, G. PCT, WO 94/00416, published January 6, 1994.
(16) Sakuraba, S.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 748−53.

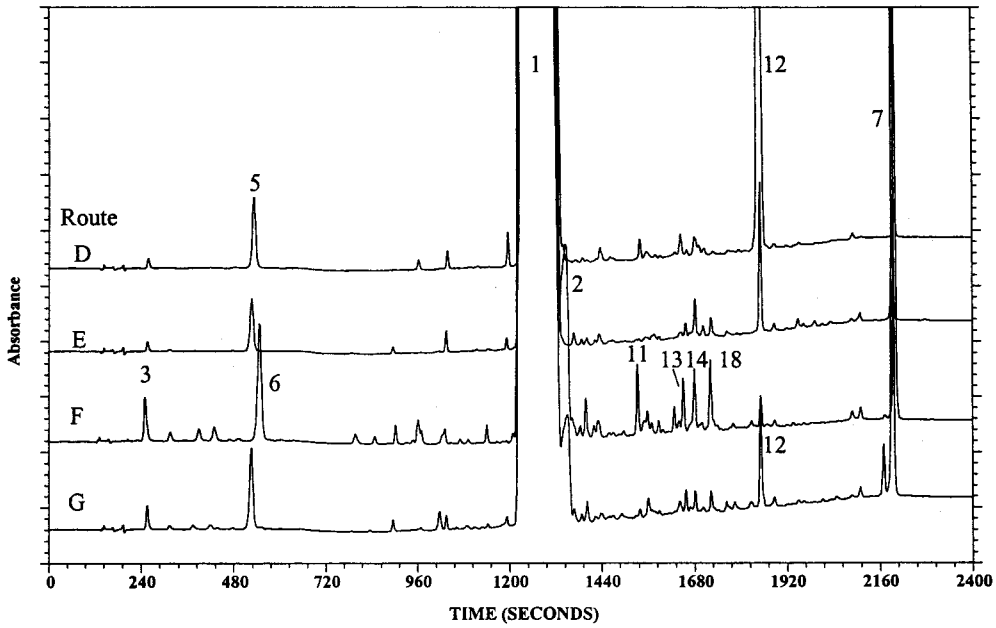


Figure 5. **Gradient HPLC chromatograms of 1 produced by Routes D−G.**

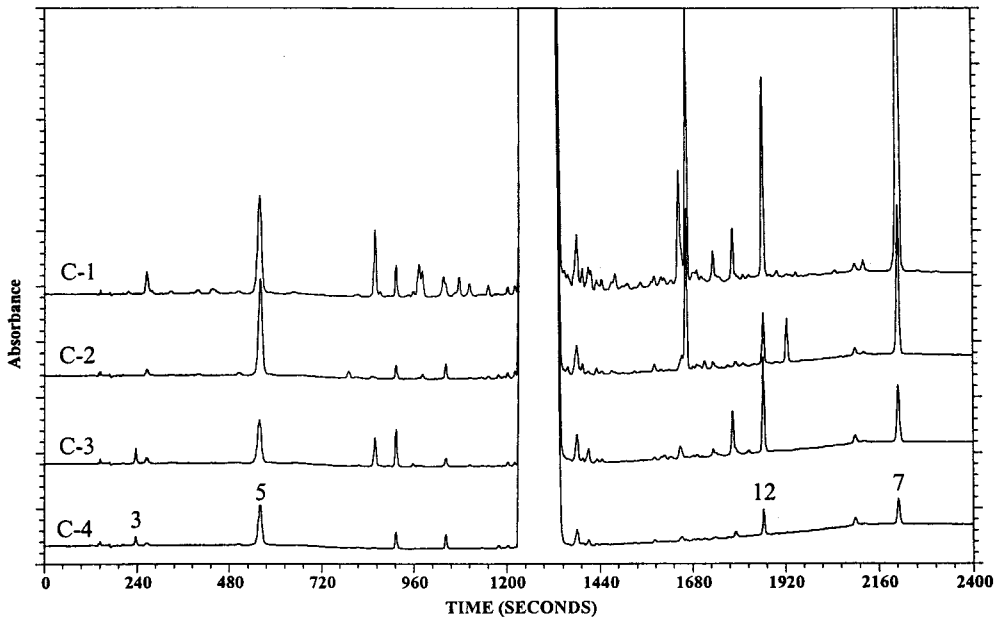


Figure 6. **Gradient HPLC chromatograms of 1 produced by Route C, C-1; from crude 3, C-2; from crystallized 3, C-3; recrystallization of 1 from sample C-1, C-4; recrystallization of 1 from sample C-2.**

in this sample. Interestingly, desmethylfluoxetine, **10**, was also present in this sample. Compound **10** cannot be well-resolved from the main peak by the gradient HPLC method, as previously reported.[7] An isocratic method was developed for analysis of this single impurity.[11] The oxazine **9**, an adduct of formaldehyde and **3**, was also observed in fluoxetine prepared by this route. It is unstable to the acidic conditions of the HPLC but was readily identified by the GC/MS method.

Route G was originally developed to produce enantiomerically enriched **10**, which is a known metabolite of fluoxetine.[12] Methylation of **10** via its carbamate derivative resulted in fluoxetine HCl that contained both the over-methylated product **2**, and the 3° amine **12** as impurities as well as about 2.5% of unreacted **10** as its major impurity.

Other than optimization of the individual routes, typical methods to improve the quality of drug substances are purification of intermediates or recrystallization of the drug itself. Both of these have been briefly examined in this study. Figure 6 shows the quality of fluoxetine HCl made from route C when the intermediate **3** is used as a crude oil compared to when it was crystallized from hexane or heptane as suggested in the literature.[17] The total impurity levels in **1** by the gradient HPLC method were reduced from about 3% to about 1% by this purification.

To examine the impact of recrystallization of the drug itself, acetone was chosen as the solvent due to its low toxicity and the ability to achieve a recovery of at least 80%

(17) Kairisalo, P. J.; Hukka, P. J.; Jarvinen, A. H. U.S. Patent 5,166,437, issued November 24, 1992.

by simple heating and cooling of **1** in acetone. Figure 6 also shows the impact of the recrystallization of the two batches of material made by route C. Many impurities are effectively removed or minimized by this recrystallization, such that in sample C-4 of Figure 6 the level of no single impurity exceeds 0.1%. The total level of impurities has been reduced by a factor of about 5 with this purification. The efficiency of rejection of individual impurities is also of interest to the development chemist, especially in the setting of specifications and methods to examine this point have been published.[13] Impurity reduction factors are calculated as the ratio of an impurity's amount in the recrystallized material to its amount in the same lot before recrystallization (the technical material) averaged over results from several batches. For the acetone recrystallization of **1**, these factors range from more than 10 for impurity **7** (well-rejected since it is nonbasic) to about 2 for compounds **5** and **12**. These factors are somewhat difficult to predict; for example, the impurities **2** and **10** which differ from the drug only by the methyl group and thus might be predicted to be quite difficult to remove have rejection factors of about 3 and 5, respectively.

Conclusions

The identities and amounts of impurities in fluoxetine HCl, **1**, vary considerably with the route of synthesis as well as upon the quality of the starting materials. Several impurities are present in nearly all batches of the products made from the different routes since they are produced in the final, common step. Most of the identified impurities are unique to one or a few of the routes and most of these are nonpolar, late-eluting compounds, for which the isocratic (USP) HPLC is inappropriate. Several different methods, including GC/MS, gradient HPLC, and HPLC/MS, in addition to the isocratic HPLC method, were required to detect and identify the many impurities. Purification of the intermediates and recrystallization of the drug substance are quite useful for minimizing the levels of impurities and thus the differences in quality of the drug from the various synthetic routes. In total, these findings reinforce the need to rigorously compare the quality of pharmaceutical products with a variety of different analytical tools when a change in synthetic route is investigated, whether that change occurs during early (IND) phase development, or for marketed products (e.g., BACPAC guidelines).

Experimental Section

Reagents were standard laboratory grade from Aldrich Chemical Co. Solvents were reagent grade from Mallinckrodt or EM Science except for the HPLC grade CH_3CN from EM Science. The previously published gradient method[7] was modified slightly by holding the final time at 15% aqueous and 85% acetonitrile for 10 min instead of 5 min, thus allowing for elution of **7** (36.8 min, relative retention time 1.75). The isocratic HPLC for determination of **10** utilized a Zorbax RX-C8 column, 25 cm × 4.6 mm, 5 μm particles, eluted at 1.00 mL/min with 60% water (containing 0.07% TFA) and 40% acetonitrile and UV detection at 220 nm. Compound **10** elutes at 10.4 min and **1** at 12.0 min. NMR spectra were obtained on a Bruker AM-300. HPLC/MS were obtained on a system consisting of a Quattro II tandem mass spectrometer from MicroMass (Beverly, MA), in the positive electrospray mode, an Applied Biosystems 759A absorbance detector, a Waters 600S controller, and a Waters 616 LC pump. HPLC/HRMS data were obtained on a Finnigan New-Star system, an 8 T, dual-cell Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR/MS) with a concurrent ion source geometry fitted with an electrospray ionization (ESI) source. The instrument is controlled by a Sun-based Odyssey Data System. Ions generated by the external ESI source are transported to the detection cell by using a set of electrostatic injection optics (UltraSource). GC/MS were obtained by the published method using positive ion electrospray.[7] In addition to detecting **9** which is not visible by the HPLC methods, the GC/MS method provided verification of the presence of compounds **2**, **3**, **5**, **6**, **7**, **10**, **12**, **13**, **15**, and **16**.

Route A was executed with the Jakobsen procedure for the reduction and chlorination,[4] while the displacement with trifluorocresol was performed according to Molloy to yield *N*-methylfluoxetine oxalate.[3] Demethylation with ethyl chloroformate according to Reiter et al.[14] was followed by crystallization of the hydrochloride salt of **1** from ethyl acetate.[15] Fluoxetine HCl from each route was crystallized from ethyl acetate with anhydrous HCl to minimize any impact of this operation on the quality.

Arylation of **3** with 1.4 equiv of 4-chlorobenzotrifluoride was accomplished under a standard set of conditions with 3 equiv of KOH in DMSO at 100 °C for 10 h, as reported by Againe Csongor et al.[15]

For route B, *N*-benzyl-*N*-methyl-3-aminopropiophenone HCl was made by the Mannich reaction[16] and reduced by catalytic hydrogenation.[17] For route C, *N*,*N*-dimethylaminopropiophenone was reduced as in route A, and the alcohol was converted to **3** as reported by Schwartz et al.[18] For route D, compound **4** was converted to the corresponding iodide and directly to **2** by alkylation of methylamine as described for the enantiomers.[19] Route E, from ethyl benzoyl acetate, was executed according to Magnone.[20] Route F, involving the addition of methylnitrone to styrene to give an isoxazolidine, was performed by the method of Theriot.[21] For method G, the published method of Koenig and Mitchell was used.[22]

α-(2-Chloroethyl)-benzenemethanol (4). In a 500 mL round-bottom flask were combined 40 g of 3-chloropropiophenone (0.24 mol) and 200 mL of ethanol. The mixture was cooled to −10 °C. In approximately equal portions at 20 s intervals was added 8.97 g of $NaBH_4$ (0.24 mol) over 25 min, keeping the reaction temperature below 0 °C. The reaction mixture was stirred at −10 °C for 30 min. Acetone (100 mL) was added dropwise over 2 h at 0 °C. The mixture was stirred overnight at ambient temperature and evaporated

(18) Schwartz, E.; Kaspi, J.; Itov, Z.; Pilarski, G. U.S. Patent 5,225,585, issued July 6, 1993.
(19) (a) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett*. **1989**, *39*, 5207−10. (b) Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem*. **1988**, *31*, 1412−7.
(20) Magnone, G. Eur. Pat. Appl. 380,924, published August 8, 1990.
(21) Theriot, K. J. U.S. Patent 5,760,243, issued June 2, 1998.
(22) Koenig, T. M.; Mitchell, D. *Tetrahedron Lett*. **1994**, *35*, 1339−42.

to a residue, to which was added 200 mL of ether and 200 mL of water. The layers were separated and the aqueous layer was washed with 100 mL of ether. The ether layers were combined, dried with $MgSO_4$, and evaporated to give **4**, an oil (39.17 g, 89% yield). By HPLC at 260 nm, the product was 92% pure. ^{1}H NMR ($CDCl_3$) 7.31 (m, 5H), 4.83 (q, 1H, J = 4.9, 3.3 Hz), 3.64 (m, 1H), 3.46 (m, 1H), 3.25 (s, 1H), 2.14 (m, 1H), 2.00 (m, 1H). ^{13}C NMR ($CDCl_3$) 148.4, 128.4, 127.6, 125.6, 70.9, 41.5, 41.1.

***N*-Methyl-*N*-[4-(trifluoromethyl)phenyl]-γ-[4-(trifluoromethyl)phenoxy]benzenepropanamine (7).** Fluoxetine HCl (2.0 g, 5.8 mmol) and potassium carbonate (1.9 g, 13.7 mmol) were mixed in 10 mL of DMSO and warmed to 50 °C. 4-Fluorobenzotrifluoride (1.5 mL, 11.8 mmol) was added and the mixture was stirred at 100 °C for 3 h. An additional 0.9 mL of 4-fluorobenzotrifluoride (7.1 mmol) was added, and the mixture was stirred for an additional 46 h. After cooling, toluene and water, 20 mL each, were added, and the layers were separated. The organic layer was washed with 20 mL portions of water, 5% HCl, and water. The solvent was evaporated to give an oil which was purified by preparative HPLC, Zorbax RX-C8, 2.1 × 25 cm, eluted at 22 mL/min with 15% water (containing 0.07% TFA) and 85% acetonitrile. The last peak was collected and the eluent was concentrated in vacuo and the residue was extracted with methylene chloride. The organic layer was washed with water and evaporated to an oil. Gradient HPLC analysis showed a purity of 98.5%. HPLC/MS showed ions 188, 254, 270, 310, 351, and 454 (M + 1). ^{1}H NMR ($CDCl_3$) 7.5 (m, 9H), 7.0 (d, J = 7, 2H), 6.7 (d, J = 7, 2H), 5.25 (m, 1H), 3.7 (m, 2H), 3.0 (s, 3H), 2.25 (m, 2H). ^{13}C NMR ($CDCl_3$) 160.18, 150.87, 140.35, 128.79, 127.92, 126.76 (q, J = 3.5), 126.40 (q, J = 3.6), 125.51, 125.50 (q, 270), 125.0 (q, 270), 122.87 (q, J = 32), 117.33 (q, J = 32), 115.57, 110.96, 77.69, 48.52, 39.22, 35.67. ^{19}F NMR ($CDCl_3$) −60.94, −61.74.

Tetrahydro-3-methyl-6-phenyl-2H-1,3-oxazine (9). Compound **3** (0.50 g, 3 mmol) was combined with 0.23 mL (3 mmol) of 37% aqueous formaldehyde and 10 mL of ethanol. After stirring at room temperature for 1.5 h, the solvent was evaporated to give a colorless oil. ^{1}H NMR ($CDCl_3$) 7.3 (m, 5H), 4.6 (d, d J = 1.5, 9.2, 1H), 4.46 (d, d J = 2.3, 11.4, 1H), 4.22 (d, J = 9.2, 1H), 3.08 (m,d J = 2.1, 12.7, 1H), 2.86 (d,t J = 3.0, 12.5, 1H), 2.48 (s, 3H), 2.09 (d,q J = 4.4, 13.2, 1H), 1.63 (m,d J = 2.4, 12.5, 1H). ^{13}C NMR ($CDCl_3$) 142.16, 128.33, 127.51, 125.17, 89.31, 86.44, 52.40, 39.54, 30.13. GC/MS, retention 13.6 min, *m*/*e* 43, 58, 71, 72, 73, 104, 105, 117, 132, 177.

***N*-[γ-[4-(Trifluoromethyl)phenoxy]-γ-phenylpropyl]-α-[2-(methylamino)ethyl]-benzenemethanol (11).** Fluoxetine hydrochloride (2.0 g, 5.8 mmol), 3-chloropropiophenone (0.97 g, 5.8 mmol), and triethylamine (1.7 mL, 12.2 mmol) were combined with 15 mL of ether and stirred overnight. Another 0.4 mL of triethylamine and 15 mL of acetonitrile were added, and the mixture was distilled until the temperature reached 40 °C. After 1 h, the mixture was cooled and filtered, and the filtrate was evaporated to a residue. This was dissolved in 15 mL of methanol and cooled in an ice bath; water (1 mL) and sodium borohydride (0.29 g, 7.5 mmol) were added in portions. To the mixture was added 1 mL of acetone, 25 mL of water, and 25 mL of ether. The layers were separated, and the ether layer was washed with three 25 mL portions of water and evaporated to an oil, 2.38 g (93%). Gradient HPLC revealed a purity of 92% by area, retention time 27.4 min. ^{1}H NMR ($CDCl_3$) 7.45 (d, J = 7, 2H), 7.3 (m, 10H), 6.9 (d, J = 7, 2H), 5.3 (m, 1H), 4.9 (m, 1H), 2.8 (m, 2H), 2,6 (m, 2H), 2.4 (s, 3H), 2.3 (m, 1H), 2.1 (m, 1H), 1.8 (m, 2H). ^{13}C NMR ($CDCl_3$) 160.50, 145.03, 144.95, 140.93, 140.73, 122.77, 122.74, 128.13, 128.08, 127.86, 127.84, 126.86, 126.83, 126.71, 126.67, 125.83, 125.76, 125.56, 125.48, 124.45 (q, J = 270), 124.42 (q, J = 270), 122.61 (q, J = 31), 122.58 (q, J = 31), 115.77, 78.51, 78.32, 75.48, 75.12, 56.81, 56.53, 54.15, 53.88, 41.95, 41.80, 36.42, 36.20, 34.68, 34.64. ^{19}F NMR ($CDCl_3$) −61.84, −61.87. LC/MS 178, 282, 322, 444 (M + 1).

***N*,*N*-Bis-[γ-[4-(trifluoromethyl)phenoxy]-γ-phenylpropyl]-methylamine (12).** Fluoxetine HCl (2.6 g, 7.5 mmol) was treated with 50% NaOH to pH 12 in 13 mL of ether and 13 mL of water. The layers were separated, and the ether layer was evaporated in vacuo to an oil. This fluoxetine free base, crude chlorocompound, **16** (0.96 g, 0.3 mmol), sodium iodide (0.04 g, 0.3 mmol), and 5 mL of DMF were combined and heated at 80 °C for 16 h. Most of the DMF was removed by evaporation in vacuo, and the resultant oil was treated with 5 mL of ethyl acetate and 5 mL of water at pH 12. The ethyl acetate layer was washed twice with water and evaporated in vacuo to an oil, 2.14 g. A portion of the crude oil (0.5 g) was purified by flash chromatography using the Biotage Flash 40 system with a 8 cm pre-packed silica gel column with 30% ethyl acetate in heptane with 1% NH_4OH as the eluent. Combination and concentration of fractions provided an oil, 0.08 g, 91.3% pure by gradient HPLC. ^{1}H NMR ($CDCl_3$) 7.46 (d, 4H), 7.33 (m, 10H), 6.91 (d, 4H), 5.29 (m, 2H), 2.65 (m, 2H), 2.45 (m, 2H), 2.29 (s, 3H), 2.17 (m, 2H), 1.98 (m, 2H). ^{13}C NMR ($CDCl_3$) 160.6, 141.2, 128.7, 127.8, 126.7, 125.7, 124.4 (q, J = 271), 122.7 (q, J = 32.7), 115.7, 78.1, 53.7, 42.2, 36.6. ^{19}F NMR ($CDCl_3$) −61.89. LC/MS 322, 587 (M + 1).

***N*-(3-Phenylpropyl)-*N*-methyl-γ-[4-(trifluoromethyl)-phenoxy]-benzenepropanamine (13).** Fluoxetine HCl (2.0 g, 5.8 mmol) was dissolved in 10 mL of water, and 20 mL of ether was added followed by 5 N NaOH until the pH was 12. The layers were separated and the ether layer was washed with water, dried over sodium sulfate, and evaporated to an oil. The residue was dissolved in 15 mL of toluene and combined with sodium iodide (0.07 g, 0.5 mmol), tetrabutylammonium hydrogen sulfate (0.01 g, 0.3 mmol). 1-Chloro-3-phenylpropane (0.8 mL, 5.7 mmol) was added, and the mixture was refluxed for 2 days. Additional toluene and 10 mL of water was added, and the layers were separated. The organic solution was evaporated to an oil and was purified by preparative HPLC, Zorbax RX-C8, 2.1 × 25 cm, eluted at 22 mL/min with 40% water (containing 0.07% TFA) and 60% acetonitrile. The main peak was collected, and the eluent was concentrated in vacuo. Ether and aqueous NaOH, sufficient to achieve a pH of 12, were added to the residue, and the layers were separated. The ether layer was washed

with water and evaporated to an oil. The residue was dissolved in ethyl acetate, and anhydrous HCl was added. The solvent was evaporated to give ~0.2 g of yellow oil. Its purity by gradient HPLC (retention time 27.4 min) was 92%. HPLC/MS showed ions 162, 266, and 428 (M + 1). ^{1}H NMR ($CDCl_3$) 11.4 (br s, 1H), 7.2 (m, 12H), 6.8 (d, 2H), 5.4 (m, 1H), 3.1 (m, 4H), 2.7 (s, 3H), 2.6 (m, 1H), 2.35 (m, 2H), 2.05 (m, 2H). ^{13}C NMR ($CDCl_3$) 159.49, 139.24, 138.91, 138.77, 128.78, 128.43, 128.22, 128.18, 128.05, 128.03, 126.50 (q, J = 3.6), 126.32, 126.30, 124.07 (q, J = 272), 122.81 (q, J = 33), 115.61, 76.81, 55.70, 54.83, 52.45, 40.18, 39.81, 32.44, 32.33, 32.22, 24.96, 24.80, 20.67. ^{19}F NMR ($CDCl_3$) −61.96.

(*E*)-*N*-(4-Phenyl-but-3-ene-1-yl)-*N*-methyl-γ-[4-(trifluoromethyl)phenoxy]-benzenepropanamine (14). 1,2-Dibromoethane (0.82 mL, 9.5 mmol) was added slowly to magnesium turnings (0.25 g, 10.3 mmol) in 12 mL of anhydrous ether. The mixture was refluxed for 2 h, and the solution was decanted from the excess metal and added to 1-cyclopropylbenzylamine (1.0 g, 6.8 mmol). The resulting mixture was refluxed for 3 h, cooled, and filtered, and the filtrate was washed with three 20 mL portions of water. Evaporation of the ether gave 1.3 g of (*Z*)-4-bromo-1-phenyl-1-butene.[23] In a separate reactor, 2.4 g of fluoxetine HCl (7 mmol) was treated with 20 mL of ether, 10 mL of water, and 2 mL of 5 N NaOH. The ether layer was separated, washed with water, and evaporated to an oil. The fluoxetine and bromobutene were combined as neat liquids and stirred at room temperature for 2 days. The resulting mixture was purified by chromatography on an 8 cm Biotage silica gel column, eluted with ethyl acetate. Fractions rich in the R_f 0.36 spot were combined and evaporated to give 0.40 g of a colorless oil whose purity by gradient HPLC was 99.5%. ^{1}H NMR ($CDCl_3$) 7.5 (m, 12H), 7.05 (d, J = 7, 2H), 6.6 (d, J = 15, 1H), 6.4 (m, 1H), 5.5 (m, 1H), 2.8 (m, 1H), 2.65 (m, 3H), 2.5 (m, 2H), 2.4 (s, 3H), 2.35 (m, 1H), 2.15 (m, 1H). ^{13}C NMR ($CDCl_3$) 160.76, 141.30, 137.64, 130.91, 128.69, 128.63, 128.49, 127.73, 126.98, 126.70 (q, J = 3.6), 125.97, 125.90, 124.54 (q, J = 270), 122.21 (q, J = 32), 115.78, 78.23, 57.36, 53.44, 41.99, 36.51, 30.98. ^{19}F NMR ($CDCl_3$) −61.37. LC/MS 174, 278, 440 (M + 1).

***N*-Methyl-*N*-(phenylmethyl)-γ-[4-(trifluoromethyl)-phenoxy]benzenepropanamine (15).** Fluoxetine HCl (10.0 g, 28.9 mmol) was mixed with 100 mL of methyl *tert*-butyl ether and 70 mL of water. Solid KOH was added until the pH rose to 12. The layers were separated, and the organic layer was dried over sodium sulfate. To the dried solution was added 3.6 mL of benzyl bromide (30.3 mmol) and 4.4 mL of triethylamine (31.8 mmol). The mixture was stirred for 3 h at 45 °C and another 0.36 mL of benzyl bromide (3.0 mmol) was added and the reaction was stirred at 35 °C overnight. The mixture was cooled and, to it was added 50 mL of water and enough solid KOH to give a pH of 13. The layers were separated, and the organic layer was evaporated to an oil. Ethyl acetate (30 mL) was added and evaporated, and this sequence was repeated. The residue was dissolved in 100 mL of ethyl acetate and treated with anhydrous HCl until excess was present. The resulting crystal slurry was stirred for an hour at ambient temperature and filtered, and the product was dried in vacuo at 50 °C to give 9.2 g (73%) of a white solid, mp 155−157 °C. Its purity by gradient HPLC was greater than 99%. ^{1}H NMR (DMSO) 11.4 (br s, 1H), 7.6 (m, 4H), 7.4 (m, 8H), 7.0 (apparent t, 2H), 5.6 (m, 1H), 4.3 (m, 2H), 3.2 (m, 2H), 2.6 (apparent q, 3H), 2.4 (m, 2H).). ^{13}C NMR (DMSO) 160.04, 139.91, 139.73, 131.34, 131.20, 130.23, 130.09, 129.36, 129.27, 128.69, 128.67, 128.09, 126.86, 126.81, 126.04, 126.00, 124.40, (q, J = 270), 121.39, (q, J = 31), 116.18, 76.73, 76.53, 58.12, 57.85, 51.11, 51.03, 39.03, 31.84. ^{19}F NMR ($CDCl_3$) −60.27. LC/MS 134, 400 (M + 1).

1-(3-Chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene (16). Chloro alcohol **4** (5.54 g, 32.5 mmol), 5.26 g *p*-α,α,α-trifluorocresol (32.5 mmol), and 83 mL of THF were combined with stirring. An exotherm to 50 °C was observed upon the addition of 8.51 g of triphenylphosphine (32.5 mmol) and 6.56 g (32.5 mmol) of diisopropyl azodicarboxylate to the solution. The reaction mixture was stirred at ambient temperature; after 21 h, an additional 0.66 g of diisopropyl azodicarboxylate (3.24 mmol) was added. After 24 h, the reaction mixture was evaporated in vacuo to an oil. The crude oil was treated twice with 10 mL of heptane, and the triphenylphosphine oxide was removed by filtration. The heptane solution was evaporated in vacuo to an oil, which contained 36% of the desired product by HPLC area at 260 nm. A portion of the crude oil (1 g) was purified by flash chromatography with 2% ethyl acetate/heptane using the Biotage Flash 40 system with a 15 cm silica gel column, providing 0.53 g after removal of the solvents in vacuo. Its purity by gradient HPLC was 98.1%. R_f 0.21 (2% ethyl acetate/heptane). ^{1}H NMR ($CDCl_3$) 7.35 (m, 7H), 6.92 (d, 2H), 5.44 (q, 1H), 3.80 (m, 1H), 3.60 (m, 1H), 2.49 (m, 1H), 2.23 (m, 1H). ^{13}C NMR ($CDCl_3$) 160.3, 140.0, 128.9, 128.2, 126.8 (q, J = 3.5), 125.8, 124.3 (q, J = 271), 123.0 (q, J = 32.6), 115.8, 76.9, 41.2, 41.0.

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