# Fluorinated Diaryl Sulfides as Serotonin Transporter Ligands: Synthesis, Structure−Activity Relationship Study, and in Vivo Evaluation of Fluorine-18-Labeled Compounds as PET Imaging Agents

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A series of new, fluorine-containing substituted diphenyl sulfides was synthesized to serve as candidate ligands for positron emission tomography (PET) imaging of the serotonin transporter (SERT) and to further probe the structure−activity relationship (SAR) of this class of compounds. Candidate compounds were assayed for their affinities to the monoamine transporters (SERT, norepinephrine transporter (NET), and dopamine transporter (DAT)) in competitive binding experiments in vitro using cloned human transporters. From these in vitro assays, four compounds (**7c**−**f**) were chosen for further evaluation. All four compounds have nanomolar affinity for SERT ($K_i$ 1.46 nM, 1.04 nM,1.83 nM, and 3.58 nM for **7c**, **7d**, **7e**, and **7f**, respectively). The F-18-labeled compounds, **16** and **18a**−**c**, were prepared via a two-step radiosynthesis. Biodistribution studies in rats indicated that the F-18-labeled compounds localized in brain regions with high concentrations of SERT. Furthermore, competition experiments demonstrated that the binding of these radioligands in the rat brain was saturable, specific, and selective to SERT. Specific binding in the rat hypothalamus peaked at 5.6 for ligand **16** and 4.4 for **18b** at 90 min after radioactivity administration. For ligand **18a**, this same ratio was 8.4 at 120 min postinjection, while compound **18c** displayed a lower specific binding ratio of 2.4. In summary, four F-18-labeled ligands were prepared and evaluated as candidate PET imaging agents for SERT. Among these four ligands, three appear to be promising radioligands suitable for the labeling of SERT in vivo, with **18a** providing a higher specific binding in vivo than **16** or **18b**.

## Introduction

The neurotransmitter serotonin (5-HT) is involved in the regulation of many brain functions such as mood, appetite, sleep, pain, and aggressive behavior.[1] The serotonin transporter (SERT), located on the cell bodies and terminals of the 5-HT neurons, is a marker of 5-HT innervation.[2] Alterations in SERT densities have been reported in a number of neuropsychiatric conditions, including major depression, anxiety disorders, schizophrenia, drug abuse, alcoholism, eating disorders, and Alzheimer's and Parkinson's disease.[3−7] Many of the currently available antidepressants are selective serotonin reuptake inhibitors (SSRIs) and are believed to exert their antidepressant effect through inhibition of the SERT.[8] Thus, in vivo imaging of SERT regional brain distribution using the noninvasive positron emission tomography (PET) or Single Photon Emission Computed Tomography (SPECT) provides an important tool to study the role of the 5-HT system in the pathophysiology and treatment of neuropsychiatric disorders.

The road toward the development of useful radioligands for in vivo imaging of SERT has been long and difficult. Many compounds have been tried but failed to show promising imaging properties due to a combination of deficient selectivity, inappropriate kinetics and/or inadequate in vivo binding specificity.[9] Over the past decade, efforts in the development of PET and SPECT imaging agents have been concentrated on three major classes of compounds: the tropane series, the quipazine series, and the pyrroloisoquinoline series. From the tropane series, two SPECT radioligands have reached human applications: [$^{123}$I]$\beta$-CIT and [$^{123}$I]nor-$\beta$-CIT. However, these two SPECT ligands are nonselective and have equal affinities for the dopamine transporter (DAT) and SERT.[10] More recently, Goodman et al. reported the synthesis and characterization of new tropane derivatives, such as [$^{123}$I]ZIENT and others, as putative SPECT or PET imaging agents for SERT.[11,12] Yet the suitability of these new ligands for imaging the SERT in humans remains to be demonstrated.

In the quipazine series, several I-123-, Br-76-, F-18-, and C-11-labeled ligands were reported as potential SPECT or PET imaging agents for SERT.[13−16] However, these agents either displayed relatively low specific binding signal in vivo or brain uptake kinetics that was not optimal for the intended imaging purpose. From the pyrroloisoquinoline series, [$^{11}$C]McN 5652 (Figure 1) became the first successful PET radioligand for the

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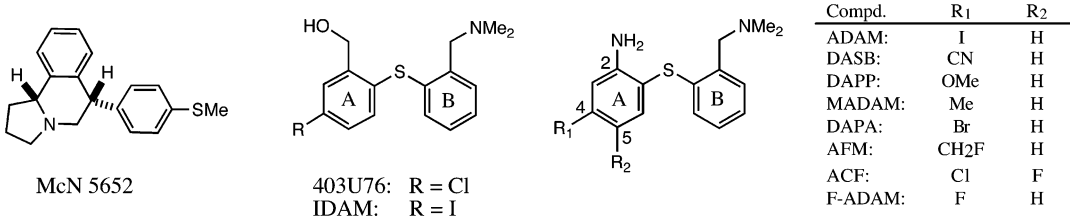
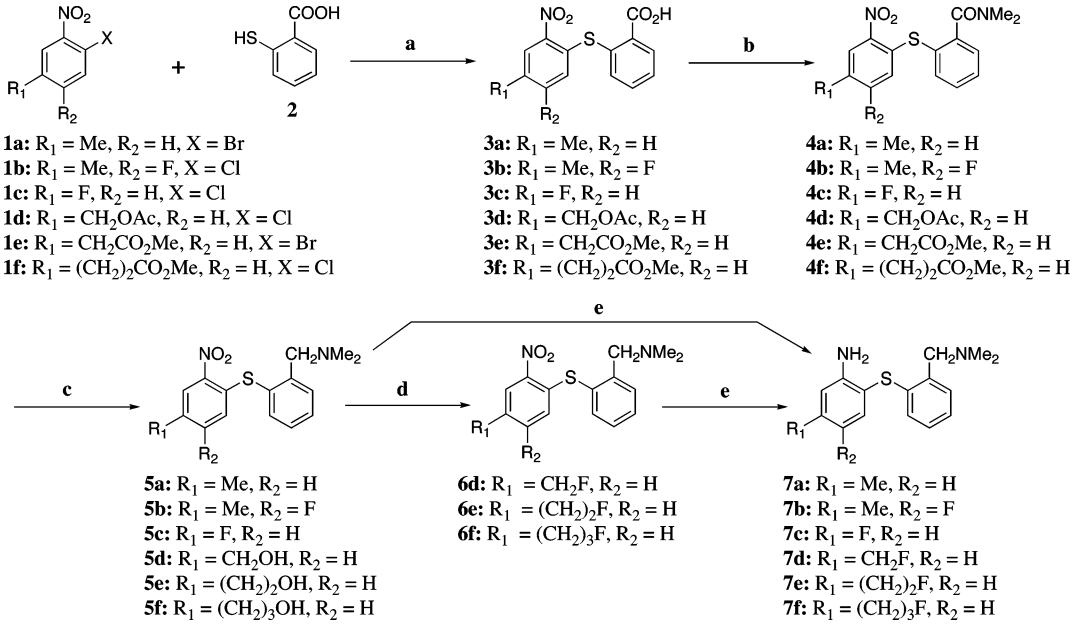



**Figure 1.** Representative ligands for the serotonin transporter (SERT).

**Scheme 1**[a]




[a] Reagents and conditions: (a) $K_2CO_3$, Cu, DMF, 65 °C; (b) 1. $SOCl_2$, 70 °C; 2. $Me_2NH{\cdot}HCl$, $K_2CO_3$, THF, rt; (c). $BH_3{\cdot}THF$, THF, rt; (d) $(MeOCH_2CH_2)_2NSF_3$, $CH_2Cl_2$, rt; (e) $SnCl_2$, HCl, MeOH, rt.

selective imaging of SERT in humans,[17,18] but this first selective SERT radioligand also presented some limitations, such as high nonspecific binding, low specific to nonspecific binding ratios, and slow brain kinetics.[19−22]

In the past few years, a new series of selective SERT ligands have emerged from the substituted diaryl sulfide class of compounds, based on the prototypical structure of the serotonin reuptake inhibitor 403U76 (Figure 1).[23] [$^{123}$I]IDAM was the first SPECT ligand coming from this new class, followed by [$^{123}$I]ADAM.[24−29] From this same class, a large collection of C-11-labeled radioligands has been synthesized and evaluated as potential PET imaging agents. These included [$^{11}$C]DASB, [$^{11}$C]DAPP, [$^{11}$C]-MADAM, [$^{11}$C]DAPA, [$^{11}$C]AFM, [$^{11}$C]AFA, and [$^{11}$C]-AFE (Figure 1).[9,30−40] All these compounds were shown to be selective serotonin transporter ligands, with varying specific to nonspecific binding ratios and brain kinetics in vivo. In nonhuman primates, [$^{11}$C]DASB and [$^{11}$C]AFM were demonstrated to be superior to [$^{11}$C]McN 5652.[9] [$^{11}$C]DASB has since advanced to imaging applications in humans.[33,34,41,42]

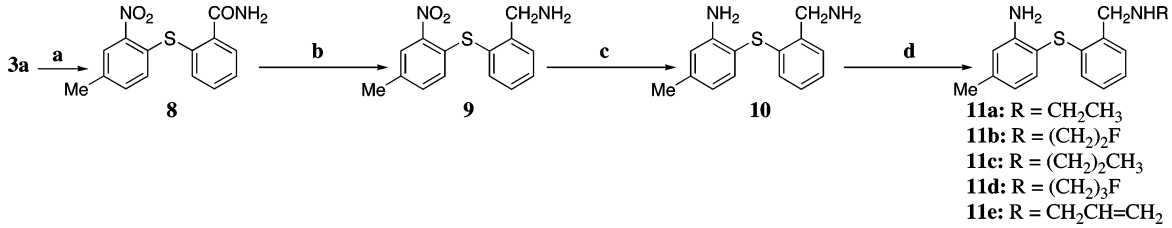
In the development of PET imaging agents, radioligands labeled with the longer-lived isotope F-18 ($t_{1/2}$ 109.8 min vs 20.4 min for C-11) maintain certain advantages, in that they can be used in longer scanning sessions and be transported for off-site imaging applications. As a result, there have been attempts to develop F-18-labeled PET ligands for SERT. In the pyrroloisoquinoline series, efforts were made to prepare [$^{18}$F]fluoromethyl and [$^{18}$F]-fluoroethyl McN 5652.[43−46] However, these two F-18-labeled ligands still gave low signal-to-noise ratios in vivo and thus offered no improvement over [$^{11}$C]McN 5652. In the quipazine series, [$^{18}$F]5-fluoro-6-nitroquipazine was synthesized and shown to lack SERT binding selectivity in vivo.[15] In the substituted diaryl sulfide series, Oya et al. reported the synthesis and characterization of one F-18-labeled compound, [$^{18}$F]-ACF, while Shiue et al. described the synthesis and preliminary evaluation of another, [$^{18}$F]F-ADAM.[47−49]

In our laboratories we have been interested in the development of SERT ligands that can be labeled with either C-11 or F-18 in the same molecule.[50] In this paper we report the synthesis and in vitro pharmacological characterization of a number of fluorinated diaryl sulfides with various substitution patterns to further probe the structure−activity relationship (SAR) of this class of compounds as selective serotonin transporter ligands. Based on the results of this SAR study, four F-18-labeled compounds were prepared and evaluated in rats to assess their potential as PET radioligands to image SERT in vivo.

## Results and Discussion

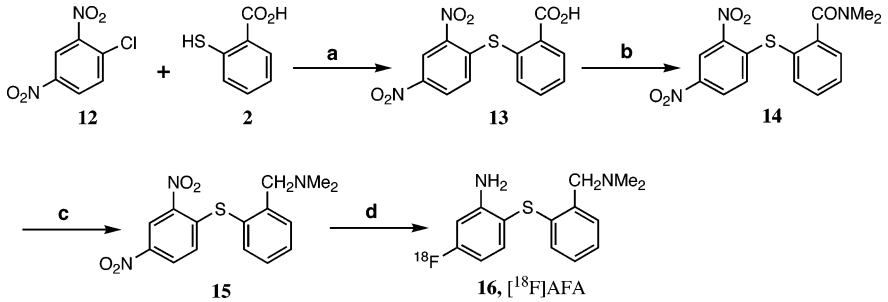
**Chemistry.** The synthesis of various substituted diaryl sulfides (compounds **7a**−**f**) is depicted in Scheme 1. Halogenated nitrobenzenes (**1a**−**f**) were coupled with thiosalicylic acid (**2**) to give benzoic acids **3a**−**f**, which were converted to the amides **4a**−**f** by first reacting with thionyl chloride to produce the acid chlorides, and subsequent reaction of the acid chlorides with *N*,*N*-

**Scheme 2**[a]



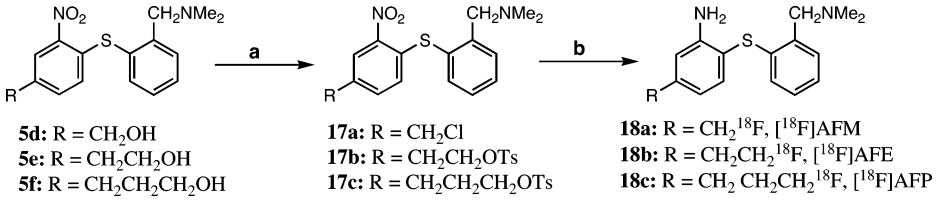

[a] Reagents and conditions: (a) 1. $SOCl_2$, 70 °C, 3 h; 2. $NH_3$, THF, rt, overnight; (b) $BH_3$·THF, THF, 70 °C, 2 h then rt, overnight; (c) $SnCl_2$, HCl, MeOH, rt, overnight; (d) $ICH_2CH_3$, $Br(CH_2)_2CH_3$, $Br(CH_2)_nF$, or allyl bromide, $K_2CO_3$, MeCN, 80 °C, overnight.

**Scheme 3**[a]




[a] Reagents and conditions: (a) $K_2CO_3$, Cu, DMF; (b) 1. $SOCl_2$, 2. $Me_2NH$·HCl, $K_2CO_3$, THF; (c) $BH_3$·THF, THF; (d) 1. $K^{18}F$, K-222, DMSO, 150 °C, 20 min; 2. $Cu(OAC)_2$ or $SnCl_2$, $NaBH_4$, EtOH, 80 °C, 10 min.

**Scheme 4**[a]




[a] Reagents and conditions: (a) 1. $SOCl_2$, 70 °C, 2 h or TsCl, pyridine, $CH_2Cl_2$, 50 °C, 12 h; (b) 1. $K^{18}F$, K-222, MeCN, 80 °C, 15 min; 2. $Cu(OAC)_2$ or $SnCl_2$, $NaBH_4$, EtOH, 80 °C, 10 min.

dimethylamine hydrochloride. Reduction of the amides **4a**−**c** with borane/THF complex gave compounds **5a**−**c**. When compounds **4d**−**f** were subjected to the same reaction conditions, concomitant cleavage of the acetyl protecting group in **4d** or reduction of the ester functionality in **4e**−**f** provided the alcohols **5d**−**f**. Deoxofluorination of compounds **5d**−**f** with bis(2-methoxyethyl)aminosulfur trifluoride led to compounds **6d**−**f**.[51] Finally, reduction of the nitro group in compounds **5a**−**c** and **6d**−**f** with tin(II) chloride under acidic conditions afforded compounds **7a**−**f**.

Preparation of compounds **11a**−**e** is depicted in Scheme 2. Starting from compound **3a**, amide formation with ammonia provided compound **8**, which underwent sequential reduction of the amide and nitro groups to afford the amine **10**. Alkylation of compound **10** with alkyl halides then gave compounds **11a**−**e**.

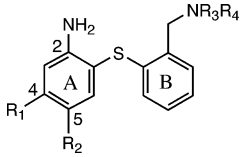
Synthesis of the radiolabeling precursor **15** and preparation of the F-18-labeled compound **16** are shown in Scheme 3. Coupling of 1-chloro-2,4-dinitrobenzene (**12**) with thiosalicylic acid (**2**) gave the benzoic acid **13**, which was converted to the amide **14**. Reduction of the amide afforded the labeling precursor **15**. Preparation of **16** was accomplished in a two-step reaction sequence. First, displacement of the 4-nitro group with F-18 fluoride produced the radiolabeled intermediate, which underwent reduction with $NaBH_4$, with either $Cu(OAc)_2$ or $SnCl_2$ as catalyst. Use of $SnCl_2$ as catalyst generally gave lower overall yield than $Cu(OAc)_2$. When $Cu(OAc)_2$ was used as the catalyst, an overall radiochemical yield of ∼11% was achieved.

Precursor preparation and radiosynthesis of **18a**−**c** are shown in Scheme 4. Alcohols **5d**−**f** were converted to either the benzyl chloride (**17a**) or the tosylates (**17b**−**c**), which served as the radiolabeling precursors. In a manner similar to the preparation of **16**, a two-step radiolabeling sequence provided **18a** ([$^{18}$F]AFM), **18b** ([$^{18}$F]AFE), and **18c** ([$^{18}$F]AFP) in ∼10% or higher overall radiochemical yield.

**In Vitro Binding Assays and Structure**−**Activity Relationship.** The initial patent literature listed the synthesis of a diverse array of substituted diaryl sulfides.[52−54] However, activity data were limited to a small number of compounds. These available activity data indicate that compounds with structure features exemplified by 403U76, IDAM, and ADAM (Figure 1) possess the highest SERT binding affinities. As an in vivo imaging agent, [$^{123}$I]ADAM displays improved qualities over [$^{123}$I]IDAM.[25,27] Therefore, our structure−activity relationship study was focused on the structural scaffold represented by ADAM, with an amino group at the 2-position of ring A and an aminomethyl group at the 2′-position of ring B (Figure 1 and Table 1).

Table 1 lists the in vitro binding data of selected compounds for human cloned monoamine transporters. A survey of these structure−activity data brings forth

**Table 1.** In Vitro Binding Data of Selected Compounds for the Monoamine Transporters




| | | | | | $K_i$ (nM)[a] | | |
|---|---|---|---|---|---|---|---|
| compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | SERT | DAT | NET |
| ADAM | I | H | $CH_3$ | $CH_3$ | 1.07 ± 0.13 | >10 000 | 1352 ± 748.0 |
| DASB | CN | H | $CH_3$ | $CH_3$ | 1.12 ± 0.14 | >10 000 | 5127 ± 1418 |
| **7a** | $CH_3$ | H | $CH_3$ | $CH_3$ | 1.19 ± 0.11 | >10 000 | 320.4 ± 74.0 |
| **7b** | $CH_3$ | F | $CH_3$ | $CH_3$ | 179.3 ± 36.3 | >10 000 | 7036 ± 3356 |
| **7c** | F | H | $CH_3$ | $CH_3$ | 1.46 ± 0.15 | >10 000 | 141.7 ± 47.4 |
| **5d** | $CH_2OH$ | H | $CH_3$ | $CH_3$ | 0.80 ± 0.03 | 3608 ± 926 | 787.4 ± 231.1 |
| **7d** | $CH_2F$ | H | $CH_3$ | $CH_3$ | 1.04 ± 0.13 | >10 000 | 663.8 ± 79.5 |
| **7e** | $(CH_2)_2F$ | H | $CH_3$ | $CH_3$ | 1.83 ± 0.07 | >10 000 | 946.2 ± 222.5 |
| **7f** | $(CH_2)_3F$ | H | $CH_3$ | $CH_3$ | 3.58 ± 0.28 | >10 000 | 505.0 ± 73.8 |
| **10** | $CH_3$ | H | H | H | 30.0 ± 4.5 | 5296 ± 1551 | 4440 ± 1189 |
| **11a** | $CH_3$ | H | H | $CH_2CH_3$ | 70.2 ± 5.4 | 2121 ± 431 | 7552 ± 1407 |
| **11b** | $CH_3$ | H | H | $(CH_2)_2F$ | 71.3 ± 25.2 | 4426 ± 1526 | 3910 ± 1199 |
| **11c** | $CH_3$ | H | H | $(CH_2)_2CH_3$ | 2177 ± 205 | 3549 ± 680 | >10 000 |
| **11d** | $CH_3$ | H | H | $(CH_2)_3F$ | 518 ± 182 | >10 000 | 4332 ±1171 |
| **11e** | $CH_3$ | H | H | $CH_2CH{=}CH_2$ | 80.9 ± 14.5 | 2908 ± 504 | 3823 ± 1071 |

[a] Inhibition constants ($K_i$) presented are the mean ± SD of four separate determinations.

several noteworthy points: (1) Substitution at the 4-position of ring A in the diphenyl sulfide structure produces high affinity compounds (**7a**, **7c**−**e**). Results from the present study and others in the literature indicate that the electronic nature of the substituent in this position has no effect on the affinity of the compounds for SERT, with groups as diverse as electron-donating (methoxy group in DAPP, Figure 1, $K_i$ 1.89 nM) to highly electron-withdrawing (e.g. cyano and fluorine groups in DASB, $K_i$ 1.10 nM, and **7c**, $K_i$ 1.46 nM) all giving high affinity ligands for SERT.[27,30,31,35,37,55] (2) Alkyl groups from methyl to fluoropropyl are well tolerated at the 4-position of ring A, although the affinity for SERT decreases as the chain becomes longer. The SERT affinity order follows: methyl (**7a**, $K_i$ 1.19 nM) ∼ fluoromethyl (**7d**, $K_i$ 1.04 nM) > fluoroethyl (**7e**, $K_i$ 1.83 nM) > fluoropropyl (**7f**, $K_i$ 3.58 nM). (3) The 4-position of ring A appears to accommodate certain steric bulk. For example, substitution with iodine produces the high affinity ligand ADAM ($K_i$ 1.07 nM), and substitution with fluoropropyl group gives **7f** ($K_i$ 3.58 nM). However, the ligand's affinity for SERT decreases with increasing bulk, as evidenced by the lower affinity of **7f** compared with **7a** ($K_i$ 1.19 nM), **7d** ($K_i$ 1.04 nM), and **7e** ($K_i$ 1.83 nM). Emond et al. reported that placement of an iodovinyl group at the 4-position of ring A resulted in a ligand with only moderate SERT affinity ($K_i$ 19.3 nM).[55] (4) Substituent placed at the 5-position of ring A greatly reduces SERT affinity. For example, compound **7b** displays a SERT $K_i$ (179.3 nM) more than 100 times higher than that of compound **7a** (1.19 nM), although its selectivity is not much affected. Oya et al. reported ACF, with a chlorine at the 4-position and a fluorine at the 5-position of ring A (Figure 1), to be a high affinity SERT ligand ($K_i$ 0.05 nM for SERT) as assayed using LLC-PK1 cells overexpressing SERT and the radioligand [$^{125}$I]IDAM. However, in vivo study revealed a low specific binding of [$^{18}$F]ACF, probably indicative of a low SERT affinity in vivo.[47] Another ligand, [$^{18}$F]5-fluoro-ADAM, with a fluorine substituent at the 5-position of ring A and no substituent at the 4-position, also gave low specific binding in vivo.[56] Taken together, these and other published results indicate that substitution at the 4-position of ring A in the diaryl sulfide skeleton is beneficial to the maintenance of high SERT affinity in vitro and/or high specific binding in vivo, while substitution at the 5-position is detrimental, although the latter observation is based on a limited number of experimental results and needs to be confirmed by a larger SAR data set.

Choi et al. have shown that placement of an alkyl, a substituted alkyl, or an arylcarbonyl group at the aniline functionality of ring A in ADAM gives rise to ligands with low SERT affinity.[57] Replacement of one methyl substituent on the *N*,*N*-dimethylbenzenemethanamine moiety in ring B with a fluoropropyl group also results in a compound with lower SERT affinity ($K_i$ 19.3 nM).[55] On the other hand, we and others have shown that monomethylation at the benzenemethanamine moiety produces compounds with high SERT affinity.[37,55,57,58] To further elucidate the structure−activity relationship at this position, the monosubstituted as well as unsubstituted benzenemethanamines (compounds **10** and **11a**−**e**) were prepared and assayed. Placement of an ethyl, fluoroethyl, propyl, fluoropropyl, or allyl group at this site affords moderate (**11a**, **11b**, and **11e**, with SERT $K_i$ of 70.2, 71.3, and 80.9 nM, respectively) or low affinity (**11c** and **11d**, $K_i$ 2177 and 518 nM) SERT ligands, indicating a strict steric and/or electronic requirement at this position. *N*-Methyl or *N*,*N*-dimethyl substitution at this position appears to be optimal in retaining high affinity for SERT.

As summarized in Table 1, results from structure−activity relationship study indicate that compounds **7c**−**f** possess the dual properties of high in vitro binding affinity for SERT and the possibility for F-18 labeling. Therefore, they were chosen for radiolabeling with F-18 and the labeled compounds, **16** and **18a**−**c**, were evaluated in biodistribution study in rats for their ability to bind the SERT in vivo.

**Table 2.** Biodistribution of F-18-Labeled Radioligands **16** and **18a**−**c** in Male Sprague−Dawley Rats (%ID/g, mean ± SD)

| time | blood | cerebellum | frontal cortex | striatum | hippocampus | hypothalamus | thalamus | specific binding[a] (hypothalamus) |
|---|---|---|---|---|---|---|---|---|
| | | | | **16** | | | | |
| 10 min | 0.27 ± 0.01 | 0.38 ± 0.09 | 0.81 ± 0.26 | 0.65 ± 0.18 | 0.54 ± 0.17 | 0.73 ± 0.26 | 0.72 ± 0.24 | 0.89 ± 0.28 |
| 30 min | 0.16 ± 0.01 | 0.20 ± 0.01 | 0.65 ± 0.08 | 0.58 ± 0.05 | 0.48 ± 0.02 | 0.66 ± 0.05 | 0.69 ± 0.03 | 2.23 ± 0.13 |
| 60 min | 0.08 ± 0.01 | 0.07 ± 0.01 | 0.28 ± 0.05 | 0.26 ± 0.02 | 0.23 ± 0.04 | 0.38 ± 0.03 | 0.34 ± 0.05 | 4.09 ± 0.19 |
| 90 min | 0.08 ± 0.00 | 0.04 ± 0.01 | 0.20 ± 0.02 | 0.19 ± 0.01 | 0.18 ± 0.01 | 0.30 ± 0.06 | 0.23 ± 0.05 | 5.61 ± 0.74 |
| 120 min | 0.07 ± 0.01 | 0.04 ± 0.00 | 0.11 ± 0.02 | 0.11 ± 0.02 | 0.10 ± 0.01 | 0.17 ± 0.01 | 0.16 ± 0.02 | 4.92 ± 0.83 |
| | | | | **18a** | | | | |
| 10 min | 0.37 ± 0.04 | 0.33 ± 0.04 | 0.82 ± 0.14 | 0.69 ± 0.15 | 0.51 ± 0.07 | 0.70 ± 0.08 | 0.72 ± 0.13 | 0.98 ± 0.22 |
| 30 min | 0.18 ± 0.02 | 0.23 ± 0.03 | 0.99 ± 0.20 | 0.83 ± 0.12 | 0.64 ± 0.12 | 0.82 ± 0.16 | 0.88 ± 0.06 | 2.27 ± 0.43 |
| 60 min | 0.10 ± 0.04 | 0.13 ± 0.02 | 0.71 ± 0.18 | 0.57 ± 0.12 | 0.45 ± 0.09 | 0.71 ± 0.14 | 0.67 ± 0.15 | 4.56 ± 0.45 |
| 90 min | 0.08 ± 0.03 | 0.08 ± 0.01 | 0.52 ± 0.19 | 0.45 ± 0.17 | 0.36 ± 0.12 | 0.58 ± 0.13 | 0.50 ± 0.15 | 5.81 ± 0.96 |
| 120 min | 0.04 ± 0.00 | 0.07 ± 0.02 | 0.38 ± 0.09 | 0.42 ± 0.10 | 0.28 ± 0.05 | 0.55 ± 0.08 | 0.56 ± 0.10 | 8.37 ± 0.18 |
| | | | | **18b** | | | | |
| 10 min | 0.25 ± 0.01 | 0.28 ± 0.02 | 0.62 ± 0.08 | 0.51 ± 0.05 | 0.38 ± 0.03 | 0.51 ± 0.05 | 0.58 ± 0.08 | 0.96 ± 0.29 |
| 30 min | 0.13 ± 0.03 | 0.13 ± 0.01 | 0.32 ± 0.01 | 0.33 ± 0.01 | 0.27 ± 0.04 | 0.41 ± 0.03 | 0.39 ± 0.01 | 2.22 ± 0.45 |
| 60 min | 0.07 ± 0.02 | 0.06 ± 0.01 | 0.19 ± 0.04 | 0.21 ± 0.05 | 0.17 ± 0.04 | 0.24 ± 0.04 | 0.27 ± 0.04 | 3.35 ± 0.43 |
| 90 min | 0.04 ± 0.01 | 0.03 ± 0.01 | 0.08 ± 0.01 | 0.10 ± 0.02 | 0.09 ± 0.01 | 0.14 ± 0.02 | 0.17 ± 0.02 | 4.36 ± 0.80 |
| 120 min | 0.02 ± 0.01 | 0.02 ± 0.00 | 0.06 ± 0.00 | 0.08 ± 0.01 | 0.07 ± 0.00 | 0.10 ± 0.01 | 0.13 ± 0.02 | 4.50 ± 0.90 |
| | | | | **18c** | | | | |
| 10 min | 0.18 ± 0.02 | 0.31 ± 0.08 | 0.47 ± 0.15 | 0.41 ± 0.09 | 0.36 ± 0.07 | 0.42 ± 0.09 | 0.44 ± 0.10 | 0.34 ± 0.12 |
| 30 min | 0.15 ± 0.07 | 0.14 ± 0.01 | 0.21 ± 0.01 | 0.21 ± 0.02 | 0.19 ± 0.01 | 0.21 ± 0.02 | 0.28 ± 0.01 | 0.57 ± 0.17 |
| 60 min | 0.14 ± 0.06 | 0.07 ± 0.00 | 0.12 ± 0.01 | 0.11 ± 0.02 | 0.13 ± 0.01 | 0.13 ± 0.02 | 0.16 ± 0.01 | 0.85 ± 0.27 |
| 90 min | 0.08 ± 0.06 | 0.03 ± 0.00 | 0.05 ± 0.01 | 0.08 ± 0.00 | 0.07 ± 0.00 | 0.10 ± 0.00 | 0.10 ± 0.02 | 1.85 ± 0.28 |
| 120 min | 0.04 ± 0.00 | 0.03 ± 0.00 | 0.08 ± 0.03 | 0.08 ± 0.01 | 0.08 ± 0.01 | 0.10 ± 0.01 | 0.10 ± 0.01 | 2.40 ± 0.25 |

[a] Specific binding in the hypothalamus is defined as [(%ID/g in hypothalamus − %ID/g in cerebellum)/%ID/g in cerebellum].

**Table 3.** Regional Uptake of F-18-Labeled Compounds **16** and **18a**−**c** in Control and Pretreated Rats[a]

| condition | blood | cerebellum | frontal cortex | striatum | hippocampus | hypothalamus | thalamus |
|---|---|---|---|---|---|---|---|
| | | | | **16** | | | |
| control | 0.10 ± 0.03 | 0.08 ± 0.00 | 0.34 ± 0.04 | 0.29 ± 0.04 | 0.24 ± 0.03 | 0.36 ± 0.05 | 0.42 ± 0.11 |
| **7c** | 0.07 ± 0.04 | 0.06 ± 0.04 | 0.14 ± 0.02 | 0.12 ± 0.02 | 0.13 ± 0.02 | 0.13 ± 0.01 | 0.15 ± 0.02 |
| citalopram | 0.08 ± 0.00 | 0.06 ± 0.00 | 0.11 ± 0.01 | 0.10 ± 0.01 | 0.11 ± 0.01 | 0.10 ± 0.01 | 0.13 ± 0.02 |
| nisoxetine | 0.10 ± 0.03 | 0.09 ± 0.01 | 0.36 ± 0.08 | 0.31 ± 0.06 | 0.28 ± 0.04 | 0.48 ± 0.15 | 0.47 ± 0.13 |
| GBR12935 | 0.09 ± 0.01 | 0.09 ± 0.01 | 0.33 ± 0.06 | 0.28 ± 0.00 | 0.28 ± 0.04 | 0.43 ± 0.03 | 0.36 ± 0.08 |
| | | | | **18a** | | | |
| control | 0.13 ± 0.01 | 0.12 ± 0.02 | 0.76 ± 0.16 | 0.67 ± 0.12 | 0.52 ± 0.11 | 0.72 ± 0.08 | 0.64 ± 0.06 |
| **7d** | 0.11 ± 0.01 | 0.09 ± 0.02 | 0.12 ± 0.04 | 0.14 ± 0.01 | 0.13 ± 0.05 | 0.17 ± 0.02 | 0.17 ± 0.03 |
| citalopram | 0.12 ± 0.03 | 0.08 ± 0.02 | 0.11 ± 0.02 | 0.12 ± 0.04 | 0.13 ± 0.01 | 0.18 ± 0.03 | 0.16 ± 0.03 |
| nisoxetine | 0.11 ± 0.02 | 0.13 ± 0.02 | 0.72 ± 0.25 | 0.58 ± 0.18 | 0.47 ± 0.07 | 0.73 ± 0.00 | 0.65 ± 0.05 |
| GBR12935 | 0.11 ± 0.01 | 0.13 ± 0.01 | 0.76 ± 0.16 | 0.70 ± 0.05 | 0.59 ± 0.04 | 0.87 ± 0.03 | 0.74 ± 0.01 |
| | | | | **18b** | | | |
| control | 0.06 ± 0.00 | 0.08 ± 0.00 | 0.16 ± 0.02 | 0.21 ± 0.03 | 0.18 ± 0.01 | 0.30 ± 0.05 | 0.24 ± 0.03 |
| **7e** | 0.06 ± 0.02 | 0.07 ± 0.02 | 0.10 ± 0.00 | 0.11 ± 0.02 | 0.11 ± 0.01 | 0.15 ± 0.04 | 0.14 ± 0.01 |
| citalopram | 0.08 ± 0.02 | 0.06 ± 0.00 | 0.08 ± 0.00 | 0.09 ± 0.01 | 0.09 ± 0.00 | 0.12 ± 0.00 | 0.11 ± 0.01 |
| nisoxetine | 0.06 ± 0.01 | 0.07 ± 0.01 | 0.19 ± 0.01 | 0.21 ± 0.04 | 0.17 ± 0.00 | 0.33 ± 0.02 | 0.29 ± 0.02 |
| GBR12935 | 0.06 ± 0.02 | 0.06 ± 0.02 | 0.17 ± 0.06 | 0.20 ± 0.07 | 0.18 ± 0.06 | 0.32 ± 0.09 | 0.25 ± 0.10 |
| | | | | **18c** | | | |
| control | 0.09 ± 0.01 | 0.08 ± 0.02 | 0.16 ± 0.09 | 0.13 ± 0.02 | 0.16 ± 0.04 | 0.16 ± 0.03 | 0.15 ± 0.03 |
| **7f** | 0.07 ± 0.02 | 0.08 ± 0.00 | 0.08 ± 0.00 | 0.08 ± 0.01 | 0.08 ± 0.00 | 0.10 ± 0.00 | 0.10 ± 0.02 |
| citalopram | 0.09 ± 0.02 | 0.08 ± 0.02 | 0.16 ± 0.05 | 0.12 ± 0.02 | 0.11 ± 0.02 | 0.13 ± 0.02 | 0.15 ± 0.02 |
| nisoxetine | 0.08 ± 0.01 | 0.08 ± 0.02 | 0.13 ± 0.03 | 0.13 ± 0.04 | 0.16 ± 0.04 | 0.15 ± 0.05 | 0.15 ± 0.04 |
| GBR12935 | 0.09 ± 0.02 | 0.09 ± 0.00 | 0.15 ± 0.00 | 0.17 ± 0.03 | 0.16 ± 0.04 | 0.17 ± 0.04 | 0.18 ± 0.03 |

[a] Uptake is expressed as %ID/g. Data presented are mean ± SD for each group ($n = 3$ animals per group). Blocking agents (2 mg/kg each) were given iv 10−15 min before radioligand, and animals sacrificed 60 min after.

**In Vivo Evaluation.** Tables 2 and 3 list the results from biodistribution studies in rats. All four labeled compounds displayed excellent entry into the rat brain and localization in SERT-rich brain regions such as the thalamus, hypothalamus, frontal cortex, striatum, and hippocampus (Table 2). In the brain, compound **18a** displayed the highest specific binding in vivo, with the specific binding ratio in the hypothalamus reaching 8.4 at 120 min after injection. Compounds **16** and **18b** showed similar brain uptake and specific binding to the SERT, with **16** giving slightly higher specific binding ratio in rats (5.6 in the hypothalamus, compared with 4.4 for **18b** at 90 min postinjection). On the other hand, compound **18c** displayed lower specific binding in rats, with ratios of 1.9 and 2.4, respectively, in the hypothalamus at 90 and 120 min postinjection.

To further demonstrate the in vivo binding specificity and selectivity of these new F-18-labeled compounds, separate groups of rats were pretreated with the cold compound, citalopram, nisoxetine, or GBR 12935 (2 mg/kg each) in saline. The rats were sacrificed 60 min after administration of the radioligand. Regional brain uptake, expressed as %ID/g, was determined for each pretreatment group and compared with the results from a control group of rats treated with saline (Table 3). Specific binding, calculated by the formula: specific

**Table 4.** Specific Binding of Compounds **16** and **18a**−**c** in Control and Pretreated Rats[a]

| condition | frontal cortex | striatum | hippocampus | hypothalamus | thalamus |
|---|---|---|---|---|---|
| | | | **16** | | |
| control | 3.33 ± 0.33 | 2.79 ± 0.44 | 2.17 ± 0.32 | 4.02 ± 0.37 | 4.07 ± 0.41 |
| **7c** | 0.53 ± 0.18 | 0.37 ± 0.10 | 0.55 ± 0.10 | 0.62 ± 0.13 | 0.81 ± 0.15 |
| citalopram | 0.64 ± 0.17 | 0.60 ± 0.22 | 0.81 ± 0.13 | 0.65 ± 0.17 | 0.98 ± 0.17 |
| nisoxetine | 2.88 ± 0.92 | 2.45 ± 0.27 | 1.96 ± 0.51 | 3.82 ± 0.96 | 3.53 ± 0.21 |
| GBR12935 | 2.81 ± 0.49 | 2.56 ± 0.45 | 2.21 ± 0.50 | 4.30 ± 0.60 | 4.57 ± 0.81 |
| | | | **18a** | | |
| control | 4.89 ± 0.68 | 4.40 ± 0.53 | 3.23 ± 0.41 | 5.05 ± 0.37 | 4.33 ± 0.72 |
| **7d** | 0.31 ± 0.21 | 0.53 ± 0.31 | 0.45 ± 0.31 | 0.84 ± 0.27 | 0.85 ± 0.15 |
| citalopram | 0.36 ± 0.15 | 0.52 ± 0.15 | 0.67 ± 0.24 | 1.37 ± 0.50 | 1.05 ± 0.12 |
| nisoxetine | 4.02 ± 0.54 | 3.59 ± 0.72 | 2.72 ± 0.03 | 5.24 ± 0.10 | 4.71 ± 0.49 |
| GBR12935 | 3.83 ± 0.02 | 4.37 ± 0.93 | 3.51 ± 0.74 | 5.30 ± 0.39 | 4.38 ± 0.10 |
| | | | **18b** | | |
| control | 1.62 ± 0.37 | 2.36 ± 0.27 | 1.88 ± 0.17 | 3.92 ± 0.42 | 3.85 ± 0.35 |
| **7e** | 0.48 ± 0.38 | 0.61 ± 0.19 | 0.65 ± 0.26 | 1.21 ± 0.26 | 1.06 ± 0.36 |
| citalopram | 0.31 ± 0.03 | 0.50 ± 0.21 | 0.54 ± 0.04 | 1.00 ± 0.10 | 0.89 ± 0.22 |
| nisoxetine | 1.82 ± 0.65 | 2.10 ± 0.59 | 1.63 ± 0.61 | 4.00 ± 1.08 | 3.56 ± 1.36 |
| GBR12935 | 1.98 ± 0.37 | 2.62 ± 0.54 | 2.18 ± 0.32 | 3.85 ± 1.26 | 3.38 ± 0.69 |
| | | | **18c** | | |
| control | 0.97 ± 0.77 | 0.65 ± 0.21 | 1.03 ± 0.18 | 1.04 ± 0.04 | 0.89 ± 0.16 |
| **7f** | 0.05 ± 0.07 | 0.07 ± 0.04 | 0.03 ± 0.03 | 0.26 ± 0.09 | 0.35 ± 0.32 |
| citalopram | 0.84 ± 0.27 | 0.45 ± 0.24 | 0.32 ± 0.04 | 0.66 ± 0.47 | 0.74 ± 0.09 |
| nisoxetine | 0.72 ± 0.19 | 0.58 ± 0.15 | 1.02 ± 0.20 | 0.84 ± 0.26 | 0.88 ± 0.03 |
| GBR12935 | 0.64 ± 0.05 | 0.84 ± 0.35 | 0.77 ± 0.39 | 0.87 ± 0.41 | 0.98 ± 0.38 |

[a] Specific binding is defined as [(%ID/g in the region of interest − %ID/g in the cerebellum)/%ID/g in the cerebellum]. Data presented are mean ± SD for each group (three animals per group).

binding = [(activity in the region of interest − activity in the cerebellum)/activity in the cerebellum], was determined for all SERT-rich regions and listed in Table 4. In rats pretreated with either the cold compound or the selective serotonin reuptake inhibitor citalopram, there was a significant reduction in the uptake of the radioligands in SERT-rich brain regions, while the uptake in the cerebellum, a region with negligible SERT, was little affected. As a result, significant reductions of specific binding were observed in all SERT-containing regions such as hypothalamus, thalamus, frontal cortex, striatum, and hippocampus (Tables 3 and 4). For ligand **16** ([$^{18}$F]AFA or ([$^{18}$F]F-ADAM), specific binding was reduced by 63% to 84% in these regions in the cold compound-treated rats and by 75% to 87% in the citalopram-treated animals. For ligand **18a** ([$^{18}$F]-AFM), specific binding decreased by 80% to 94% in the cold compound-treated group and by 73% to 93% in the citalopram-treated group. For ligand **18b** ([$^{18}$F]AFE), specific binding decreased by 64% to 74% in the cold compound-treated rats and by 71% to 81% in the citalopram-treated animals (Table 4). As for ligand **18c**, there was a 61 to 97% reduction in specific binding when the rats were pretreated with the cold compound **7f**, whereas these reductions were generally lower when the rats were pretreated with citalopram (ranging from 13% in the cortex to 69% in the hippocampus). On the other hand, there were no significant changes in either brain uptake or specific binding in rats pretreated with nisoxetine, a selective norepinephrine reuptake inhibitor, or GBR 12935, a selective dopamine reuptake inhibitor (Table 4). In summary, results from these in vivo competition experiments indicate that the binding of ligands **16** and **18a**−**c** in the rat brain is not only specific, but also selective for the SERT. Taken together, in vitro and in vivo pharmacological studies demonstrate that all four F-18-labeled compounds are selective radioligands suitable for the in vivo investigation of SERT.

Shiue et al. have reported the biodistribution study of compound **16** (termed [$^{18}$F]F-ADAM) in rats and found the specific binding in the hypothalamus reaching ~11 at 120 min postinjection, while our data indicated that this ratio was ~5.[49] It is not clear what causes this discrepancy. We have conducted experiments in rats and baboons for the C-11-labeled counterparts of compounds **16**, **18a**, and **18b** (termed [$^{11}$C]AFA, [$^{11}$C]AFM, and [$^{11}$C]AFE).[38−40] The results from these studies are consistent with the data obtained with the F-18-labeled compounds. For example, at 90 min after tracer injection, [$^{11}$C]AFA ([$^{11}$C]**16**) displays a specific binding of 5.4 in the hypothalamus vs 5.6 for compound **16**.[39] In baboons, [$^{11}$C]AFA ([$^{11}$C]**16**) and [$^{11}$C]AFE ([$^{11}$C]**18b**) display similar specific binding signals that are lower than those of [$^{11}$C]AFM ([$^{11}$C]**18a**),[38] a result that is expected from the findings of the present study, which show that radioligands **16** ([$^{18}$F]AFA) and **18b** ([$^{18}$F]-AFE) possess similar specific binding ratios in rats that are lower than those of **18a** ([$^{18}$F]AFM).

Results from the literature indicate that among the F-18-labeled PET ligands for SERT, [$^{18}$F]ACF (Figure 1) displays specific binding similar to that for **18c**, but lower than those of **16**, **18a**, or **18b**.[47] For example, at 120 min after tracer injection, specific binding in the rat hypothalamus is 2.2 for [$^{18}$F]ACF, 2.4 for **18c**, 4.9 for **16**, 8.4 for **18a**, and 4.5 for **18b** (Table 2). The other F-18-labeled SERT ligand, [$^{18}$F]fluoromethyl McN 5652, displays a specific binding of 3.9 in the hypothalamus at 90 min after ligand injection,[59] which is higher than that from **18c** (1.9) or [$^{18}$F]ACF, but lower than those from **16** (5.6), **18a** (5.8), and **18b** (4.4) (Table 2). In PET imaging study in a piglet, [$^{18}$F]fluoromethyl McN 5652 displays a slightly faster brain uptake kinetics, but lower specific binding signals than [$^{11}$C]McN 5652.[46] On the other hand, PET imaging studies in baboons have shown that [$^{11}$C]**16** and [$^{11}$C]**18b** display specific binding signals similar to those of [$^{11}$C]McN 5652, but with a much faster uptake kinetics, while [$^{11}$C]**18a** possesses

a slightly faster uptake kinetics and much higher specific binding signals than [$^{11}$C]McN 5652.[9,38–40] The equilibrium specific-to-nonspecific binding coefficients ($V_3''$), as a quantitative measure of specific binding signal, are 1.04 for [$^{11}$C]McN 5652, 1.10 for ([$^{11}$C]**16**, 1.07 for [$^{11}$C]**18b**, and 2.31 for [$^{11}$C]**18a**, respectively, in the baboon thalamus.[38] From these published data it can be expected that ligands **16**, **18a**, and **18b** will provide better specific binding signals than either [$^{18}$F]ACF or [$^{18}$F]fluoromethyl McN 5652.

In summary, four fluorinated diaryl sulfides were identified as selective and potent ligands for the serotonin transporters as a result of the present structure–activity relationship study. These four ligands were labeled with the positron-emitting isotope F-18, and the radiolabeled compounds, **16** and **18a**–**c**, were evaluated as candidate radioligands for positron emission tomography imaging of SERT. Biodistribution studies in rats demonstrate that ligands **16** and **18a**–**b** display high brain uptake and high specific binding in vivo, while ligand **18c** shows lower specific binding. Competition experiments reveal that the F-18-labeled ligands **16** and **18a**–**c** display high SERT binding selectivity and specificity in vivo. In conclusion, results from these studies indicate that compounds **16** and **18a**–**b** are promising PET radioligands for the in vivo imaging of SERT. The current data also suggest that compound **18a** might be a better PET imaging agent than **16** or **18b**, as it provides higher specific binding signals in rats. However, other parameters, such as blood metabolism, brain uptake kinetics, and nonspecific binding of the radioligands, are also important factors in the evaluation and selection of PET imaging agents. A comprehensive PET imaging study in nonhuman primates, with brain and blood measurements and full kinetic modeling, is needed to better assess the merits and suitability of these new F-18 ligands to image the SERT in vivo.

## Experimental Section

**General.** All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. When reactions were worked up by extraction with dichloromethane ($CH_2Cl_2$), chloroform ($CHCl_3$), ethyl acetate (EtOAc), or ethyl ether ($Et_2O$), organic solutions were dried with anhydrous $MgSO_4$ and concentrated with a rotary evaporator under reduced pressure. Reactions requiring anhydrous conditions were carried out in oven-dried glassware under an inert atmosphere of nitrogen. Anhydrous $Et_2O$ and THF were prepared by distilling over Na/benzophenone. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Column chromatography was performed using silica gel 60, 230–400 mesh (Aldrich). Unless otherwise noted, $^1$H NMR spectra were recorded on a Bruker DRX400 spectrometer at 400 MHz, with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard (0 ppm). Mass spectra were run on a JMS-110HX spectrometer. Elemental analyses were performed at Midwest Microlab, Indianapolis, IN.

**2-[(4-Methyl-2-nitrophenyl)thio]benzoic Acid (3a).** A mixture of 4-bromo-3-nitrotoluene (**1a**, 4.54 g, 21 mmol), thiosalicylic acid (**2**, 3.1 g, 20 mmol), Cu powder (365 mg, 5.74 mmol), and $K_2CO_3$ (6.4 g, 46.4 mmol) in DMF (50 mL) was heated at 65 °C overnight, cooled to room temperature, and poured to ice–water. The mixture was filtered through a layer of Celite. The filtrate was made acidic with 6 N HCl and extracted with $CH_2Cl_2$ (70 mL × 3). The combined organic layers were washed with $H_2O$, dried, and concentrated. The crude product was crystallized from EtOH/$H_2O$ to provide the title compound as a yellowish solid (4.97 g, 86%), mp 189–191 °C. $^1$H NMR: $\delta$ 8.13 (dd, 1H, $J$ = 1.6, 7.7 Hz), 7.93 (s, 1H), 7.51 (dd, 1H, $J$ = 1.6, 7.6 Hz), 7.44 (dt, 1H, $J$ = 1.2, 7.6 Hz), 7.25–7.35 (m, 2H), 7.13 (d, 1H, $J$ = 8.1 Hz), 2.47 (s, 3H). Anal. ($C_{14}H_{11}NO_4S$) C, H, N.

**2-[(5-Fluoro-4-methyl-2-nitrophenyl)thio]benzoic Acid (3b).** In an analogous manner the title compound was prepared from 4-chloro-2-fluoro-5-nitrotoluene (**1b**) in 61% yield as a yellowish solid, mp 167–169 °C. $^1$H NMR: $\delta$ 8.16–8.04 (m, 2H), 7.57–7.55 (m, 3H), 6.61(d, 1H, $J$ = 10.0 Hz), 2.31 (s, 3H). Anal. ($C_{14}H_{10}FNO_4S\cdot0.2H_2O$) C, H, N.

**2-[(4-Fluoro-2-nitrophenyl)thio]benzoic Acid (3c).** In an analogous manner the title compound was prepared from 2-chloro-5-fluoronitrobenzene (**1c**) in 40% yield as a yellowish solid, mp 167–168 °C. $^1$H NMR: $\delta$ 8.13 (dd, 1H, $J$ = 1.2, 7.7 Hz), 7.86 (dd, 1H, $J$ = 2.3, 8.0 Hz), 7.45–7.58 (m, 2H), 7.30–7.38 (m, 1H), 7.18–7.25 (m, 2H). Anal. ($C_{13}H_8FNO_4S$) C, H, N.

**2-[[4-[(Acetyloxy)methyl]-2-nitrophenyl]thio]benzoic Acid (3d).** In an analogous manner the title compound was prepared from 4-chloro-3-nitrobenzyl acetate (**1d**) in 39% yield as a yellowish solid, mp 150–151 °C. $^1$H NMR: $\delta$ 8.16 (d, 1H, $J$ = 1.1 Hz), 8.12 (dd, 1H, $J$ = 1.1, 7.2 Hz), 7.60–7.38 (m, 4H), 7.08 (d, 1H, $J$ = 8.3 Hz), 5.15 (s, 2H), 2.15 (s, 3H). Anal. ($C_{16}H_{13}NO_6S$) C, H, N.

**4-[(2-Carboxyphenyl)thio]-3-nitrobenzeneacetic Acid α-Methyl Ester (3e).** In an analogous manner the title compound was prepared from methyl 4-bromo-3-nitrophenylacetate (**1e**) in 56% yield as a yellowish solid, mp 135–136 °C. $^1$H NMR: $\delta$ 8.12–8.04 (m, 2H), 7.54–7.45 (m, 2H), 7.42 (d, 1H, $J$ = 7.7 Hz), 7.34 (d, 1H, $J$ = 8.3 Hz), 7.06 (d, 1H, $J$ = 8.3 Hz), 3.72 (s, 3H), 3.67 (s, 2H). Anal. ($C_{16}H_{13}NO_6S$) C, H, N.

**4-[(2-Carboxyphenyl)thio]-3-nitrobenzenepropanoic Acid α-Methyl Ester (3f).** In an analogous manner the title compound was prepared from methyl 3-(4-chloro-3-nitrophenyl)propanoate (**1f**) in 46% yield as a yellowish solid, mp 155–157 °C. $^1$H NMR: $\delta$ 8.09 (dd, 1H, $J$ = 1.6, 7.7 Hz), 7.85 (d, 1H, $J$ = 1.7 Hz), 7.50 (dt, 1H, $J$ = 1.6, 7.6 Hz), 7.44 (dt, 1H, $J$ = 1.6, 7.6 Hz), 7.35 (dd, 1H, $J$ = 1.0, 7.7 Hz), 7.29 (dd, 1H, $J$ = 1.8, 8.4 Hz), 6.87 (d, 1H, $J$ = 8.4 Hz), 3.66 (s, 3H), 2.94 (t, 2H, $J$ = 7.6), 2.61 (t, 2H, $J$ = 7.6). Anal. ($C_{17}H_{15}NO_6S$) C, H, N.

**2-[(2,4-Dinitrophenyl)thio]benzoic Acid (13).** In an analogous manner the title compound was prepared from bromo-2,4-dinitrobenzene (**12**) in 20% yield as a yellow solid, mp 179–181 °C. $^1$H NMR: $\delta$ 9.07 (d, 1H, $J$ = 2.4 Hz), 8.18–8.08 (m, 2H), 7.76–7.64 (m, 3H), 6.97 (d, 1H, $J$ = 9.0 Hz). Anal. ($C_{13}H_8N_2O_6S$) C, H, N.

**2-[(4-Methyl-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (4a).** A solution of compound **3a** (2.0 g, 6.9 mmol) in thionyl chloride (20 mL) was heated at 70 °C for 3 h, cooled to room temperature, and the excess thionyl chloride removed in vacuo. The residue was redissolved in THF (25 mL), and to this solution were added *N*,*N*-dimethylamine hydrochloride (1.2 g, 13.8 mmol) and $K_2CO_3$ (1.9 g, 13.8 mmol). The reaction mixture was stirred overnight at room temperature, diluted with $H_2O$, and extracted with $CH_2Cl_2$ (60 mL × 4). The combined organic layers were washed with $H_2O$, dried, and concentrated. Column chromatography of the crude product on silica gel and elution with EtOAc/hexane (60:40) afforded the title compound (2.04 g, 93%) as a yellow solid, mp 105–106 °C. $^1$H NMR: $\delta$ 8.02 (d, 1H, $J$ = 1.5 Hz), 7.40–7.63 (m, 4H), 7.21 (dd, 1H, $J$ = 1.5, 8.3 Hz), 6.88 (d, 1H, $J$ = 8.3 Hz), 3.08 (s, 3H), 2.88 (s, 3H), 2.36 (s, 3H). Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N.

**2-[(5-Fluoro-4-methyl-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (4b).** In an analogous manner the title compound was prepared from compound **3b** in 85% yield as a yellow solid, mp 140–141 °C. $^1$H NMR: $\delta$ 8.13 (d, 1H, $J$ = 7.1 Hz), 7.67–7.57 (m, 2H, $J$ = 7.6 Hz), 7.51 (d, 1H, $J$ = 7.5 Hz), 7.47 (d, 1H, $J$ = 7.6 Hz), 6.53 (d, 1H, $J$ = 10.3 Hz), 3.07 (s, 3H), 2.87 (s, 3H), 2.27 (s, 3H). Anal. ($C_{16}H_{15}FN_2O_3S$) C, H, N.

**2-[(4-Fluoro-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (4c).** In an analogous manner the title compound was prepared from compound **3c** in 93% yield as a yellowish solid, mp 56−57 °C. $^1$H NMR: $\delta$ 7.90 (dd, 1H, $J$ = 2.8, 8.3 Hz), 7.65−7.55 (m, 2H), 7.49 (dt, 1H, $J$ = 1.5, 7.6 Hz), 7.43 (dd, 1H, $J$ = 1.2, 7.6 Hz), 7.15 (ddd, 1H, $J$ = 2.8, 7.2, 9.1 Hz), 6.96 (dd, 1H, $J$ = 5.2, 9.1 Hz), 3.08 (s, 3H), 2.88 (s, 3H). Anal. ($C_{15}H_{13}FN_2O_3S$) C, H, N.

**2-[[4-[(Acetyloxy)methyl]-2-nitrophenyl]thio]-*N*,*N*-dimethylbenzamide (4d).** In an analogous manner the title compound was prepared from compound **3d** in 58% yield as a yellow solid, mp 117−118 °C. $^1$H NMR: $\delta$ 8.22 (d, 1H, $J$ = 0.9 Hz), 7.63−7.42 (m, 4H), 7.37 (dd, 1H, $J$ = 1.5, 8.4 Hz), 6.95 (d, 1H, $J$ = 8.4 Hz), 5.09 (s, 2H), 3.07 (s, 3H), 2.88 (s, 3H), 2.12 (s, 3H). Anal. ($C_{18}H_{18}N_2O_5S$) C, H, N.

**4-[[2-[(Dimethylamino)carbonyl]phenyl]thio]-3-nitrobenzeneacetic Acid Methyl Ester (4e).** In an analogous manner the title compound was prepared from compound **3e** in 53% yield as a yellowish solid, mp 124−125 °C. $^1$H NMR: $\delta$ 8.12 (d, 1H, $J$ = 2.0 Hz), 7.58 (dd, 1H, $J$ = 1.2, 7.6 Hz), 7.55 (dd, 1H, $J$ = 1.5, 7.6 Hz), 7.48 (dd, 1H, $J$ = 1.5, 7.6 Hz), 7.42 (dd, 1H, $J$ = 1.5, 7.6 Hz), 7.29 (dd, 1H, $J$ = 2.0, 8.4 Hz), 6.89 (d, 1H, $J$ = 8.4 Hz), 3.69 (s, 3H), 3.62 (s, 2H), 3.05 (s, 3H), 2.85 (s, 3H). Anal. ($C_{18}H_{18}N_2O_5S$) C, H, N.

**4-[[2-[(Dimethylamino)carbonyl]phenyl]thio]-3-nitrobenzenepropanoic Acid Methyl Ester (4f).** In an analogous manner the title compound was prepared from compound **3f** in 60% yield as yellow oil. $^1$H NMR: $\delta$ 8.03 (d, 1H, $J$ = 1.6 Hz), 7.56 (d, 1H, $J$ = 7.8 Hz), 7.53 (d, 1H, $J$ = 7.8 Hz), 7.46 (dt, 1H, $J$ = 1.4, 7.6 Hz), 7.42 (d, 1H, $J$ = 7.6 Hz), 7.21 (dd, 1H, $J$ = 1.6, 8.4 Hz), 6.86 (d, 1H, $J$ = 8.4 Hz), 3.67 (s, 3H), 3.04 (s, 3H), 2.94 (t, 2H, $J$ = 7.6 Hz), 2.85 (s, 3H), 2.61 (t, 2H, $J$ = 7.6 Hz). Anal. ($C_{19}H_{20}N_2O_5S\cdot 0.2H_2O$) C, H, N.

**2-[(4-Methyl-2-nitrophenyl)thio]benzamide (8).** In an analogous manner the title compound was prepared from compound **3a** and ammonia in 89% yield. Recrystallization in $CH_2Cl_2$/hexane afforded an analytical sample as a yellow solid, mp 143−144 °C. $^1$H NMR: $\delta$ 8.02 (m, 1H), 7.92 (m, 1H), 7.64−7.48 (m, 3H), 7.20 (m, 1H), 6.78 (d, 1H, $J$ = 8.3 Hz), 6.61 (br s, 1H), 5.62 (br s, 1H), 2.37 (s, 3H). Anal. ($C_{14}H_{12}N_2O_3S$) C, H, N.

**2-[(2,4-Dinitrophenyl)thio]-*N*,*N*-dimethylbenzamide (14).** In an analogous manner the title compound was prepared from compound **13** and *N*,*N*-dimethylamine hydrochloride in 85% yield as a yellow solid, mp 144−145 °C [lit.[48] mp 147−149 °C]. $^1$H NMR: $\delta$ 9.06 (d, 1H, $J$ = 2.4 Hz), 8.18−8.10 (dd, 1H, $J$ = 2.4, 9.1 Hz), 7.66−7.44 (m, 4H), 7.06 (d, 1H, $J$ = 9.1 Hz), 3.03 (s, 3H), 2.87 (s, 3H).

***N*,*N*-Dimethyl-2-[(4-methyl-2-nitrophenyl)thio]benzenemethanamine (5a).** To a solution of compound **4a** (1.3 g, 4.2 mmol) in THF (10 mL), cooled at 0 °C, was introduced the $BH_3$·THF complex (10 mL, 1 M solution in THF, 10.0 mmol) via a syringe. The solution was heated at 70 °C for 2 h and then stirred overnight at room temperature. The reaction mixture was cooled to 0 °C and concentrated HCl added. The solvent was removed. The aqueous phase was diluted with $H_2O$ (20 mL), heated to reflux for 20 min, and, after cooling to room temperature, adjusted to pH 8 with 10% $NaHCO_3$. The mixture was extracted with $CH_2Cl_2$ (30 mL × 4). The combined organic layers were dried and concentrated. Column chromatography on silica gel and elution with EtOAc/hexane (60:40) afforded the title compound (1.05 g, 83%) as a yellow solid, mp 109−111 °C. $^1$H NMR: $\delta$ 8.09 (d, 1H, $J$ = 1.5 Hz), 7.78 (dd, 1H, $J$ = 1.5, 7.6 Hz), 7.65 (dd, 1H, $J$ = 1.5, 7.6 Hz), 7.58 (dt, 1H, $J$ = 1.5, 7.6 Hz), 7.51 (dt, 1H, $J$ = 1.5, 7.6 Hz), 7.17 (dd, 1H, $J$ = 1.5, 8.3 Hz), 6.44 (d, 1H, $J$ = 8.3 Hz), 4.24 (s, 2H), 2.65 (s, 6H), 2.40 (s, 3H). Anal. ($C_{16}H_{18}N_2O_2S$) C, H, N.

**2-[(5-Fluoro-4-methyl-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzenemethanamine (5b).** In an analogous manner the title compound was prepared from compound **4b** in 78% yield as a yellowish solid, mp 59−60 °C. $^1$H NMR: $\delta$ 8.19 (d, 1H, $J$ = 7.1 Hz), 7.68 (d, 1H, $J$ = 7.6 Hz), 7.58−7.51 (m, 2H), 7.38 (dt, 1H, $J$ = 1.3, 7.5 Hz), 6.28 (d, 1H, $J$ = 10.6 Hz), 3.55 (s, 2H), 2.28 (s, 3H), 2.22 (s, 6H). Anal. ($C_{16}H_{17}FN_2O_2S$) C, H, N.

**2-[(4-Fluoro-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzenemethanamine (5c).** In an analogous manner the title compound was prepared from compound **4c** in 58% yield as yellowish thick oil. $^1$H NMR: $\delta$ 7.98 (dd, 1H, $J$ = 2.8, 8.4 Hz), 7.67 (d, 1H, $J$ = 7.7 Hz), 7.56 (d, 1H, $J$ = 7.6 Hz), 7.52 (t, 1H, $J$ = 7.6 Hz), 7.47 (t, 1H, $J$ = 7.6 Hz), 7.1 (ddd, 1H, $J$ = 2.8, 7.2, 9.1 Hz), 6.72 (dd, 1H, $J$ = 5.2, 9.1 Hz), 3.55 (s, 2H), 2.20 (s, 6H). Anal. ($C_{15}H_{15}FN_2O_2S$) C, H, N.

**4-[[2-[(Dimethylamino)methyl]phenyl]thio]-3-nitrobenzenemethanol (5d).** In an analogous manner the title compound was prepared from compound **4d** in 67% yield as yellowish thick oil, which solidified upon standing, mp 91−93 °C. $^1$H NMR: $\delta$ 8.22 (d, 1H, $J$ = 1.1 Hz), 7.64 (d, 1H, $J$ = 8.1 Hz), 7.58−7.43 (m, 2H), 7.38−7.25 (m, 2H), 6.67 (d, 1H, $J$ = 8.4 Hz), 4.69 (s, 2H), 3.54 (s, 2H), 2.19 (s, 6H). Anal. ($C_{16}H_{18}N_2O_3S$) C, H, N.

**4-[[2-[(Dimethylamino)methyl]phenyl]thio]-3-nitrobenzeneethanol (5e).** In an analogous manner the title compound was prepared from compound **4e** in 80% yield as yellowish thick oil. $^1$H NMR: $\delta$ 8.12 (d, 1H, $J$ = 1.7 Hz), 7.66 (d, 1H, $J$ = 7.6 Hz), 7.54 (d, 1H, $J$ = 7.7 Hz), 7.48 (dt, 1H, $J$ = 1.0, 7.5 Hz), 7.33 (dt, 1H, $J$ = 1.1, 7.6 Hz), 7.20 (dd, 1H, $J$ = 1.9, 8.3 Hz), 6.62 (d, 1H, $J$ = 8.3 Hz), 3.87 (t, 2H, $J$ = 6.4 Hz), 3.55 (s, 2H), 2.87 (t, 2H, $J$ = 6.4 Hz), 2.20 (s, 6H). Anal. ($C_{17}H_{20}N_2O_3S$) C, H, N.

**4-[[2-[(Dimethylamino)methyl]phenyl]thio)-3-nitrobenzenepropanol (5f).** In an analogous manner the title compound was prepared from compound **4f** in 60% yield as yellowish thick oil. $^1$H NMR: $\delta$ 8.07 (d, 1H, $J$ = 1.7 Hz), 7.66 (d, 1H, $J$ = 7.7 Hz), 7.53 (dd, 1H, $J$ = 0.9, 7.7 Hz), 7.48 (dt, 1H, $J$ = 1.1, 7.6 Hz), 7.33 (dt, 1H, $J$ = 1.1, 7.5 Hz), 7.15 (dd, 1H, $J$ = 1.6, 8.4 Hz), 6.62 (d, 1H, $J$ = 8.4 Hz), 3.66 (t, 2H, $J$ = 6.3 Hz), 3.54 (s, 2H), 2.73 (t, 2H, $J$ = 7.6 Hz), 2.20 (s, 6H), 1.92−1.82 (m, 2H). Anal. ($C_{18}H_{22}N_2O_3S$) C, H, N.

**2-[(4-Methyl-2-nitrophenyl)thio]benzenemethanamine (9).** In an analogous manner the title compound was prepared from compound **8** in 85% yield. Recrystallization in $CH_2Cl_2$/hexane afforded an analytical sample as a yellowish solid, mp 94−96 °C. $^1$H NMR: $\delta$ 8.06 (d, 1H, $J$ = 0.9 Hz), 7.61−7.47 (m, 3H), 7.35 (dt, 1H, $J$ = 1.4, 7.5 Hz), 7.14 (m, 1H), 6.59 (d, 1H, $J$ = 8.3 Hz), 3.91 (br s, 2H), 2.36 (s, 3H). Anal. ($C_{14}H_{14}N_2O_2S$) C, H, N.

**2-[(2,4-Dinitrophenyl)thio]-*N*,*N*-dimethylbenzenemethanamine (15).** In an analogous manner the title compound was prepared from compound **14** in 52% yield as a yellowish solid, mp 128−129 °C [lit.[48] mp 122−124 °C]. $^1$H NMR: $\delta$ 9.11 (d, 1H, $J$ = 2.5 Hz), 8.08 (dd, 1H, $J$ = 2.5, 9.1 Hz), 7.69−7.38 (m, 4H), 6.82 (d, 1H, $J$ = 9.1 Hz), 3.50 (s, 2H), 2.15 (s, 6H).

**2-[[4-(Fluoromethyl)-2-nitrophenyl]thio]-*N*,*N*-dimethylbenzenemethanamine (6d).** To a solution of compound **5d** (228 mg, 0.72 mmol) in $CH_2Cl_2$ (10 mL) was added [bis(2-methoxyethyl)amino]sulfur trifluoride (0.15 mL, 0.80 mmol) at 0 °C. The solution was stirred for 2 h at room temperature. The reaction mixture was then diluted with $CH_2Cl_2$ (30 mL) and washed with 10% $NaHCO_3$ (25 mL × 3). The aqueous phase was combined and back extracted once with $CH_2Cl_2$. The organic layers were washed with $H_2O$, dried, and concentrated. The crude product was purified by column chromatography on silica gel (MeOH/$CH_2Cl_2$, 5:95) to provide the title compound as yellowish thick oil (76 mg, 33%). $^1$H NMR: $\delta$ 8.25 (s, 1H), 7.65 (d, 1H, $J$ = 7.7 Hz), 7.55 (d, 1H, $J$ = 7.7 Hz), 7.50 (dt, 1H, $J$ = 1.3, 7.6 Hz), 7.35 (dt, 1H, $J$ = 1.3, 7.6 Hz), 7.30 (d, 1H, $J$ = 8.4 Hz), 6.72 (d, 1H, $J$ = 8.4 Hz), 5.36 (d, 2H, $J$ = 47.3 Hz), 3.53 (s, 2H), 2.19 (s, 6H). Anal. ($C_{16}H_{17}FN_2O_2S$) C, H, N.

**2-[[4-(2-Fluoroethyl)-2-nitrophenyl]thio]-*N*,*N*-dimethylbenzenemethanamine (6e).** In an analogous manner the title compound was obtained from compound **5e** in 52% yield as yellowish oil. $^1$H NMR: $\delta$ 8.12 (d, 1H, $J$ = 1.7 Hz), 7.66 (d, 1H, $J$ = 7.7 Hz), 7.52 (d, 1H, $J$ = 7.5 Hz), 7.48 (t, 1H, $J$ = 7.6 Hz), 7.33 (t, 1H, $J$ = 7.5 Hz), 7.18 (dd, 1H, $J$ = 1.8, 8.4 Hz), 6.63 (d, 1H, $J$ = 8.4 Hz), 4.63 (td, 2H, $J$ = 6.0, 46.9 Hz), 3.55 (s, 2H), 3.00 (td, 2H, $J$ = 6.0, 25.7 Hz), 2.20 (s, 6H). Anal. ($C_{17}H_{19}FN_2O_2S$) C, H, N.

**2-[[4-(3-Fluoropropyl)-2-nitrophenyl]thio]-*N,N*-dimethylbenzenemethanamine (6f).** In an analogous manner the title compound was obtained from compound **5f** in 88% yield as yellowish oil. $^1$H NMR: $\delta$ 8.07 (d, 1H, $J$ = 1.8 Hz), 7.64 (d, 1H, $J$ = 7.7 Hz), 7.53 (d, 1H, $J$ = 7.7 Hz), 7.49 (t, 1H, $J$ = 7.6 Hz), 7.33 (t. 1H. $J$ = 7.6 Hz), 7.16 (dd, 1H, $J$ = 1.8, 8.4 Hz), 6.63 (d, 1H, $J$ = 8.4 Hz), 4.44 (td, 2H, $J$ = 5.8, 47.1 Hz), 3.54 (s, 2H), 2.77 (t, 2H, $J$ = 7.8 Hz), 2.19 (s, 6H), 2.06−1.93 (m, 2H). Anal. ($C_{18}H_{21}FN_2O_2S$) C, H, N.

**2-[(2-Amino-4-methylphenyl)thio]-*N,N*-dimethylbenzenemethanamine (7a).** To a solution of compound **5a** (100 mg, 0.33 mmol) in MeOH (4 mL) was added concentrated HCl (2 mL). The suspension was cooled to 0 °C, $SnCl_2$ (378 mg, 1.98 mmol) was added, and the reaction mixture stirred overnight at room temperature. The mixture was then diluted with $H_2O$ (10 mL) and extracted with EtOAc (10 mL × 2). The organic layers were discarded. The aqueous layer was adjusted to pH 10 with 1 N NaOH and extracted with EtOAc (15 mL × 4). The combined organic layers were washed with $H_2O$, dried, and concentrated to give compound **7a** (66.2 mg, 73%) as colorless oil. $^1$H NMR: $\delta$ 7.43 (d, 1H, $J$ = 7.7 Hz), 7.22−7.32 (m, 1H), 7.05−7.15 (m, 2H), 6.88 (m, 1H), 6.55−6.65 (m, 2H), 4.42 (br s, 2H), 3.62 (s, 2H), 2.38 (s, 6H), 2.32 (s, 3H).

**2-[(2-Amino-4-fluoro-5-methylphenyl)thio]-*N,N*-dimethylbenzenemethanamine (7b).** In an analogous manner compound **7b** was prepared from compound **5b** in 88% yield as colorless oil. $^1$H NMR: $\delta$ 8.20 (d, 1H, $J$ = 7.1 Hz), 7.87 (d, 1H, $J$ = 7.7 Hz), 7.63−7.57 (m, 2H), 7.43 (t, 1H, $J$ = 7.6 Hz), 6.21 (d, 1H, $J$ = 10.4 Hz), 4.11 (br s, 2H), 3.75 (s, 2H), 2.34 (s, 6H), 2.28 (s, 3H). An analytical sample was prepared by reaction with tartaric acid in acetone to give a colorless solid, mp 192−193 °C. Anal. ($C_{16}H_{19}FN_2S\cdot C_4H_6O_6\cdot H_2O$) C, H, N.

**2-[(2-Amino-4-fluorophenyl)thio]-*N,N*-dimethylbenzenemethanamine (7c).** In an analogous manner compound **7c** was prepared from compound **5c** in 74% yield as colorless oil. $^1$H NMR: $\delta$ 7.48 (m, 1H), 7.23 (m, 1H), 7.07−7.18 (m, 2H), 6.90 (m, 1H), 6.40−6.53 (m, 2H), 4.80 (br s, 2H), 3.60 (s, 2H), 2.32 (s, 6H). An analytical sample was prepared by reaction with tartaric acid in acetone to give a colorless solid, mp 158−159 °C. Anal. ($C_{15}H_{17}FN_2S\cdot C_4H_6O_6$) C, H, N.

**2-[(2-Amino-4-fluoromethylphenyl)thio]-*N,N*-dimethylbenzenemethanamine (7d).** In an analogous manner compound **7d** was prepared from compound **6d** in 54% yield as colorless oil. $^1$H NMR: $\delta$ 7.51 (d, 1H, $J$ = 7.8 Hz), 7.30−7.24 (m, 1H), 7.16−7.07 (m, 2H), 6.95−6.90 (m, 1H), 6.77 (s, 1H), 6.74 (d, 1H, $J$ = 7.8 Hz), 5.32 (d, 2H, $J$ = 47.6 Hz), 4.76 (br s, 2H), 3.69 (s, 2H), 2.32 (s, 6H). An analytical sample was prepared by reaction with tartaric acid in acetone to give a colorless solid, mp 142−143 °C. Anal. ($C_{16}H_{19}FN_2S\cdot C_4H_6O_6$) C, H, N.

**2-[[2-Amino-4-(2-fluoroethyl)phenyl]thio]-*N,N*-dimethylbenzenemethanamine (7e).** In an analogous manner compound **7e** was obtained from compound **6e** in 77% yield as colorless oil, which solidified over time to give a colorless solid, mp 54−56 °C. $^1$H NMR: $\delta$ 7.42 (d, 1H, $J$ = 7.6 Hz), 7.28−7.20 (m, 1H), 7.13−7.05 (m, 2H), 6.92−6.87 (m, 1H), 6.65−6.57 (m, 2H), 4.62 (dt, 2H, $J$ = 6.6, 47.1 Hz), 4.50 (br s, 2H), 3.57 (s, 2H), 2.95 (td, 2H, $J$ = 6.6, 23.3 Hz), 2.31 (s, 6H). Anal. ($C_{17}H_{21}FN_2S$) C, H, N.

**2-[[2-Amino-4-(3-fluoropropyl)phenyl]thio]-*N,N*-dimethylbenzenemethanamine (7f).** In an analogous manner compound **7f** was obtained from compound **6f** in 79% yield as colorless oil. $^1$H NMR: $\delta$ 7.39 (d, 1H, $J$ = 8.3 Hz), 7.27−7.20 (m, 1H), 7.13−7.05 (m, 2H), 6.90−6.82 (m, 1H), 6.63−6.55 (m, 2H), 4.47 (td, 2H, $J$ = 5.9, 47.2 Hz), 4.45 (br s, 2H), 3.57 (s, 2H), 2.68 (t, 2H, $J$ = 7.5 Hz), 2.29 (s, 6H), 2.06−1.92 (m, 2H). An analytical sample was prepared by reaction with tartaric acid in acetone to give a colorless solid (hygroscopic). Anal. ($C_{18}H_{23}FN_2S\cdot C_4H_6O_6$) C, H, N.

**2-[(2-Amino-4-methylphenyl)thio]benzenemethanamine (10).** In an analogous manner compound **10** was prepared from compound **9** in 77% yield as colorless oil. $^1$H NMR: $\delta$ 7.34−7.26 (m, 2H), 7.11 (dt, 1H, $J$ = 1.4, 7.4 Hz), 7.06 (dt, 1H, $J$ = 1.6, 7.6 Hz), 6.79 (dd, 1H, $J$ = 1.4, 7.6 Hz), 6.65−6.57 (m, 2H), 4.02 (s, 2H), 2.30 (s, 3H). An analytical sample was prepared by reaction with tartaric acid in acetone to give a colorless solid, mp 203−205 °C. Anal. ($C_{14}H_{16}N_2S\cdot C_4H_6O_6$) C, H, N.

**2-[(2-Amino-4-methylphenyl)thio]-*N*-ethylbenzenemethanamine (11a).** A mixture of amine **10** (100 mg, 0.25 mmol), 1-iodoethane (51.4 mg, 0.33 mmol), and $K_2CO_3$ (138.2 mg, 1.0 mmol) in anhydrous $CH_3CN$ (20 mL) was refluxed overnight. The reaction mixture was concentrated, mixed with $H_2O$ (30 mL), and extracted with $Et_2O$ (20 mL × 4). The combined organic layers were washed with saturated NaCl solution, dried, and concentrated to give compound **11a** (30.4 mg, 45%) as colorless oil. $^1$H NMR: $\delta$ 7.35−7.28 (m, 2H), 7.14−7.03 (m, 2H), 6.85−6.78 (m, 1H), 6.64−6.56 (m, 2H), 4.30 (br s, 2H), 3.96 (s, 2H), 2.75 (q, 2H, $J$ = 7.1 Hz), 2.30 (s, 3H), 1.17 (t, 3H, $J$ = 7.1 Hz). An analytical sample was prepared by reaction with tartaric acid in acetone to afford a colorless solid, mp 162−164 °C. Anal. ($C_{16}H_{20}N_2S\cdot C_4H_6O_6$) C, H, N.

**2-[(2-Amino-4-methylphenyl)thio]-*N*-(2-fluoroethyl)benzenemethanamine (11b).** In an analogous manner compound **11b** was prepared from compound **10** and 1-bromo-2-fluoroethane in 60% yield as colorless oil. $^1$H NMR: $\delta$ 7.35−7.27 (m, 2H), 7.14−7.05 (m, 2H), 6.83 (m, 1H), 6.62−6.57 (m, 2H), 4.59 (td, 2H, $J$ = 4.8, 47.5 Hz), 4.02 (s, 2H), 2.99 (td, 2H, $J$ = 4.8, 28.0 Hz), 2.30 (s, 3H). An analytical sample was prepared by reaction with tartaric acid in acetone to give a colorless solid, mp 99−101 °C. Anal. ($C_{16}H_{19}FN_2S\cdot C_4H_6O_6.0.5H_2O$) C, H, N.

**2-[(2-Amino-4-methylphenyl)thio]-*N*-propylbenzenemethanamine (11c).** In an analogous manner compound **11c** was prepared from compound **10** and 1-bromopropane in 51% yield as colorless oil. $^1$H NMR: $\delta$ 7.33−7.27 (m, 2H), 7.12−7.03 (m, 2H), 6.84−6.78 (m, 1H), 6.63−6.55 (m, 2H), 4.29 (br s, 2H), 3.95 (s, 2H), 2.66 (t, 2H, $J$ = 7.2 Hz), 2.30 (s, 3H), 1.64−1.50 (m, 2H), 0.95 (t, 3H, $J$ = 7.4 Hz). Anal. ($C_{17}H_{22}N_2S$) C, H, N.

**2-[(2-Amino-4-methylphenyl)thio]-*N*-(3-fluoropropyl)benzenemethanamine (11d).** In an analogous manner compound **11d** was prepared from compound **10** and 1-bromo-3-fluoropropane in 80% yield as colorless oil. $^1$H NMR: $\delta$ 7.33−7.25 (m, 2H), 7.14−7.03 (m, 2H), 6.82 (m, 1H), 6.65−6.55 (m, 2H), 4.59 (td, 2H, $J$ = 5.9, 47.3 Hz), 4.28 (br s, 2H), 3.95 (s, 2H), 2.83 (t, 2H, $J$ = 6.9 Hz), 2.30 (s, 3H), 2.00−1.85 (m, 2H). Anal. ($C_{17}H_{21}FN_2S$) C, H, N.

***N*-Allyl-2-[(2-amino-4-methylphenyl)thio]-benzenemethanamine (11e).** In an analogous manner compound **11e** was prepared from compound **10** and allyl bromide in 79% yield as colorless oil. $^1$H NMR: $\delta$ 7.35−7.27 (m, 2H), 7.14−7.03 (m, 2H), 6.86−6.78 (m, 1H), 6.64−6.56 (m, 2H), 5.97 (tdd, 1H, $J$ = 6.0, 10.3, 17.2 Hz), 5.23 (dd, 1H, $J$ = 1.6, 17.2 Hz), 5.13 (dd, 1H, $J$ = 1.4, 10.3 Hz), 4.30 (br s, 2H), 3.96 (s, 2H), 3.34 (td, 2H, $J$ = 1.4, 6.0 Hz), 2.31 (s, 3H). Anal. ($C_{17}H_{20}N_2S\cdot 0.2H_2O$) C, H, N.

**2-[[4-(Chloromethyl)-2-nitrophenyl]thio]-*N,N*-dimethylbenzenemethanamine (17a).** To a solution of compound **5d** (10 mg, 0.031 mmol) in anhydrous $CHCl_3$ (5 mL) were added $Et_3N$ (5 $\mu$L, 0.031 mmol) and $SOCl_2$ (300 $\mu$L). The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and washed with $H_2O$. The aqueous phase was removed. The organic layer was neutralized with 10% aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were washed with $H_2O$, dried, and concentrated to give compound **17a** (7.0 mg, 66%) as yellowish thick oil. $^1$H NMR: $\delta$ 8.28 (d, 1H, $J$ = 2.0 Hz), 7.80−7.30 (m, 5H), 6.68 (d, 1H, $J$ = 8.4 Hz), 4.56 (s, 2H), 3.20 (s, 2H), 2.19 (s, 6H). HRMS: calcld for $C_{16}H_{18}ClN_2O_2S$ ($MH^+$): $m/z$ 337.0772; found: 337.0763.

**4-[[2-[(Dimethylamino)methyl]phenyl]thio]-3-nitrobenzeneethanol 4-Methylbenezenesulfonate (17b).** To a solution of compound **5e** (17 mg, 0.051 mmol) in $CH_2Cl_2$ (2 mL) were added toluenesulfonyl chloride (11 mg, 0.056 mmol) and pyridine (5.4 $\mu$L, 0.067 mmol). The reaction mixture was refluxed overnight, cooled to room temperature, and washed with 10% aqueous $Na_2CO_3$. The organic layer was separated,

dried, and concentrated. The crude product was purified by silica gel column ($MeOH/CH_2Cl_2$ 2:98) to provide compound **17b** (13 mg, 60%) as yellowish oil. $^1H$ NMR: $\delta$ 7.89 (d, 1H, $J = 1.8$ Hz), 7.67 (m, 1H), 7.64 (d, 2H, $J = 8.3$ Hz), 7.57−7.47 (m, 2H), 7.35 (m, 1H), 7.28 (d, 2H, $J = 8.3$ Hz), 7.10 (dd, 1H, $J = 1.8$, 8.4 Hz), 6.59 (d, 1H, $J = 8.4$ Hz), 4.22 (t, 2H, $J = 6.4$ Hz), 3.55 (s, 2H), 2.94 (t, 2H, $J = 6.4$ Hz), 2.44 (s, 3H), 2.21 (s, 6H). HRMS: calcld for $C_{24}H_{27}N_2O_5S_2$ ($MH^+$): *m/z* 487.1356; found: 487.1362.

**4-[[2-[(Dimethylamino)methyl]phenyl]thio]-3-nitrobenzenepropanol 4-Methylbenzenesulfonate (17c).** In an analogous manner compound **17c** was prepared from compound **5f** in 59% yield as yellowish oil. $^1H$ NMR: $\delta$ 7.95 (d, 1H, $J = 1.7$ Hz), 7.77 (d, 2H, $J = 8.3$ Hz), 7.67 (d, 1H, $J = 7.5$ Hz), 7.57−7.44 (m, 2H), 7.39−7.30 (m, 3H), 7.05 (dd, 1H, $J =$ 1.7, 8.3 Hz), 6.58 (d, 1H, $J = 8.3$ Hz), 4.02 (t, 2H, $J = 6.0$ Hz), 3.56 (s, 2H), 2.68 (t, 2H, $J = 7.7$ Hz), 2.44 (s, 3H), 2.14 (s, 6H), 1.95 (m, 2H). HRMS: calcld for $C_{25}H_{29}N_2O_5S_2$ ($MH^+$): *m/z* 501.1512; found: 501.1516.

**Radiochemistry**. Instruments used for radiochemistry are as follows: a semipreparative HPLC system including a Waters 515 HPLC pump, a Rheodyne 7010 injector with a 2 mL loop, a Phenomenex Prodigy C18 ODS Prep column (10 $\mu$m, 10 × 250 mm), an Alltech Model 450 UV detector, a custom-made gamma detector, and a PC running LookOut HPLC data acquisition software; an analytical HPLC system consisting of a Waters 515 HPLC pump, a Rheodyne 7125 injector, a Phenomenex Prodigy C18 ODS-3 column (5 $\mu$m, 4.6 × 250 mm), a Waters PDA 996 detector, a Flow Cell gamma detector (Bioscan) and a PC with the Empower software used for system control.

Anhydrous [$^{18}$F]fluoride was prepared from aqueous [$^{18}$F]-NaF produced via the (p, n) nuclear reaction of [$^{18}$O]$H_2O$ in a RDS-112 cyclotron. Aqueous [$^{18}$F]NaF was mixed with $K_2CO_3$ and Kryptofix 222 in a 5 mL reaction vial. Water was removed by repeated addition of anhydrous MeCN and azeotropic evaporation of the resulting mixture to bring the [$^{18}$F]fluoride to complete dryness and ready for use in fluorination reaction. Irradiation of the target with a beam current of 30 $\mu$A for 60 min typically produces about 1000 mCi of [$^{18}$F]fluoride.

**2-[(2-Amino-4-[$^{18}$F]fluorophenyl)thio]-*N,N*-dimethylbenzenemethanamine (16, [$^{18}$F]AFA).** The precursor **15** (3 mg) in DMSO (1 mL) was added to the reaction vial containing anhydrous [$^{18}$F]fluoride. The mixture was heated at 150 °C for 20 min, cooled, and then diluted with $H_2O$ (50 mL). The resulting aqueous solution was passed through a C18 SepPak and the SepPak rinsed with 25% aqueous MeOH (20 mL). The crude product, eluted off the SepPak with EtOH (1.5 mL), was then heated at 80 °C for 10 min with a combination of $SnCl_2$ (2 mg) or $Cu(OAc)_2$ (2 mg) with $NaBH_4$ (4 mg, added in two portions, 5 min apart). The reaction mixture was diluted with $H_2O$ (50 mL). The aqueous solution was passed through a second C18 SepPak and the SepPak rinsed with 10% aqueous EtOH (10 mL), followed by $H_2O$ (10 mL). The crude product, eluted off the SepPak with EtOH (1 mL), was then purified by preparative HPLC (mobile phase: 25% MeCN/75% 0.1 M ammonium formate, flow rate: 8 mL/min). The product fraction, eluted off the column at ~30 min, was collected, diluted with $H_2O$ (100 mL), and passed through a third C18 SepPak. The SepPak was washed with 0.01 N HCl (10 mL) and $H_2O$ (10 mL). The final product **16** was eluted off the SepPak with EtOH (1 mL) and formulated by dilution of the EtOH solution with sterile normal saline (9 mL) and filtration of the solution through a sterile membrane filter (0.22 $\mu$m). Radiochemical purity of the final product was >98%. Radiochemical yield was 10.8%. Identity of the labeled compound **16** was confirmed by coinjection of the product in saline with the cold standard (**7c**) onto the analytical HPLC (mobile phase: 35% MeCN/65% 0.1 M ammonium formate; flow rate: 2 mL/min; retention time for product: 8.5 min). The radiolabeled product and the cold compound (**7c**) coeluted from the column, and only one single UV peak was detected.

**2-[[2-Amino-4-([$^{18}$F]fluoromethyl)phenyl]thio]-*N,N*-dimethylbenzenemethanamine (18a, [$^{18}$F]AFM).** The radiolabeling precursor **17a** (2 mg) was dissolved in MeCN (1 mL) and reacted with anhydrous [$^{18}$F]fluoride at 80 °C for 15 min to effect F-18 fluorination. Subsequent workup and reaction procedures are similar to those for the synthesis of compound **16**. Radiochemical purity of the final product **18a** was >98%. Radiochemical yield was 9.8%. The radiolabeled compound (**18a**) and the cold standard (**7d**) coeluted on the analytical HPLC (mobile phase: 35% MeCN/65% 0.1 M ammonium formate; flow rate: 2 mL/min; retention time for product: 7.6 min).

**2-[[2-Amino-4-(2-[$^{18}$F]fluoroethyl)phenyl]thio]-*N,N*-dimethylbenzenemethanamine (18b, [$^{18}$F]AFE).** In analogy to the preparation of **18a**, compound **18b** was prepared from the radiolabeling precursor (**17b**) in >99% radiochemical purity and 14.2% radiochemical yield. The radiolabeled product **18b** and the cold standard **7e** coeluted on the analytical HPLC (mobile phase: 35% MeCN/65% 0.1 M ammonium formate; flow rate: 2 mL/min; retention time for product: 8.2 min).

**2-[[2-Amino-4-(3-[$^{18}$F]fluoropropyl)phenyl]thio]-*N,N*-dimethylbenzenemethanamine (18c, [$^{18}$F]AFP).** In analogy to the preparation of **18a**, compound **18c** was prepared from the radiolabeling precursor (**17c**) in >98% radiochemical purity and 15.5% radiochemical yield. The labeled product **18c** and the cold standard **7f** coeluted on HPLC (mobile phase: 40% MeCN/60% 0.1 M ammonium formate; flow rate: 2 mL/min; retention time for product: 7.6 min).

**In Vitro Binding Assays.** Candidate compounds were assayed for their affinities to the monoamine transporters (SERT, NET and DAT) in competitive binding experiments in vitro using cloned human receptors (hSERT, hNET, and hDAT) expressed on HEK-293 cells and the radioligands [3H]-paroxetine (SERT), [$^3$H]nisoxetine (NET), and [$^3$H]GBR12935 (DAT), in accordance with the published procedures.[37]

**Biodistribution Studies in Rats.** Experiments in rodents were carried out according to protocols approved by the Institutional Animal Care and Use Committee (IACUC) of New York State Psychiatric Institute and Columbia University. Specifically, the F-18-labeled compound in saline (~20 $\mu$Ci for each rat at the time of injection) was injected into groups of male Sprague−Dawley rats (three animals for each group) via the tail vein and the rats were sacrificed by decapitation, following anesthesia with $CO_2$, at 10, 30, 60, 90, and 120 min after radioactivity injection. The brain regions (cerebellum, hippocampus, striatum, frontal cortex, thalamus, and hypothalamus), along with sample of blood, were removed, weighed, and counted in a Packard Cobra II gamma counter. A section of the tail, where the injection took place, was cut and counted for residual activity. This residual activity was then used to correct the individual injected dose by subtraction from the total radioactivity injected for each rat. The percent injected dose (%ID) of the decay- and tail-corrected activity in the brain regions and blood were calculated based upon F-18 standards prepared from the injection solution, and the %ID/g were calculated using the tissue weights. In another set of experiments, three groups of rats (three animals per group) were treated with citalopram (selective serotonin re-uptake inhibitor), nisoxetine (selective norepinephrine reuptake inhibitor), GBR12935 (selective dopamine reuptake inhibitor), or the cold compound (**16**, or **18a**−**c**) (2 mg/kg each, iv) 10−15 min before the radiotracer injection. In a control group, rats ($n = 3$) were injected with saline. Each group of rats was sacrificed 60 min after the injection of the radioactivity. Blood sample and brain tissues were taken, counted, and weighed, and %ID/g was calculated as described above. The average %ID/g in the control group was then compared with that from each of the treatment groups.

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**Supporting Information Available:** Elemental analysis of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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