Synthesis, in Vitro Characterization, and Radiolabeling of *N*,*N*-Dimethyl-2-(2′-amino-4′-substituted-phenylthio)benzylamines: Potential Candidates as Selective Serotonin Transporter Radioligands

Nachwa Jarkas,[†] Jonathan McConathy,[†] Ronald J. Voll,[†] and Mark M. Goodman*[,†,‡]

Division of Radiological Sciences, Department of Radiology, and Department of Psychiatry and Behavior Sciences, Emory University, Atlanta, Georgia 30322

Received January 28, 2005

A series of N,N-dimethylated and N-monomethylated analogues of *N*,*N*-dimethyl-2-(2′-amino-4′-iodophenylthio)benzylamine substituted at the 4′-phenyl position have been prepared and evaluated in vitro for serotonin transporter (SERT) selectivity. Several derivatives were prepared where the 4′-position was either unsubstituted **13** and **33a** or substituted with methyl **14a** and **33b**, ethenyl **14b** and **34**, ethyl **16** and **35**, hydroxymethyl **20** and **41**, hydroxyethyl **22**, fluoroethyl **23**, hydroxypropyl **27**, and fluoropropyl **28**. Competition binding in cells stably expressing the transfected human SERT, dopamine transporter (DAT), and norepinephrine transporter (NET) using [^{3}H]citalopram, [^{3}H]WIN 35,428 or [^{125}I]RTI-55, and [^{3}H]nisoxetine, respectively, demonstrated the following order of SERT affinity (K_i (nM)): **14a** (0.25) > **16** (0.49) > **20** (0.57) > **14b** (1.12) > **13** (1.59) > **33b** (1.94) = **35** (2.04) ≫ **23** (8.50) = **28** (8.55) > **41** (15.11) ≫ **22** (51) > **33a** (83.43) > **27** (92). The K_i values revealed that most of these derivatives displayed a high affinity for the SERT and a high selectivity over the DAT and NET. Moreover, substitution at the 4′-position of the dimethylated and monomethylated benzylamines differently influenced SERT binding: (i) the dimethylated benzylamines exhibited higher SERT affinity than the monomethylated ones, (ii) alkyl, alkenyl, or hydroxymethyl functions at the 4′-position afford compounds with high SERT affinity, and (iii) ω-hydroxy and fluoro-substituted ethyl and propyl groups at the 4′-position decrease the SERT affinity. From this series, the dimethylated derivatives **13**, **14a**, **14b**, **16**, and **20** were radiolabeled with carbon-11 and their log $P_{7.4}$ was calculated as a measure of their potential brain penetrance as positron emission tomography SERT imaging agents.

Introduction

Serotonin is an essential neurotransmitter in both the central and peripheral nervous system. The widespread distribution of serotonin neurons and fibers provides the anatomical basis for the involvement of serotonin in the modulation of cortical functions.[1,2] Serotonin neurons originate in the raphe nuclei, from where they project into numerous brain regions including the olfactory bulb, cerebral cortex, hippocampus, and basal ganglia. The serotonin transporter (SERT), located on the cell bodies of the raphe nuclei and the terminals of the presynaptic serotonergic neurons in the brain, is necessary for the regulation of synaptic serotonin levels.[3−5] SERT is the target of several antidepressant drugs (selective serotonin reuptake inhibitors), such as fluoxetine, paroxetine, and sertraline which are designed to preferentially increase serotonin transmission by inhibiting binding of serotonin to SERT.[6,7] Recent reviews have suggested that dysfunctions of serotonin neurotransmission could be associated with neurological and psychiatric disorders. Postmortem brain sections of patients with depression and Alzheimer's and Parkinson's diseases have shown a decrease in the SERT density.[8−11] However, the precise role of the SERT system in these neuropsychiatric disorders remains to be clarified. For this reason, in vivo mapping of the SERT in the living human brain would provide a useful tool to better understand how alterations of this system are related to depressive illness and other neurodegenerative disorders as well as to assess the quantification of SERT occupancy in relation to the antidepressant drug treatment.

There has been a considerable interest in the development of suitable radiotracers for imaging the SERT either by positron emission tomography (PET) or by single photon emission computed tomography (SPECT). Many classes of compounds such as pyrroloisoquinoline,[12] quipazine,[13] and phenyl nortropane[14] derivatives have been screened for their affinities for the SERT. The (+) enantiomer of *trans*-1,2,3,5,6,10β-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-*a*]-isoquinoline ([^{11}C]-(+)McN5652),[15] from the pyrroloisoquinoline series, was the first successful ligand for imaging the SERT in humans by PET. Unfortunately, this radiotracer has several shortcomings: (i) the time required to reach quasi-equilibrium, a condition when the ratio of region of interest to reference region stays constant, is slow, requiring at least 120 min of data acquisition; (ii) the nonspecific binding is relatively high, which precludes the measurements of lower SERT density regions such as the frontal cortex and cingulate; (iii) the plasma free

* To whom correspondence should be addressed: Mark M. Goodman, Ph. D. Tel: (404) 727-9366. Fax: (404) 727-3488.
† Department of Radiology, Emory University.
‡ Department of Psychiatry and Behavior Sciences, Emory University.

10.1021/jm050079o CCC: $30.25
Published on Web 06/04/2005

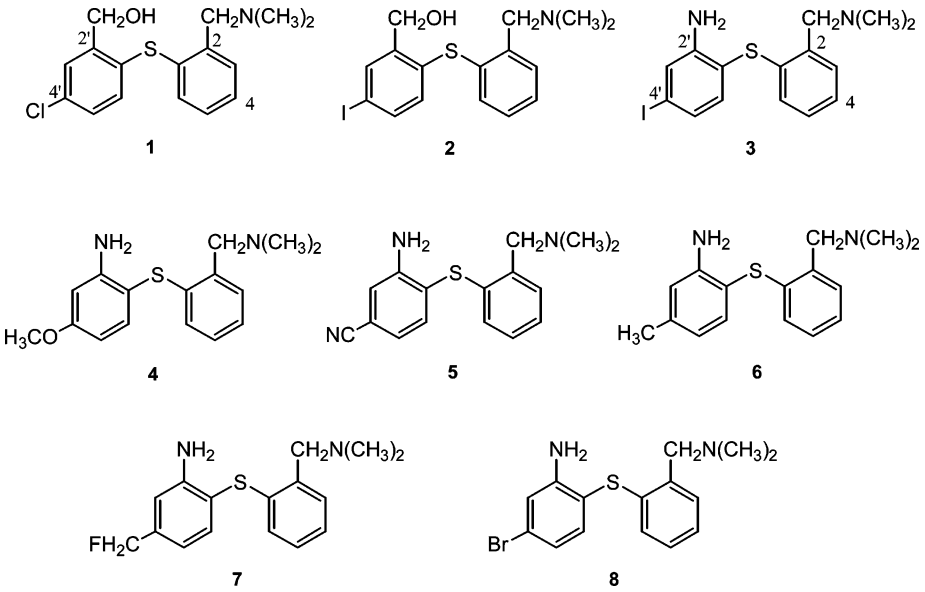
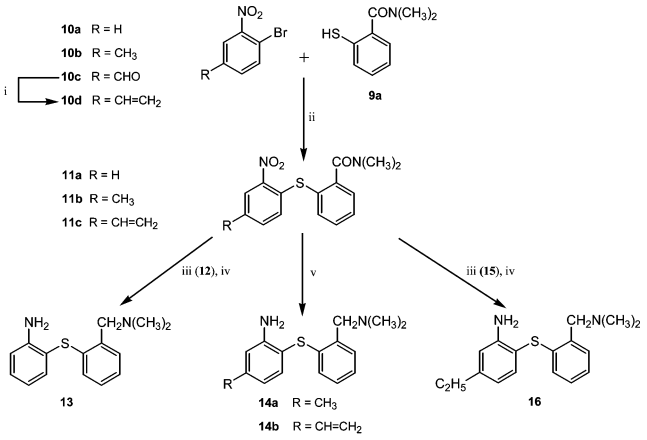


Figure 1. Diphenyl sulfide derivatives.

fraction is very low (<1%), and it interferes with the kinetic modeling using this tracer.[16] In the quipazine derivatives, only 5-iodo-6-nitroquipazine showed promising properties as an in vivo tracer for mapping the SERT sites in a monkey's brain. However, human study of this agent has not been reported. In the phenyl nortropane series, such as 3β-(4-ethyl-3-iodophenyl)-nortropane-2-beta-carboxylic acid methyl ester,[17] 3β-(4′-n-propylphenyl)nortropane-2β-carboxylic acid methyl ester,[14] 3β-(4′-isopropylphenyl)nortropane-2β-carboxylic acid methyl ester,[14] 2β-carbomethoxy-3β-(4′-(2-fluoroisopropenyl)phenyl)nortropane,[18] 2β-carbomethoxy-3β-(4′-(2-fluoroethyl)-3′-iodophenyl)nortropane,[19] 2β-carbomethoxy-3β-(4′-(2-fluoroethyl)-3′-bromophenyl)nortropane,[19] and 2β-carbomethoxy-3β-(4′-(2-fluoroethyl)-3′-chlorophenyl)nortropane,[19] none of these compounds except 2β-carbomethoxy-3β-(4′-((*Z*-2-iodoethenyl)phenyl)nortropane[20] and 2β-carbomethoxy-3β-(4′-((*Z*-2-iodoethenyl)-phenyl)tropane[21] have physiochemical and kinetic properties desirable for optimal imaging of the SERT in the human brain: the most common limitation has been a relatively poor signal-to-noise ratio, limiting their use in vivo for the quantification of the SERT. In contrast, 2β-carbomethoxy-3β-(4′-((*Z*-2-iodoethenyl)phenyl)tropane and 2β-carbomethoxy-3β-(4′-((*Z*-2-iodoethenyl)-phenyl)nortropane displayed a high SERT specific binding with a low nonspecific accumulation and have been proposed as potential radioligands for PET and SPECT imaging of the SERT, respectively.

Recently, it has been reported that a novel antidepressant, *N*,*N*-dimethyl-2-(4′-chloro-2′-hydroxymethylphenylthio)benzylamine (**1**) (Figure 1), was a high affinity and selective SERT ligand.[22] On the basis of the substituted phenylthiophenyl motif of this compound, a number of analogues were prepared and were reported as potent and selective candidate SERT radioligands (Figure 1). The iodo analogues *N*,*N*-dimethyl-2-(2′-hydroxymethyl-4′-iodophenylthio)benzylamine (**2**) and *N*,*N*-dimethyl-2-(2′-amino-4′-iodophenylthio)benzylamine (**3**) (Figure 1) were labeled with iodine-123 and showed promise as new SPECT imaging agents for the SERT.[22−28] [^{11}C]-**3** was prepared and evaluated as a PET SERT radioligand. However, the slow binding kinetics displayed by [^{11}C]-**3** were found to be inappropriate for the short-lived carbon-11 labeled PET radioligand.[29] In attempts to develop a SERT imaging agent with kinetic properties compatible with the 20 min half-life of carbon-11, several alternative substituted benzylamines have been synthesized, characterized, and evaluated by PET imaging in nonhuman primates and humans. PET imaging with carbon-11 labeled *N*,*N*-dimethyl-2-(2′-amino-4′-methoxyphenylthio)benzylamine ([^{11}C]-**4**)[30] and *N*,*N*-dimethyl-2-(2′-amino-4′-cyanophenylthio)benzylamine ([^{11}C]-**5**)[30] in humans and [^{11}C]-**5**,[16] *N*,*N*-dimethyl-2-(2′-amino-4′-methylphenylthio)benzylamine ([^{11}C]-**6**),[31−33] *N*,*N*-dimethyl-2-(2′-amino-4′-fluoromethylphenylthio)benzylamine ([^{11}C]-**7**),[16,34] and *N*,*N*-dimethyl-2-(2′-amino-4′-bromophenylthio)benzylamine ([^{11}C]-**8**)[16,35] (Figure 1) in nonhuman primates has been reported. These carbon-11 compounds displayed good specific-to-nonspecific (cerebellum) ratios in SERT-rich thalamus from 2:1 to 3.5:1. PET imaging studies in baboons with carbon-11 analogues [^{11}C]-**3**, [^{11}C]-**8**, [^{11}C]-**5**, and [^{11}C]-**7**[16] demonstrated that only [^{11}C]-**5** reached a state of quasi-equilibrium in the thalamus within 40 min postinjection as determined from fitted time activity curves between thalamus and cerebellum and supported its candidacy as the preferred radioligand for imaging SERT sites by PET. Thalamus-to-cerebellum ratios of [^{11}C]-**3**, [^{11}C]-**8**, and [^{11}C]-**7** increased continuously up to 90 min postinjection. [^{11}C]-**7** displayed the highest specific-to-nonspecific ratio in the thalamus (3.5) but did not achieve a state of quasi-equilibrium in the thalamus by 90 min postinjection. These findings prompted us to incorporate alternative alkyl-containing substituents at the 4′-position of the diphenyl sulfide. These new *N*,*N*-dimethyl-2-(2′-amino-4′-iodophenylthio)benzylamine **3** analogues may provide better candidates for developing PET ligands for imaging the SERT in the living human brain. Reported herein are the synthesis and in vitro evaluation of several derivatives of *N*,*N*-dimethyl-2-(2′-amino-4′-iodophenylthio)benzylamine where the 4′-position of the aniline ring was either unsubstituted **13** and **33a** or substituted with methyl **14a**[31−33] and **33b**, ethenyl **14b**[33] and **34**, ethyl **16**[33,36] and **35**, hydroxymethyl **20**[37] and **41**, hydroxyethyl **22**, fluoroethyl **23**,[33,34,38]

Scheme 1



Conditions: (i) Ph_3PCH_3Br, BuLi, THF, -78°C; (ii) Cs_2CO_3, CuI, toluene, reflux; (iii) 10% Pd/C, H_2, abs. EtOH, rt; (iv) BH_3-THF, reflux, 2 h, rt; (v) 1M LAH/THF, reflux

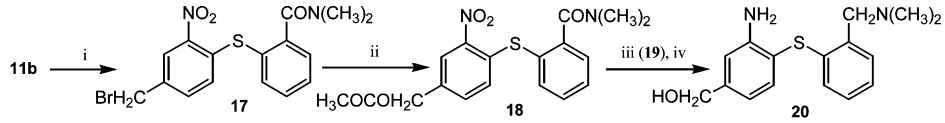
hydroxypropyl **27**, and fluoropropyl **28**.[33] The in vitro biological properties of the **3** analogues were characterized. Compounds **13**, **14a**, **14b**, **16**, and **20** showed both good affinity and selectivity for the SERT and were radiolabeled with carbon-11, and their lipophilicities were determined: [^{11}C]-**13**, [^{11}C]-**14a**, [^{11}C]-**14b**, [^{11}C]-**16**, and [^{11}C]-**20** were prepared by a one-step reaction involving the alkylation of the precursors (the monomethylbenzylamines) **33a**, **33b**, **34**, **35**, and **41**, respectively, with the carbon-11 iodomethane.

Results and Discussion

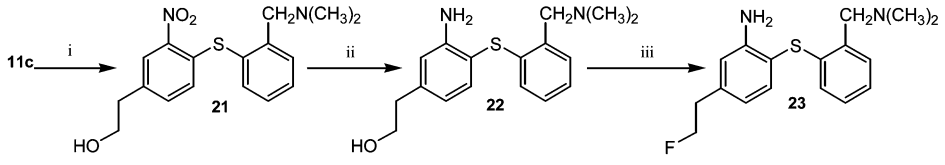
Chemistry. The synthesis of the new target ligands **13**, **14a**, **14b**, **16**, **20**, **22**, **23**, **27**, and **28**, as well as the normethyl derivatives **33a**, **33b**, **34**, **35**, and **41**, required as precursors for radiolabeling with [^{11}C]iodomethane, is presented in Schemes 1−4. Compounds **10a** and **10b** were commercially available. Compounds **9a**, **9b**, and **10c** were prepared from thiosalicylic acid and **10b**, respectively, using previously described procedures.[39,40,41] The 4-bromo-3-nitro-styrene (**10d**) was obtained from the 4-bromo-3-nitro-benzaldehyde (**10c**)[41] under Wittig reaction conditions. Copper-catalyzed coupling[42] of compounds **10a**, **10b**, and **10d** with either 2-thio-*N*,*N*-dimethylbenzamide (**9a**)[39] or ethylthiosalicylate (**9b**)[40] gave the aryl thioethers **11a**−**c** and **29a**−**c**, respectively, in good yields (Schemes 1 and 3). In the case of the dimethyl derivatives (Schemes 1 and 2), only when compound **9a** was freshly prepared was a good coupling yield achieved. Palladium-catalyzed reduction of the nitro group of compound **11a** under a hydrogen atmosphere provided **12** which, after reduction of the amide group with the diborane−tetrahydrofuran (1 M) complex, was transformed to **13** in good yield. Reduction of the nitro as well as the amide groups of compounds **11b**−**c** was achieved using the lithium aluminum hydride−tetrahydrofuran (1 M) complex to give *N*,*N*-dimethyl-2-(2′-amino-4′-methylphenylthio)benzylamine (**14a**) and *N*,*N*-dimethyl-2-(2′-amino-4′-ethenylphenylthio)benzylamine (**14b**). *N*,*N*-Dimethyl-2-(2′-amino-4′-ethylphenylthio)benzylamine (**16**) was obtained from **11c** following the same conditions used to prepare **13**. Radical bromination with *N*-bromosuccinimide of **11b** proceeded smoothly in carbon tetrachloride[43] yielding **17** which was transformed to **18** after a nucleophilic substitution with potassium acetate. *N*,*N*-Dimethyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamine (**20**) was obtained in good yield from **18**, after reduction with the diborane−tetrahydrofuran (1 M) complex followed by a palladium-catalyzed reduction (Scheme 2).

The syntheses of the ω-hydroxyalkyl and the ω-fluoroalkyl derivatives **22** and **27** and **23** and **28,** respec-

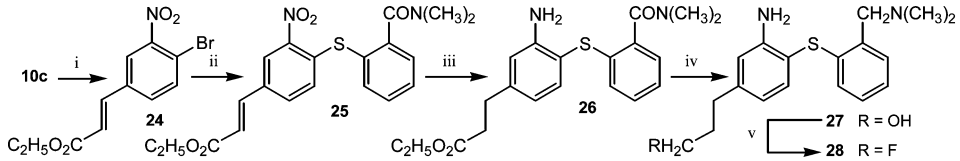
Scheme 2



Conditions: (i) NBS, AIBN, CCl_4, reflux; (ii) CH_3CO_2K, DMF, 100°C; (iii) BH_3-THF, reflux, 2 h, rt; (iv) 10% Pd/C, H_2, abs. EtOH, rt

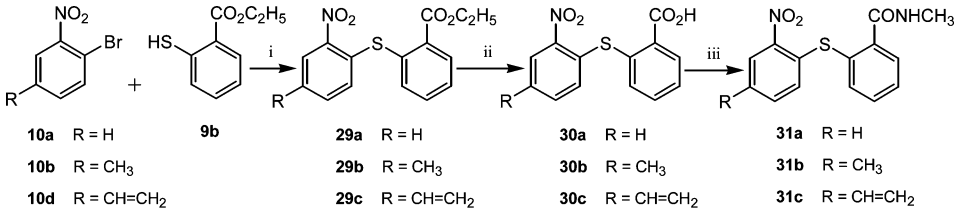


Conditions: (i) BH_3-THF, H_2O_2, NaOH, rt; (ii) 10% Pd/C, H_2, abs. EtOH, rt; (iii) DAST, DCM, -78°C

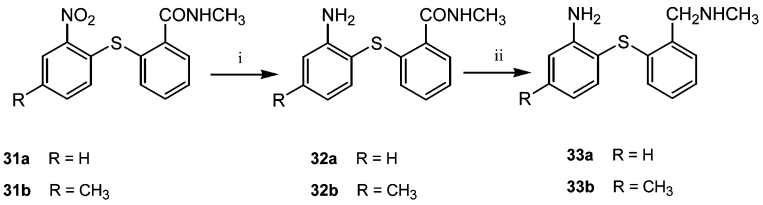


Conditions: (i) $Ph_3P{=}CHCO_2Et$, CH_3CN, reflux; (ii) 2-$HSC_6H_4CON(CH_3)_2$, Cs_2CO_3, CuI, toluene, reflux; (iii) $Pd(OH)_2$, H_2, abs. EtOH, rt; (iv) BH_3-THF, reflux, 2 h, rt; (v) DAST, DCM, -78°C

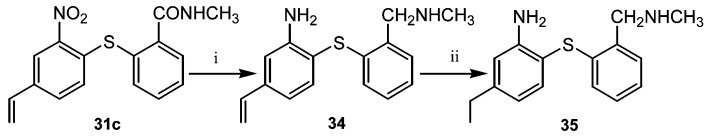
Scheme 3



Conditions: (i) Cs_2CO_3, CuI, toluene, reflux; (ii) 3 N NaOH, reflux; (iii) 1- $SOCl_2$, DCM, reflux; 2- DCM/Et_3N, $MeNH_2$.HCl, -70°C



Conditions: (i) 10% Pd/C, H_2, abs.EtOH, rt; (ii) BH_3-THF, reflux, 2 h, rt

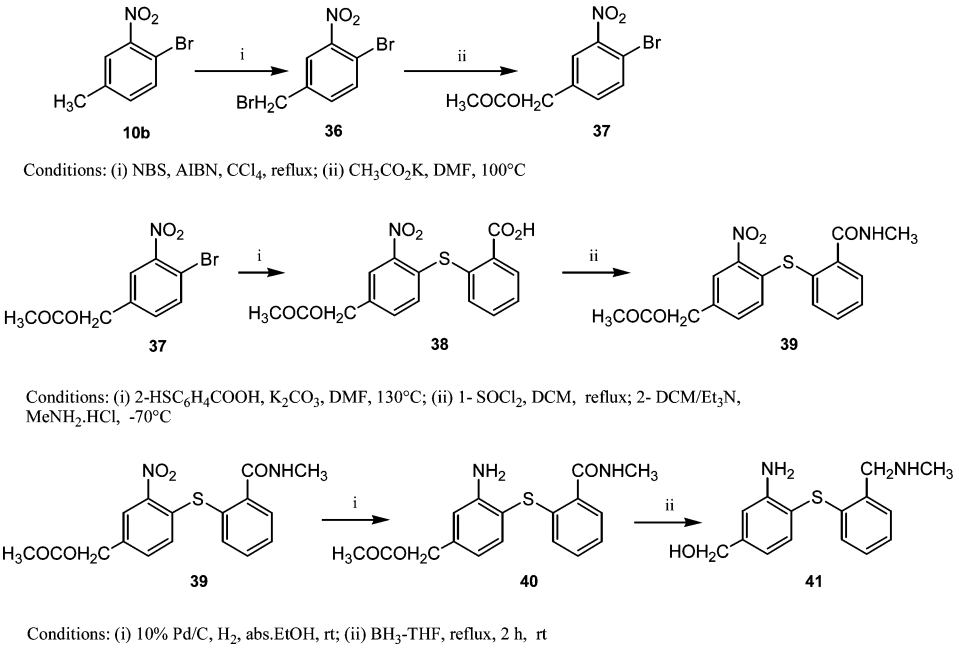


Conditions: (i) 1 M LAH/THF, reflux; (ii) $Pd(OH)_2$, H_2, abs. EtOH, rt

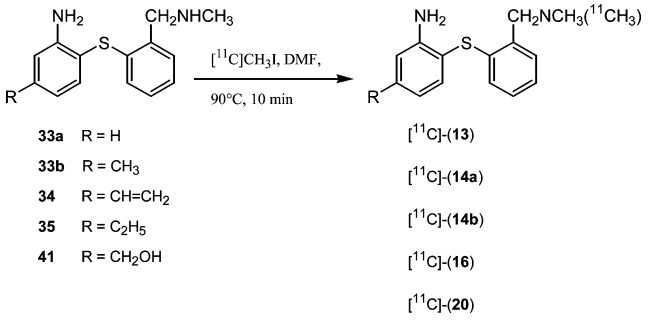
tively, are outlined in Scheme 2. The 4′-(2-hydroxyethyl)-dimethylamine (**21**), was prepared by hydroboration of **11c**, followed by hydrogenation in the presence of a stoichiometric amount of palladium on charcoal to afford *N*,*N*-dimethyl-2-(2′-amino-4′-(ethan-2-ol)phenylthio)benzylamine (**22**). Compound **22** was promptly converted to *N*,*N*-dimethyl-2-(2′-amino-4′-(2-fluoroethyl)phenylthio)benzylamine (**23**) with diethylaminosulfur trifluoride (DAST)[44] at low temperature (Scheme 2). The synthesis of fluoropropyl aniline **28** was initiated by the copper-catalyzed coupling of **24**, prepared by the Wittig reaction of **10c** using ethyl (triphenylphosphoranylidine) acetate,[45] with **9a** to afford **25** in satisfactory yield (Scheme 2). Hydrogenolysis of **25** over palladium hydroxide in absolute ethanol gave **26** which, after reduction with the diborane−tetrahydrofuran (1 M) complex, was converted to *N*,*N*-dimethyl-2-(2′-amino-4′-(propan-3-ol)phenylthio)benzylamine (**27**). Conversion of **27** to *N*,*N*-dimethyl-2-(2′-amino-4′-(3-fluoropropyl) phenylthio)benzylamine (**28**) was accomplished using DAST in dichloromethane (DCM) (Scheme 2).The syntheses of monomethylaminoanilines **33a**, **33b**, **34**, **35**, and **41** were analogous to the synthetic approaches reported in Scheme 3 and Scheme 4. Saponification of the previously prepared esters **29a**, **29b**, and **29c** afforded the acids **30a**, **30b**, and **30c** in very good yields. Treatment of these acids with thionyl chloride in refluxing DCM with a catalytic amount of dimethylformamide gave crude acid chlorides which reacted, without further purification, with methylamine hydrochloride in dichloromethane to yield the desired benzamides **31a**, **31b**, and **31c** (Scheme 3). Monomethylaminoanilines **33a** and **33b** (Scheme 3) were prepared starting from amides **31a** and **31b** using the same reaction conditions applied to obtain **13**. Lithium aluminum hydride reduction of nitro amide **31c** yielded monomethylaminoaniline **34** which, after chromatographic purification, was converted to amine **35** under the same hydrogenolysis conditions used to reduce compound **25** (Scheme 3). Under the same conditions used to prepare **18**, **10b** was transformed to **37**. Condensation of **37** with thiosalicylic acid proceeded smoothly in dimethylformamide yielding **38** which, under the appropriate conditions, was transformed to **39**. Compound **39** gave **41** in good yield (Scheme 4) when the same procedure was used to prepare **13**.

Radiochemistry. The radiotracers [^{11}C]-**13**, [^{11}C]-**14a**, [^{11}C]-**14b**, [^{11}C]-**16**, and [^{11}C]-**20** were all synthesized in a similar fashion as depicted in Scheme 5. Cyclotron-produced [^{11}C]iodomethane was trapped in solutions of the monomethyl precursors **33a**−**35** and **41** at −20 °C in *N*,*N*-dimethylformamide and heated to 90 °C for 10 min. Purification of the resultant reaction mixtures was accomplished by reverse-phase high-performance liquid chromatography (HPLC) followed by a solid-phase extraction purification[46] (see Experimental Section) and formulation in saline (containing 10% ethanol) to give [^{11}C]-**13**, **14a**, **14b**, **16**, and **20** in 24 ± 3% (n = 2), 30 ± 9% (n = 6), 4 ± 1% (n = 3), 24 ± 1% (n = 6), and 21 ± 6% (n = 6), respectively, radiochemical yield EOS (decay corrected, from [^{11}C]iodomethane production). Quality control tests showed that the final products were sterile, pyrogen free, and radiochemically pure (>98%) and contained no precursors. The total synthesis time was 65 min from the end of the bombardment and the specific activity was 500−1200 mCi/μmol at the end of the synthesis. A possible side reaction in these syntheses is the methylation of the aromatic

Scheme 4



Scheme 5



amino group, a site that should be less nucleophilic than the targeted aliphatic amino group: no radioactive byproducts were observed upon HPLC analysis of the final products.

Biological Results: in Vitro Competition Assays. The affinities of *N,N*-dimethyl derivatives **13, 14a, 14b, 16, 20, 22, 23, 27,** and **28** and *N*-methyl derivatives **33a, 33b, 35**, and **41** for the human SERT (hSERT), human DAT (hDAT), and human NET (hNET) were determined through in vitro competition assays. These data are shown in Table 1 along with the previously determined K_i values for **3**.

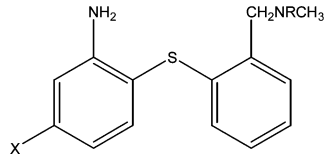
[^{3}H]Citalopram (SERT ligand), [^{3}H]WIN 35,428 or [^{125}I]RTI-55 (DAT ligand), and [^{3}H]nisoxetine (NET ligand) were used as radiotracers during the in vitro displacement experiments. The *N,N*-dimethyl derivatives **13**, **14a, 14b, 16, 20, 22, 23, 27**, and **28** displayed high affinity and selectivity for the SERT over the DAT and NET. The rank of order of hSERT affinity (K_i in nM) for the *N,N*-dimethyl derivatives was **3**[26] (0.013) > **14a** (0.25) > **16** (0.49) > **20** (0.57) > **14b** (1.12) > **13** (1.59) ≫ **23** (8.50) = **28** (8.55) ≫ **22** (51) > **27** (92). In comparison with the *N,N*-dimethyl derivatives, the hSERT affinities of the corresponding *N*-methyl derivatives were an order of magnitude or lower.

The *N,N*-dimethyl derivatives exhibited very low affinities for the DAT (~600 ≤ K_i ≤ 5000) as well as moderate to very low affinities for the NET (37 ≤ K_i ≤ 5000) except for the 4′-unsubstituted derivative **13** with K_i = 279 nM and K_i = 4.95 nM for the DAT and NET, respectively. In comparison with the *N,N*-dimethyl derivatives, the hNET affinities of the corresponding *N*-methyl derivatives were an order of magnitude lower. Thus, the substitution at the 4′-position of the aniline ring of the phenylthiophenyl core structure and demethylation of the *N,N*-dimethylbenzylamine substituent are responsible for the decrease of the DAT and NET affinities.

In our series, derivatives with hydrogen (**13**), methyl (**14a**), ethenyl (**14b**), ethyl (**16**), and hydroxymethyl (**20**) at the 4′-position showed nM or higher affinity, K_i = 1.59, 0.25, 1.12, 0.49, and 0.57 nM, respectively, for the SERT. These five compounds differ from the other derivatives by introduction of a short chain alkyl, alkenyl, and ω-hydroxylalkyl group onto the 4′-position of the aniline ring. Compared to the ethyl derivative (**16**) (K_i = 0.49 nM), the ω-hydroxyethyl (**22**) and ω-fluoroethyl (**23**) derivatives displayed lower affinities K_i = 51 and 8.50 nM, respectively, for the SERT. Lengthening the ω-hydroxyethyl (**22**) and ω-fluoroethyl (**23**) derivatives by one carbon afforded ω-propyl derivatives **27** and **28**, respectively, that possessed approximately the same SERT affinity as their ethyl homologues, K_i = 92 and 8.55 nM, respectively. Thus, a bulk steric effect at that 4′-position of the aniline ring and the introduction of polar atoms on the alkyl groups diminished the binding potency of such derivatives.

The derivatives with the highest SERT binding, **13**, **14a**, **14b**, **16**, and **20**, were radiolabeled with carbon-11 to determine their log *P* at pH 7.4. The log *P* values of compounds **13**, **14a**, **14b**, **16**, and **20** are presented in Table 1. The lipophilicity (octanol/water partition), log $P_{7.4}$, is an important parameter for correlating structure with brain penetrance and ligand-transporter kinetic behavior. Compounds **13**, **14a**, **14b**, **16**, and **20** had log $P_{7.4}$ values of 2.28, 2.46, 2.47, 2.60, and 1.6, respectively. Comparison between the parent 4′-unsubstituted compound **13** and the 4′-substituted series

Table 1. Relative Transporters Affinities K_i (nM) of Candidate SERT Ligands in Transfected Cell Lines and log *P*



compd	X	R	SERT[a] (*n*)[d]	DAT[b] (*n*)	NET[c] (*n*)	log $P_{7.4}$
3[26]	I	CH_3	0.013 ± 0.003	840 ± 100	699 ± 80	2.52
13	H	CH_3	1.59 ± 1.23 (3)	279 ± 51.10 (3)	4.95 ± 0.71 (3)	2.28 ± 0.02
14a	CH_3	CH_3	0.25 ± 0.12 (4)	532 ± 106.00 (3)	61 ± 14.85 (2)	2.46 ± 0.09
14b	CH=CH_2	CH_3	1.12 ± 1.40 (3)	962 ± 116.60 (3)	269 ± 113.85 (2)	2.47 ± 0.09
16	C_2H_5	CH_3	0.49 ± 0.38 (5)	>2000 (3)	370 ± 181.70 (3)	2.60 ± 0.02
20	CH_2OH	CH_3	0.57 ± 0.05 (3)	>1000 (3)	303 ± 225.57 (2)	1.60 ± 0.02
22	$(CH_2)_2OH$	CH_3	50.58 (1)	>1000 (1)	194 (1)	
23	$(CH_2)_2F$	CH_3	8.50 ± 3.53 (1)	>5000 (1)	>5000 (1)	
27	$(CH_2)_3OH$	CH_3	92.26 (1)	>5000 (1)	108 (1)	
28	$(CH_2)_3F$	CH_3	8.55 ± 3.46 (1)	>5000 (1)	219 (1)	
31a	H	H	83.43 (1)	969 ± 27.03 (1)	37.52 ± 2.18 (2)	
31b	CH_3	H	1.94 ± 0.31 (3)	698 ± 250 (2)	191 ± 14.14 (2)	
35	C_2H_5	H	2.04 ± 0.29 (3)	>1000 (2)	445.36 ± 134.30 (2)	
41	CH_2OH	H	15.11 ± 2.25 (2)	>1000 (2)	483.55 ± 207.11 (2)	

[a] Competitive binding vs [^{3}H]citalopram in human kidney cells transfected with human serotonin transporters. [b] Competitive binding vs[^{3}H]WIN 35,428 or [^{125}I]RTI-55 in canine kidney cells transfected with human dopamine transporters. [c] Competitive binding vs [^{3}H]nisoxetine in human kidney cells transfected with human norepinephrine transporters. [d] Number of assays. Values were obtained from the mean ± standard deviation of at least two independent assays, each in duplicates, except for compounds **22**, **23**, **27**, **28**, and **31a**.

demonstrated that a methyl, vinyl, and ethyl group increased log $P_{7.4}$ by 0.18−0.32 and that the hydroxylmethyl group decreased log $P_{7.4}$ by 0.68. These effects can be explained by an increased polarity of **20**, resulting in an increased solubility in the buffer caused by the hydroxyl group forming intermolecular hydrogen bonds with the aqueous buffer. Introduction of methyl, vinyl, and ethyl groups caused the opposite effect because the nonpolar alkyl and vinyl groups will orient themselves toward and be attracted to the nonpolar octanol. The initial brain uptake and specific and nonspecific binding ratios in rats of a series carbon-11 analogues with CN (2.71, **5**), CF_3 (3.77), Cl (3.55), and OCH_3 (2.83) substituted at the 4′-position of the aniline ring have been reported to be optimum when log $P_{7.4}$ = 2.71 (**5**).[47−49] The analogue with the lowest log $P_{7.4}$ value of 2.71, **5**, appeared to provide the best combination of initial brain uptake (1.22% in dose/g) and specific to nonspecific binding ratios, 7.9 to 1, for SERT-rich midbrain regions to cerebellum, respectively, at 60 min postinjection. The octanol/water partition method at pH 7.4 used for this study was identical to the method employed for **5**.[47−49] Compounds **13**, **14a**, **14b**, and **16** exhibiting log $P_{7.4}$ values 2.28−2.60 were lower than **5**. The measured log $P_{7.4}$ value for **20** of 1.6 was significantly lower than **5**. Although the log $P_{7.4}$ value for **20** was 1.6, the recently reported tropanes [^{11}C]2β-carbomethoxy-3β-(4′-((*Z*-2-iodoethenyl)phenyl)tropane [21] and [^{11}C]2β-carbomethoxy-3β-(4′-((*Z*-2-bromoethenyl)phenyl)tropane [21] with log $P_{7.4}$ values 1.5 and 1.3, respectively, showed good brain penetrance and good specific (midbrain) to nonspecific binding (cerebellum) ratios 2.1:1 and 1.9:1, respectively, at 85 min postinjection in nonhuman primates. A preliminary microPET screening of carbon-11 labeled **13, 14a, 16**, and **20** in anesthetized macaques demonstrated that the cooperative properties of K_i = 0.57 and log $P_{7.4}$ = 1.6 for **20** resulted in the highest specific accumulation in brain regions rich in SERT, with a midbrain-to-cerebellum uptake ratio of 4.0. These results with **20** correlated well with the findings reported with [^{11}C]2β-carbomethoxy-3β-(4′-((*Z*-2-iodoethenyl)phenyl)tropane and [^{11}C]2β-carbomethoxy-3β-(4′-((*Z*-2-bromoethenyl)phenyl)tropane. In addition, **20** binding at the SERT exhibited the fastest kinetics and achieved a quasi-equilibrium within 55 min.

Conclusion

Chemical modifications of a series of diphenyl sulfides at the 2- and 4′-positions were performed. Evaluation of the in vitro affinities to the human monoamine transporters, SERT, DAT, and NET and log $P_{7.4}$ values showed that (i) the dimethylamino group at the 2-position increases the SERT affinity; (ii) the substituent at the 4′-position is critical for SERT binding; (iii) the introduction of an alkyl substituent at the 4′-position increases SERT affinity; (iv) the introduction of OH and F at the ω-position of an alkyl group markedly decreases the SERT affinity; (v) the introduction of an OH and F at the ω-position of increasing larger alkyl groups does not increase SERT affinity; (vi) the substituent at the 4′-position significantly influenced log $P_{7.4}$ values with short chain alkyl and alkenyl groups yielding log $P_{7.4}$ values = ∼2.5 and the introduction of OH, **20**, affording a significantly lower log $P_{7.4}$ = 1.6. Preliminary microPET screening of carbon-11 labeled **13**, **14a**, **16**, and **20** in anesthetized macaques demonstrated that **20** had the highest peak midbrain-to-cerebellum ratios (∼ 4) and the most favorable SERT binding kinetics reaching quasi-equilibrium by 55 min postinjection. The full in vivo characterization of **20** for mapping the SERT in the macaque and human brain is currently under investigation.

Experimental Section

Melting points were determined with a Laboratory Device MEL-TEMP II and uncorrected. Proton NMR spectra were run on a Varian Unity 400 at 400 MHz (^{1}H) in $CDCl_3$ with tetramethylsilane as an internal standard. Elemental analyses were performed by Atlantic Microlabs, Inc. (Atlanta, GA) and were within ±0.4% of the theoretical values. Starting materials

9b[40] and **10c**[41] were prepared and purified by methods previously reported.[40,41] Compound **9a** was freshly prepared and used without further purification. All of the other chemicals were purchased from Aldrich Chemical Co. and were used without further purification. Purification and analyses of radioactive compounds by HPLC were performed with in-line UV (254 nm) detectors in series with a radioactivity detector. The HPLC columns used were either a Waters C_{18} reverse phase (25 mm × 100 mm) (column A) for purification or a Waters C_{18} reverse phase (3.9 mm × 150 mm) (column B) for quality control.

4-Bromo-3-nitrostyrene (10d). To a suspension of methyltriphenylphosphonium bromide (1.98 g, 5.6 mmol) in dry tetrahydrofuran (THF) (15 mL), was added butyllithium (1.6 M in hexane, 3.48 mL, 5.6 mmol) at room temperature and stirred for 20 min. The mixture was then cooled to −78 °C and **10c** (0.64 g, 2.8 mmol) in dry THF (10 mL) was added dropwise. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The solvent was concentrated under vacuo, and the residue was extracted with dichloromethane (DCM). Organic layers were washed with saturated aqueous Na_2CO_3 solution and water, dried over Na_2SO_4, and concentrated under vacuo to give the crude product. Purification by silica gel flash column chromatography (DCM) afforded the product **10d** as a yellow oil (400 mg, 63%). ^{1}H NMR ($CDCl_3$, δ): 5.45 (d, 1H, J = 10.8 Hz, −CH=CH_2), 5.85 (d, 1H, J = 18 Hz, −CH=CH_2), 6.66 (dd, 1H, J = 17.2, 11.2 Hz, −CH=CH_2), 7.42 (dd, 1H, J = 8.4, 2.0 Hz, ArH), 7.66 (d, 1H, J = 8.8 Hz, ArH), 7.83 (d, 1H, J = 1.6 Hz, ArH). Anal. ($C_8H_6BrNO_2$) C, H, N.

General Procedure for the Copper-Catalyzed Coupling. To a solution of differently substituted bromo-nitro compounds **10a**, **10b**, **10d**, or **24** (1 equiv) in toluene was added Cs_2CO_3 (3 equiv) followed by CuI (0.1 equiv) as a catalyst. The reaction mixture was stirred at 100 °C for 15 min. **9a** (2 equiv) or **9b** (2 equiv) was added, and the mixture was refluxed overnight. After the mixture was cooled to room temperature, the solvent was concentrated under vacuo and the residue was extracted with DCM. Organic layers were washed with saturated aqueous Na_2CO_3 solution and water, dried over Na_2SO_4, and concentrated under vacuo to give the crude product. Purification by silica gel flash column chromatography (hexane/EtOAc, 9:1) afforded the desired compound in good yield.

***N,N*-Dimethyl-2-(2′-nitrophenylthio)benzamide (11a).** When the general coupling procedure was followed, condensation of **10a** (1.11 g, 5.14 mmol) with **9a** (1.86 g, 10.28 mmol) afforded **11a** as a light brown oil (1.18 g, 76%). ^{1}H NMR ($CDCl_3$, δ): 2.85 (s, 3H, NCH_3), 3.03 (s, 3H, NCH_3), 7.21 (m, 1H, ArH), 7.43 (m, 4H, ArH), 7.57 (m, 2H, ArH), 8.18 (dd, 1H, J = 10.8, 2.0 Hz, ArH). Anal. ($C_{15}H_{14}N_2O_3S$) C, H, N.

***N,N*-Dimethyl-2-(4′-methyl-2′-nitrophenylthio)benzamide (11b).** When the general coupling procedure was followed, condensation of **10b** (3.29 g, 15.23 mmol) with **9a** (5.52 g, 30.5 mmol) afforded **11b** as an orange solid (2.13 g, 44%): mp = 102 °C. ^{1}H NMR ($CDCl_3$, δ): 2.33 (s, 3H, CH_3), 2.84 (s, 3H, NCH_3), 3.03 (s, 3H, NCH_3), 6.84 (d, 1H, J = 8.0 Hz, ArH), 7.18 (dd, 1H, J = 8.0, 1.6 Hz, ArH), 7.44 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.98 (d, 1H, J = 1.2 Hz, ArH). Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N.

***N,N*-Dimethyl-2-(4′-ethenyl-2′-nitrophenylthio)benzamide (11c).** When the general coupling procedure was followed, condensation of **10d** (3.02 g, 13.24 mmol) with **9a** (4.80 g, 26.49 mmol) afforded **11c** as a light brown oil (0.93 g, 21%). ^{1}H NMR ($CDCl_3$, δ): 2.85 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3), 5.34 (d, 1H, J = 10.8 Hz, −CH=CH_2), 5.76 (d, 1H, J = 17.6 Hz, −CH=CH_2), 6.63 (dd, 1H, J = 17.2, 11.1 Hz, −CH=CH_2), 6.89 (d, 1H, J = 8.6 Hz, ArH), 7.45 (m, 3H, ArH), 7.55 (m, 2H, ArH), 8.17 (d, 1H, J = 1.6 Hz, ArH). Anal. ($C_{17}H_{16}N_2O_3S$) C, H, N.

***N,N*-Dimethyl-2-(2′-aminophenylthio)benzamide (12).** To a solution of the compound **11a** (1.18 g, 3.90 mmol) dissolved in absolute EtOH (25 mL) was added 10% Pd/C (1.18 g). The resulting black slurry was stirred under a hydrogen atmosphere for 24 h. The slurry was then filtered through Celite, and the Celite filter cake was washed with several portions of EtOH. The combined filtrate was concentrated under vacuo. Purification by silica gel flash column chromatography (DCM/MeOH, 9:1) afforded **12** as an orange oil (0.87 g, 82%). ^{1}H NMR ($CDCl_3$, δ): 2.90 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), 4.45 (s, 2H, NH_2), 6.72 (m, 2H, ArH), 6.98 (m, 1H, ArH), 7.19 (m, 4H, ArH), 7.46 (dd, 1H, J = 7.6, 1.6 Hz, ArH). Anal. ($C_{15}H_{16}N_2OS$) C, H, N.

***N,N*-Dimethyl-2-(2′-aminophenylthio)benzylamine (13).** BH_3−THF complex (1 M solution in THF) (15 mL, 15 mmol) was added dropwise at 5 °C to a solution of compound **12** (0.83 g, 3.67 mmol) in dry THF (15 mL). The mixture was heated to reflux for 2 h and left at room temperature overnight. The reaction was quenched by the addition of concentrated HCl at 0 °C, and the solvent was removed under vacuo. To the residue, water (15 mL) was added, and the mixture was refluxed for 30 min with vigorous stirring. After the mixture was cooled to room temperature, a saturated solution of $NaHCO_3$ was added to neutralize the solution to pH values of ∼7−8. The resulting aqueous solution was extracted with Et_2O. Combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuo. Silica gel flash column chromatography purification (DCM/MeOH, 9:1) afforded **13** as an orange oil (0.48 g, 50%). ^{1}H NMR ($CDCl_3$, δ): 2.49 (s, 6H, NCH_3), 3.76 (s, 2H, CH_2), 4.67 (s, 2H, NH_2), 6.91 (m, 2H, ArH), 7.06 (m, 1H, ArH), 7.25 (m, 2H, ArH), 7.40 (m, 2H, ArH), 7.66 (dd, 1H, J = 8.0, 1.6 Hz, ArH). Anal. ($C_{15}H_{18}N_2S$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-methylphenylthio)benzylamine**[31−33] **(14a).** To a 1 M lithium aluminum hydride solution in THF (9.48 mL, 9.48 mmol) was added a solution of amide **11b** (0.60 g, 1.89 mmol) in dry THF (3 mL) at room temperature under argon. The resulting brown solution was refluxed overnight. After the mixture was cooled to room temperature, it was quenched with a saturated NH_4Cl solution and extracted with ether. Combined organic layers were washed with 1 N HCl solution. Aqueous layers were basified with saturated Na_2CO_3 solution and extracted with Et_2O. Concentration of the solvent gave the crude product. Silica gel flash column chromatography purification (DCM/MeOH, 9:1) afforded **14a** as an orange oil (0.20 g, 39%). ^{1}H ($CDCl_3$, δ): 2.29 (s, 3H, CH_3), 2.31 (s, 6H, NCH_3), 3.57 (s, 2H, CH_2N), 4.30 (s, 2H, NH_2), 6.59 (m, 2H, ArH), 6.86 (m, 1H, ArH), 7.07 (m, 2H, ArH), 7.23 (m, 1H, ArH), 7.37 (dd, 1H, J = 7.2, 0.8 Hz, ArH). Anal. ($C_{16}H_{20}N_2S$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-ethenylphenylthio)benzylamine (14b).** The alkene **14b** was prepared by the method described for **14a**, by reduction of amide **11c** (0.10 g, 0.30 mmol) with 1 M LAH/THF (1.52 mL, 1.52 mmol). Silica gel flash column chromatography purification (DCM/MeOH, 9:1) afforded **14b** as a colorless oil (30 mg, 35%). ^{1}H NMR ($CDCl_3$, δ): 2.55 (s, 6H, NCH_3), 3.94 (s, 2H, CH_2N), 5.30 (d, 1H, J = 11.2 Hz, −CH=CH_2), 5.78 (d, 1H, J = 16.8 Hz, −CH=CH_2), 6.64 (dd, 1H, J = 10.4, 7.2 Hz, −CH=CH_2), 6.83 (m, 2H, ArH), 6.90 (m, 1H, ArH), 7.15 (m, 2H, ArH), 7.35 (d, 1H, J = 7.6 Hz, ArH), 7.45 (m, 1H, ArH). Anal. ($C_{17}H_{20}N_2S$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-ethylphenylthio)benzamide (15).** Compound **15** was prepared by the method described for amine **12**, through the reduction of compound **11c** (0.12 g, 0.36 mmol) with 10% Pd/C (0.12 g). Silica gel flash column chromatography purification (DCM/EtOAc, 8:2) afforded **15** as a yellow solid (90 mg, 82%): mp = 105 °C. ^{1}H NMR ($CDCl_3$, δ): 1.32 (t, 3H, J = 7.6 Hz, CH_3), 2.65 (q, 2H, J = 8.0 Hz, CH_2), 2.99 (s, 3H, NCH_3), 3.24 (s, 3H, NCH_3), 4.51 (s, 2H, NH_2), 6.67 (m, 2H, ArH), 7.05 (d, 1H, J = 8.0 Hz, ArH), 7.25 (m, 3H, ArH), 7.44 (d, 1H, J = 8.0 Hz, ArH). Anal. ($C_{17}H_{20}N_2OS$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-ethylphenylthio)benzylamine (16).** Compound **16** was prepared by the method described for amine **13**, through the reduction of amide **15** (0.20 g, 0.67 mmol) with BH_3−THF (1 M solution in THF) (3.35 mL, 3.35 mmol). Silica gel flash column chromatography purification (DCM/MeOH, 9:1) afforded **16** as a yellow oil (80 mg, 42%). ^{1}H NMR ($CDCl_3$, δ): 1.23 (t, 3H, J = 10.0 Hz, CH_3), 2.31 (s, 6H, NCH_3), 2.58 (q, 2H, J = 10.0 Hz, CH_2), 3.57 (s,

2H, CH_2N), 4.35 (s, 2H, NH_2), 6.60 (m, 2H, ArH), 6.87 (m, 1H, ArH), 7.05 (m, 2H, ArH), 7.28 (m, 1H, ArH), 7.38 (dd, 1H, J = 6.8, 4.0 Hz, ArH). Anal. ($C_{17}H_{22}N_2S$) C, H, N.

***N,N*-Dimethyl-2-(4′-bromomethyl-2′-nitrophenylthio)-benzamide (17).** A mixture of **11b** (0.50 g, 1.6 mmol), *N*-bromosuccinimide (0.42 g, 2.4 mmol), and azobisisobutyronitrile (AIBN) (25 mg) was refluxed for 16 h in CCl_4 (15 mL). The solvent was removed under vacuo, and the residue was purified by silica gel flash column chromatography using (DCM/EtOAc, 8:2) as the eluent. Compound **17** was obtained as a yellow oil (0.30 g, 47%). ^{1}H NMR ($CDCl_3$, δ): 2.85 (s, 3H, NCH_3), 3.03 (s, 3H, NCH_3), 4.42 (s, 2H, CH_2Br), 7.38 (dd, 1H, J = 8.4, 2.0 Hz, ArH), 7.51 (m, 1H, ArH), 7.56 (m, 2H, ArH), 7.60 (m, 2H, ArH), 8.21 (d, 1H, J = 2.0 Hz, ArH). Anal. ($C_{16}H_{15}BrN_2O_3S$) C, H, N.

***N,N*-Dimethyl-2-(4′-acetoxymethyl-2′-nitrophenylthio)-benzamide (18).** A mixture of compound **17** (69.0 mg, 0.17 mmol) and CH_3CO_2K (17.17 mg, 0.17 mmol) was stirred at 100 °C for 15 h in DMF (2 mL). The mixture was cooled to room temperature, poured into cold acidic water, and extracted several times with DCM. The combined organic layers were washed thoroughly with water, dried over Na_2SO_4, and concentrated under vacuo. Silica gel flash column chromatography purification (DCM/EtOAc, 8:2) afforded **18** as a yellow oil (31.8 mg, 49%). ^{1}H NMR ($CDCl_3$, δ): 2.09 (s, 3H, $OCOCH_3$), 2.85 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3), 5.06 (s, 2H, CH_2O), 6.93 (d, 1H, J = 8.4 Hz, ArH), 7.34 (dd, 1H, J = 8.4, 2.4 Hz, ArH), 7.47 (m, 2H, ArH), 7.57 (m, 2H, ArH), 8.19 (d, 1H, J = 2.0 Hz, ArH). Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N.

***N,N*-Dimethyl-2-(4′-hydroxymethyl-2′-nitrophenylthio)-benzylamine (19).** Compound **19** was prepared by the method described for amine **13**, through the reduction of amide **18** (31.8 mg, 0.085 mmol) with BH_3−THF (1 M solution in THF) (0.42 mL, 0.42 mmol). Silica gel flash column chromatography purification (DCM/MeOH, 9:1) afforded **19** as an orange oil (11.6 mg, 43%). ^{1}H NMR ($CDCl_3$, δ): 2.21 (s, 6H, NCH_3), 3.57 (s, 2H, CH_2N), 4.71 (s, 2H, CH_2OH), 6.68 (d, 1H, J = 8.4 Hz, ArH), 7.33 (m, 2H, ArH), 7.52 (m, 2H, ArH), 7.70 (d, 1H, J = 7.6 Hz, ArH), 8.24 (m, 1H, ArH). Anal. ($C_{16}H_{18}N_2O_3S$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamine (20).** Compound **20** was prepared by the method described for amine **12**, through the reduction of **19** (35.6 mg, 0.11 mmol) with 10% Pd/C (36 mg). Silica gel flash column chromatography purification (DCM/MeOH/Et_3N, 9:1:0.1) afforded **20** as a yellow oil (29 mg, 90%). ^{1}H NMR ($CDCl_3$, δ): 2.34 (s, 6H, NCH_3), 3.64 (s, 2H, CH_2N), 4.59 (s, 2H, CH_2OH), 6.69 (dd, 1H, J = 7.6, 1.6 Hz, ArH), 6.83 (m, 1H, ArH), 7.06 (m, 2H, ArH), 7.09 (m, 1H, ArH), 7.27 (m, 1H, ArH), 7.40 (d, 1H, J = 8.0 Hz, ArH). Anal. ($C_{16}H_{20}N_2OS$) C, H, N.

***N,N*-Dimethyl-2-(4′-(ethan-2-ol)-2′-nitrophenylthio)-benzylamine (21).** BH_3−THF complex (1 M solution in THF) (3.04 mL, 3.04 mmol) was added dropwise at 5 °C to a solution of compound **11c** (0.20 g, 0.61 mmol) in dry THF (4 mL). The mixture was heated to reflux for 15 h. A few drops of 3 N NaOH solution followed by a few drops of 30−35% H_2O_2 were added at 0 °C, and the reaction mixture was left at room temperature for 1 h. The solvent was removed under vacuo, and the resulting aqueous solution was extracted with DCM. Combined organic layers were dried over Na_2SO_4 and concentrated under vacuo. Silica gel flash column chromatography purification (DCM/EtOAc, 8:2) afforded **21** as an orange oil (24 mg, 12%).^{1}H NMR ($CDCl_3$, δ): 2.60 (s, 6H, NCH_3), 2.87 (t, 2H, J = 6.4 Hz, $PhCH_2$), 3.88 (t, 2H, J = 6.0 Hz, CH_2OH), 4.20 (s, 2H, CH_2N), 6.43 (d, 1H, J = 8.4 Hz, ArH), 7.23 (dd, 1H, J = 6.8, 2.0 Hz, ArH), 7.49 (m, 1H, ArH), 7.56 (m, 1H, ArH), 7.64 (d, 1H, J = 7.6 Hz, ArH), 7.75 (d, 1H, J = 6.4 Hz, ArH), 8.15 (d, 1H, J = 6.4 Hz, ArH). Anal. ($C_{17}H_{20}N_2O_3S$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-(ethan-2-ol)phenylthio)-benzylamine (22).** Compound **22** was prepared by the method described for amine **12**, through the reduction of **21** (48 mg, 0.14 mmol) with 10% Pd/C (48 mg). Silica gel flash column chromatography purification (DCM/EtOAc, 8:2) afforded **22** as a colorless oil (8.40 mg, 19%). ^{1}H NMR ($CDCl_3$, δ): 2.65 (s, 6H, NCH_3), 2.82 (t, 2H, J = 6.4 Hz, $PhCH_2$), 3.89 (t, 2H, J = 6.4 Hz, CH_2OH), 4.19 (s, 2H, NH_2), 4.29 (s, 2H, CH_2N), 6.65 (dd, 1H, J = 8.0, 1.6 Hz, ArH), 6.69 (d, 1H, J = 1.6 Hz, ArH), 6.89 (dd, 1H, J = 7.6, 1.6 Hz, ArH), 7.18 (m, 2H, ArH), 7.29 (d, 1H, J = 8.0 Hz, ArH), 7.37 (dd, 1H, J = 7.2, 1.6 Hz, ArH). Anal. ($C_{17}H_{22}N_2OS$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-(2-fluoroethyl)phenylthio)benzylamine (23).** A solution of DAST (0.13 mL, 0.96 mmol) in DCM (1 mL) was slowly added to a solution of compound **22** (0.15 g, 0.49 mmol) in DCM (2 mL) cooled to −70 °C. The reaction mixture was warmed to room temperature and mixed with cold water. The organic phase was washed with saturated aqueous Na_2CO_3 followed by water, and the resulting organic layers were combined, dried over Na_2SO_4, and concentrated under vacuo. After silica gel flash column chromatography purification (DCM/MeOH, 9:1), compound **23** was obtained as a yellow oil (16.8 mg, 11%). ^{1}H NMR ($CDCl_3$, δ): 2.67 (s, 6H, NCH_3), 2.85 (dt, 2H, J = 24.3, 6.1 Hz, $PhCH_2$), 4.59 (s, 2H, CH_2N), 4.69 (d t, 2H, J = 47.2, 6.1 Hz, CH_2F), 6.68 (dd, 1H, J = 8.0, 1.6 Hz, ArH), 6.80 (m, 2H, ArH), 7.20 (m, 2H, ArH), 7.32 (m, 1H, ArH), 7.40 (d, 1H, J = 8.1 Hz, ArH). Anal. ($C_{17}H_{21}FN_2S$) C, H, N.

***trans*-Ethyl-3-(5-(2-bromonitrophenyl))-2-propenoate (24).** A solution of ethyl triphenylphosphoranylidine acetate (0.38 g, 1.08 mmol) dissolved in CH_3CN (3 mL) was added while stirring, to a CH_3CN solution (2 mL) containing **10c** (0.25 g, 1.08 mmol). The reaction mixture was refluxed overnight. After the mixture was cooled, the solvent was removed under vacuo to afford a crude solid that was purified by silica gel flash column chromatography using (hexane/EtOAc, 9:1) as the eluent. Compound **24** was obtained as a white solid (0.26 g, 80%): mp = 130 °C. ^{1}H NMR ($CDCl_3$, δ): 1.34 (t, 3H, J = 6.8 Hz, CH_3), 4.29 (q, 2H, J = 7.2 Hz, CH_2), 6.53 (d, 1H, J = 16.4 Hz, $-CHCO_2C_2H_5$), 7.55 (dd, 1H, J = 8.8, 2.6 Hz, ArH), 7.63 (d, 1H, J = 16.4 Hz, $-CH{=}CHCO_2C_2H_5$), 7.77 (d, 1H, J = 8.6 Hz, ArH), 7.97 (d, 1H, J = 2.6 Hz, ArH). Anal. ($C_{11}H_{10}BrNO_4$) C, H, N.

***trans*-1-Ethyl-3-(4′-(2-(*N,N*-dimethylamido)phenylthio)-2′-nitro-phenyl)-2-propenoate (25).** When the general coupling procedure was followed, condensation of **24** (0.23 g, 0.76 mmol) with **9a** (0.28 g, 1.53 mmol) afforded, after silica gel flash column chromatography purification (DCM/EtOAc, 8:2), **25** as an orange solid (0.21 g, 68%): mp = 105 °C. ^{1}H NMR ($CDCl_3$, δ): 1.32 (t, 3H, J = 7.6 Hz, CH_3), 2.85 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 6.40 (d, 1H, J = 16.4 Hz, $-CHCO_2C_2H_5$), 6.92 (d, 1H, J = 8.8 Hz, ArH), 7.50 (m, 3H, ArH), 7.57 (d, 1H, J = 16.4 Hz, $-CH{=}CHCO_2C_2H_5$), 7.60 (m, 2H, ArH), 8.32 (d, 1H, J = 2.8 Hz, ArH). Anal. ($C_{20}H_{20}N_2O_5S$) C, H, N.

1-Ethyl-3-(4′-(2-(*N,N*-dimethylamido)phenylthio)-2′-phenylamine)propanoate (26). To a suspension of palladium hydroxide (1.00 g) in absolute EtOH (10 mL) was slowly added the amide **25** (1.50 g, 3.74 mmol) in EtOH (40 mL). The mixture was stirred under a hydrogen atmosphere for 20 h. Filtration through Celite and concentration gave a green solid. Purification by silica gel flash column chromatography (DCM/EtOAc, 8:2) afforded **26** as a yellow oil (0.28 g, 20%). ^{1}H NMR ($CDCl_3$, δ): 1.23 (t, 3H, J = 7.6 Hz, CH_3), 2.59 (t, 2H, J = 7.6 Hz, CH_2), 2.86 (t, 2H, J = 8.0 Hz, CH_2), 2.89 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), 4.14 (q, 2H, J = 7.6 Hz, CH_2), 6.96 (m, 1H, ArH), 7.18 (m, 2H, ArH), 7.37 (d, 1H, J = 8.0 Hz, ArH), 7.45 (m, 2H, ArH), 7.67 (d, 1H, J = 8.4 Hz, ArH). Anal. ($C_{20}H_{24}N_2O_3S$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-(propan-3-ol)phenylthio)-benzylamine (27).** Compound **27** was prepared by the method described for amine **13**, through the reduction of compound **26** (0.50 g, 1.34 mmol) with BH_3−THF (1 M solution in THF) (6.71 mL, 6.71 mmol). Silica gel flash column chromatography purification (DCM/MeOH, 9:1) afforded **27** as a white solid (0.11 g, 26%): mp = 94 °C. ^{1}H NMR ($CDCl_3$, δ): 1.89 (m, 2H, CH_2), 2.31 (s, 6H, NCH_3), 2.64 (t, 2H, J = 7.2 Hz, $PhCH_2$), 3.58 (s, 2H, CH_2N), 3.68 (t, 2H, J = 6.4 Hz, CH_2OH), 4.41 (s, 2H, NH_2), 6.60 (dd, 1H, J = 12.0, 1.6 Hz, ArH), 6.86 (m, 2H,

ArH), 7.07 (m, 2H, ArH), 7.24 (m, 1H, ArH), 7.39 (d, 1H, J = 8.4 Hz, ArH). Anal. ($C_{18}H_{24}N_2OS$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-(3-fluoropropyl)phenylthio)-benzylamine (28).** The fluoropropylamine **28** was prepared by the method described for the fluoroethylamine **23**, by the reaction of **27** (0.20 g, 0.63 mmol) with DAST (0.18 mL, 1.3 mmol). After silica gel flash column chromatography purification (DCM/MeOH, 9:1), compound **28** was obtained as a yellow oil (20 mg, 10%). ^{1}H NMR ($CDCl_3$, δ): 2.01 (dtt, 2H, J = 25.2, 7.2, 6.0 Hz, CH_2), 2.33 (s, 6H, NCH_3), 2.67 (t, 2H, J = 8.0 Hz, $PhCH_2$), 3.61(s, 2H, CH_2N), 4.48 (d t, 2H, J = 47.2, 6.0 Hz, CH_2F), 6.58 (m, 2H, ArH), 6.86 (m, 1H, ArH), 7.08 (m, 2H, ArH), 7.24 (m, 1H, ArH), 7.38 (d, 1H, J = 8.0 Hz, ArH). Anal. ($C_{18}H_{23}FN_2S$) C, H, N.

Ethyl 2-(2′-Nitrophenylthio)benzoate (29a). When the general coupling procedure was followed, condensation of **10a** (0.33 g, 1.63 mmol) with **9b** (0.6 g, 3.27 mmol) afforded **29a** as a yellow oil (0.41 g, 83%). ^{1}H NMR ($CDCl_3$, δ): 0.96 (t, 3H, J = 7.2 Hz, CH_3), 4.03 (q, 2H, J = 6.8 Hz, CH_2), 6.78 (dd, 1H, J = 8.4, 1.2 Hz, ArH), 7.04 (m, 1H, ArH), 7.14 (m, 1H, ArH), 7.25 (m, 3H, ArH), 7.67 (m, 1H, ArH), 7.93 (dd, 1H, J = 8.5, 1.6 Hz, ArH). Anal. ($C_{15}H_{13}NO_4S$) C, H, N.

Ethyl 2-(4′-Methyl-2′-nitrophenylthio)benzoate (29b). When the general coupling procedure was followed, condensation of **10b** (2.00 g, 9.26 mmol) with **9b** (3.37 g, 18.52 mmol) afforded **29b** as a yellow solid (1.69 g, 58%): mp = 80 °C. ^{1}H NMR ($CDCl_3$, δ): 1.25 (t, 3H, J = 7.2 Hz, CH_3), 2.39 (s, 3H, CH_3), 4.29 (q, 2H, J = 6.8 Hz, CH_2), 7.00 (d, 1H, J = 8.4 Hz, ArH), 7.23 (dd, 1H, J = 8.4, 1.2 Hz, ArH), 7.35 (m, 1H, ArH), 7.44 (m, 2H, ArH), 7.92 (m, 2H, ArH). Anal. ($C_{16}H_{15}NO_4S$) C, H, N.

Ethyl 2-(4′-Ethenyl-2′-nitrophenylthio)benzoate (29c). When the general coupling procedure was followed, condensation of **10d** (0.31 g, 1.36 mmol) with **9b** (0.50 g, 2.72 mmol) afforded **29c** as a yellow oil (0.30 g, 67%). ^{1}H NMR ($CDCl_3$, δ): 1.22 (t, 3H, J = 6.8 Hz, CH_3), 4.27 (q, 2H, J = 7.2 Hz, CH_2), 5.39 (d, 1H, J = 10.8 Hz, $-CH=CH_2$), 5.82 (d, 1H, J = 17.6 Hz, $-CH=CH_2$), 6.67 (dd, 1H, J = 18.0, 10.8 Hz, $-CH=CH_2$), 6.96 (d, 1H, J = 17.6 Hz, ArH), 7.42 (dd, 1H, J = 8.0, 2.4 Hz, ArH), 7.48 (m, 3H, ArH), 7.92 (m, 1H, ArH), 8.15 (d, 1H, J = 2.0 Hz, ArH). Anal. ($C_{17}H_{15}NO_4S$) C, H, N.

2-(2′-Nitrophenylthio)benzoic Acid (30a). Compound **29a** (0.51 g, 1.68 mmol) was heated in 3 N NaOH (16 mL) solution at 120 °C for 20 min. After the solution was cooled to room temperature, the reaction mixture was acidified with concentrated HCl. Filtration gave the desired compound **30a** as an orange solid (0.41 g, 89%): mp >250 °C. **30a** was spectroscopically pure and used in the next step without further purification. ^{1}H NMR ($CDCl_3$, δ): 7.11 (dd, 1H, J = 8.0, 1.2 Hz, ArH), 7.34 (m, 1H, ArH) 7.41 (dd, 1H, J = 7.6, 1.6 Hz, ArH), 7.49 (m, 3H, ArH), 8.11 (m, 2H, ArH). Anal. ($C_{13}H_9NO_4S$) C, H, N.

2-(4′-Methyl-2′-nitrophenylthio)benzoic Acid (30b). Acid **30b** was prepared from ester **29b** (1.64 g, 5.17 mmol) as described for the preparation of **30a**. Hydrolysis of **29b** afforded **30b** as an orange solid (1.46 g, 98%): mp = 245 °C. **30b** was spectroscopically pure and used in the next step without further purification. ^{1}H NMR ($CDCl_3$, δ): 2.42 (s, 3H, CH_3), 7.12 (d, 1H, J = 8.4 Hz, ArH), 7.27 (m, 2H, ArH), 7.40 (m, 1H, ArH), 7.47 (m, 1H, ArH), 7.89 (m, 1H, ArH), 8.10 (dd, 1H, J = 8.0, 1.6 Hz, ArH). Anal. ($C_{14}H_{11}NO_4S$) C, H, N.

2-(4′-Ethenyl-2′-nitrophenylthio)benzoic Acid (30c). Acid **30c** was prepared from ester **29c** (0.33 g, 1.00 mmol) as described for the preparation of **30a**. Hydrolysis of **29c** afforded **30c** as a yellow solid (0.21 g, 70%): mp = 172 °C. **30c** was spectroscopically pure and used in the next step without further purification. ^{1}H NMR ($CDCl_3$, δ): 5.41 (d, 1H, J = 10.8 Hz, $-CH=CH_2$), 5.83 (d, 1H, J = 17.6 Hz, $-CH=CH_2$), 6.69 (dd, 1H, J = 17.6, 10.8 Hz, $-CH=CH_2$), 7.06 (d, 1H, J = 8.4 Hz, ArH), 7.45 (m, 4H, ArH), 8.10 (m, 2H, ArH). Anal. ($C_{17}H_{11}NO_4S$) C, H, N.

***N*-Methyl-2-(2′-nitrophenylthio)benzamide (31a).** To a suspension of the acid **30a** (0.41 g, 1.49 mmol) in anhydrous DCM (16 mL) were added thionyl chloride (0.27 g, 2.23 mmol) and a few drops of DMF. The reaction mixture was refluxed for 90 min under argon. The solvent was evaporated, and the solid was used without further purification.

A solution of triethylamine (1.20 g, 11.91 mmol) and methylamine hydrochloride (0.40 g, 5.96 mmol) in anhydrous DCM (20 mL) was cooled to −70 °C. The acid chloride (freshly prepared) in DCM was added dropwise under argon. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, and mixed with cold water. The organic phase was washed with 1 N HCl solution followed by water, and the resulting organic layers were combined, dried over Na_2SO_4, and concentrated under vacuo. The product was purified by silica gel flash column chromatography (DCM/EtOAc, 8:2) to yield the desired **31a** as an orange oil (0.37 g, 86%). ^{1}H NMR ($CDCl_3$, δ): 2.55 (d, 3H, NCH_3), 6.09 (s, 1H, NH), 6.63 (d, 1H, J = 8.0 Hz, ArH), 6.96 (m, 1H, ArH), 7.08 (m, 1H, ArH), 7.24 (m, 3H, ArH), 7.48 (dd, 1H, J = 7.6, 1.6 Hz, ArH), 7.91 (dd, 1H, J = 8.4, 0.8 Hz, ArH). Anal. ($C_{14}H_{12}N_2O_3S$) C, H, N.

***N*-Methyl-2-(4′-methyl-2′-nitrophenylthio)benzamide (31b).** Acid **30b** (0.89 g, 3.08 mmol) was treated with thionyl chloride (0.91 g, 7.69 mmol) as described for **31a**. The crude acid chloride was treated with methylamine hydrochloride (0.83 g, 12.30 mmol) in the presence of triethylamine (2.49 g, 24.61 mmol). The monomethylamide derivative **31b** was purified by silica gel flash column chromatography (DCM/EtOAc, 8:2) to give a yellow solid (0.67 g, 72%): mp = 140 °C. ^{1}H NMR ($CDCl_3$, δ): 2.35 (s, 3H, CH_3), 2.84 (d, 3H, J = 4.8 Hz, NCH_3), 6.41 (s, 1H, NH), 6.81 (d, 1H, J = 8.0 Hz, ArH), 7.22 (dd, 1H, J = 8.0, 1.2 Hz, ArH), 7.52 (m, 3H, ArH), 7.77 (dd, 1H, J = 7.6, 1.6 Hz, ArH), 7.98 (m, 1H, ArH). Anal. ($C_{15}H_{14}N_2O_3S$) C, H, N.

***N*-Methyl-2-(4′-ethenyl-2′-nitrophenylthio)benzamide (31c).** Acid **30c** (0.21 g, 0.70 mmol) was treated with thionyl chloride (0.21 g, 1.74 mmol) as described for **31a**. The crude acid chloride was treated with methylamine hydrochloride (0.19 g, 2.79 mmol) in the presence of triethylamine (0.56 g, 5.57 mmol). The monomethylamide derivative **31c** was purified by silica gel flash column chromatography (DCM/EtOAc, 8:2) to give an orange oil (0.19 g, 87%). ^{1}H NMR ($CDCl_3$, δ): 2.84 (d, 3H, J = 4.4 Hz, NCH_3), 5.36 (d, 1H, J = 10.8 Hz, $-CH=CH_2$), 5.77 (d, 1H, J = 17.6 Hz, $-CH=CH_2$), 6.32 (s, 1H, NH), 6.65 (dd, 1H, J = 18.0, 10.8 Hz, $-CH=CH_2$), 6.80 (d, 1H, J = 8.4 Hz, ArH), 7.41 (dd, 1H, J = 8.4, 1.6 Hz, ArH), 7.55 (m, 3H, ArH), 7.75 (dd, 1H, J = 7.6, 1.6 Hz, ArH), 8.18 (d, 1H, J = 1.6 Hz, ArH). Anal. ($C_{16}H_{14}N_2O_3S$) C, H, N.

***N*-Methyl-2-(2′-aminophenylthio)benzamide (32a).** Amide **31a** (0.37 g, 1.28 mmol) was treated with 10% Pd/C (0.37 g) as described for **12**. The desired compound **32a** was obtained as an orange oil (0.27 g, 82%). **32a** was spectroscopically pure and used in the next step without further purification. ^{1}H NMR ($CDCl_3$, δ): 3.04 (d, 3H, NCH_3), 4.38 (s, 2H, NH_2), 6.11 (s, 1H, NH), 6.76 (m, 1H, ArH), 6.86 (dd, 1H, J = 8.0, 0.8 Hz, ArH), 7.18 (m, 4H, ArH), 7.44 (m, 2H, ArH).

***N*-Methyl-2-(4′-methyl-2′-aminophenylthio)benzamide (32b).** Amide **31b** (0.67 g, 2.22 mmol) was treated with 10% Pd/C (0.63 g) as described for **12**. The desired compound **32b** was obtained following purification by silica gel flash column chromatography (DCM/EtOAc, 8:2) as a yellow solid (0.52 g, 86%): mp = 130 °C. ^{1}H NMR ($CDCl_3$, δ): 2.29 (s, 3H, CH_3), 3.05 (d, 3H, J = 4.8 Hz, NCH_3), 4.29 (s, 2H, NH_2), 6.08 (s, 1H, NH), 6.59 (m, 2H, ArH), 6.85 (dd, 1H, J = 8.0, 1.2 Hz, ArH), 7.11 (m, 1H, ArH), 7.19 (m, 1H, ArH), 7.32 (d, 1H, J = 8.0 Hz, ArH), 7.46 (dd, 1H, J = 7.6, 1.6 Hz, ArH). Anal. ($C_{15}H_{16}N_2OS$) C, H, N.

***N*-Methyl-2-(2′-aminophenylthio)benzylamine (33a).** Amide **32a** (0.27 g, 1.04 mmol) was treated with BH_3−THF (1 M solution in THF) (4.18 mL, 4.18 mmol) as described for **13**. The desired compound **33a** was obtained following purification by silica gel flash column chromatography (DCM/MeOH, 9:1) as a colorless oil (84 mg, 33%). ^{1}H NMR ($CDCl_3$, δ): 2.55 (s, 3H, NCH_3), 3.97 (s, 2H, CH_2N), 6.79 (m, 2H, ArH), 6.86 (m, 1H, ArH), 7.13 (m, 2H, ArH), 7.28 (m, 1H, ArH), 7.35 (dd, 1H,

J = 7.2, 1.2 Hz, ArH), 7.44 (dd, 1H, J = 7.6, 1.6 Hz, ArH). Anal. ($C_{14}H_{16}N_2S$) C, H, N.

***N*-Methyl-2-(2′-amino-4′-methylphenylthio)benzylamine (33b).** Amide **32b** (0.12 g, 0.44 mmol) was treated with BH_3−THF (1 M solution in THF) (1.76 mL, 1.76 mmol) as described for **13**. The desired compound **33b** was obtained following purification by silica gel flash column chromatography (DCM/MeOH/Et_3N, 95:5:0.1) as yellow crystals (75 mg, 66%): mp = 76 °C. ^{1}H NMR ($CDCl_3$, δ): 2.30 (s, 3H, CH_3), 2.51 (s, 3H, NCH_3), 3.92 (s, 2H, CH_2N), 6.57 (dd, 1H, J = 7.6, 1.6 Hz, ArH), 6.61 (m, 1H, ArH), 6.80 (m, 1H, ArH), 7.08 (m, 2H, ArH), 7.29 (m, 2H, ArH). Anal. ($C_{15}H_{18}N_2S$) C, H, N.

***N*-Methyl-2-(2′-amino-4′-ethenylphenylthio)benzylamine (34).** Amide **31c** (0.10 g, 0.32 mmol) was treated with 1 M LAH/THF (1.60 mL, 1.60 mmol) as described for **14a**. The desired compound **34** was obtained following purification by silica gel flash column chromatography (DCM/MeOH, 9:1) as an orange oil (37 mg, 43%). ^{1}H NMR ($CDCl_3$, δ): 2.59 (s, 3H, NCH_3), 4.16 (s, 2H, CH_2N), 5.30 (d, 1H, J = 10.8 Hz, −CH=CH_2), 5.78 (d, 1H, J = 17.6 Hz, −CH=CH_2), 6.63 (dd, 1H, J = 17.6, 10.8 Hz, −CH=CH_2), 6.81 (m, 3H, ArH), 7.13 (m, 2H, ArH), 7.30 (d, 1H, J = 8.0 Hz, ArH), 7.51 (dd, 1H, J = 6.8, 1.6 Hz, ArH). Anal. ($C_{16}H_{18}N_2S$) C, H, N.

***N*-Methyl-2-(2′-amino-4′-ethylphenylthio)benzylamine (35).** Amine **34** (80 mg, 0.29 mmol) was treated with $Pd(OH)_2$ (100 mg) as described for **26**. The desired compound **35** was obtained following purification by silica gel flash column chromatography (DCM/MeOH, 9:1) as a yellow solid (22 mg, 27%): mp = 56 °C. ^{1}H NMR ($CDCl_3$, δ): 1.24 (t, 3H, J = 7.6 Hz, CH_3), 2.50 (s, 3H, NCH_3), 2.60 (q, 2H, J = 7.6 Hz, CH_2), 3.92 (s, 2H, CH_2N), 6.60 (m, 2H, ArH), 6.80 (m, 1H, ArH), 7.07 (m, 2H, ArH), 7.28 (m, 1H, ArH), 7.33 (d, 1H, J = 7.6 Hz, ArH). Anal. ($C_{16}H_{20}N_2S$) C, H, N.

2-Bromo-5-bromomethyl-nitrobenzene (36). Compound **10b** (1.0 g, 4.63 mmol) reacted with *N*-bromosuccinimide (1.23 g, 6.94 mmol) and a catalytic amount of AIBN (72 mg) in CCl_4 (40 mL) as described for **17**. In this case, the reaction mixture was refluxed for 3 days. After silica gel flash column chromatography was used (hexane/EtOAc, 9:1), **36** was obtained as a yellow oil (1.03 g, 75%). ^{1}H NMR ($CDCl_3$, δ): 4.45 (s, 2H, CH_2-Br), 7.47 (dd, 1H, J = 8.4, 2.4 Hz, ArH), 7.72 (d, 1H, J = 8.4 Hz, ArH), 7.87 (d, 1H, J = 2.0 Hz, ArH). Anal. ($C_7H_5Br_2NO_2$) C, H, N.

2-Bromo-5-acetoxymethyl-nitrobenzene (37). Compound **36** (0.20 g, 0.68 mmol) was treated with CH_3CO_2K (0.68 mmol, 66 mg) in DMF (7 mL) as described for **18**. The desired compound **37** was obtained following purification by silica gel flash column chromatography (hexane/EtOAc, 9:1) as a yellow oil (0.15 g, 81%). ^{1}H NMR ($CDCl_3$, δ): 2.13 (s, 3H, $OCOCH_3$), 5.11 (s, 2H, CH_2O), 7.43 (dd, 1H, J = 8.0, 2.0 Hz, ArH), 7.74 (d, 1H, J = 8.4 Hz, ArH), 7.84 (d, 1H, J = 2.0 Hz, ArH). Anal. ($C_9H_8BrNO_4$) C, H, N.

2-(4′-Acetoxymethyl-2′-nitrophenylthio)benzoic acid (38). Thiosalicylic acid (0.14 g, 0.91 mmol) followed by K_2CO_3 (0.38 g, 2.73 mmol) was added to a solution of **37** (0.25 g, 0.91 mmol) in DMF (3 mL). The reaction mixture was stirred at 130 °C for 18 h. The brown solution was poured into cold acidic water after it was cooled to room temperature, and the residue extracted with EtOAc. Organic layers were washed with water, dried over Na_2SO_4, and concentrated under vacuo to give the crude product. Purification by silica gel flash column chromatography (DCM/MeOH, 9:1) afforded the desired compound **38** as a yellow oil (55 mg, 17%). ^{1}H NMR ($CDCl_3$, δ): 2.10 (s, 3H, $OCOCH_3$), 5.06 (s, 2H, CH_2O), 7.03 (d, 1H, J = 8.4 Hz, ArH), 7.36 (m, 4H, ArH), 7.98 (d, 1H, J = 7.2 Hz, ArH), 8.05 (d, 1H, J = 0.8 Hz, ArH). Anal. ($C_{16}H_{13}NO_6S$) C, H, N.

***N*-Methyl-2-(4′-acetoxymethyl-2′-nitrophenylthio)benzamide (39).** Acid **38** (0.32 g, 0.92 mmol) was treated with thionyl chloride (0.27 g, 2.30 mmol) as described for **31a**. The crude acid chloride was treated with methylamine hydrochloride (0.25 g, 3.71 mmol) in the presence of triethylamine (0.75 g, 7.43 mmol). The monomethylamide derivative **39** was purified by silica gel flash column chromatography (DCM/MeOH, 9:1) to give a yellow oil (0.27 g, 81%). ^{1}H NMR ($CDCl_3$, δ): 2.09 (s, 3H, $OCOCH_3$), 2.86 (d, 3H, NCH_3), 5.06 (s, 2H, CH_2O), 6.31 (s, 1H, NH), 6.88 (d, 1H, J = 8.4 Hz, ArH), 7.35 (dd, 1H, J = 8.4, 2.0 Hz, ArH), 7.53 (m, 3H, ArH), 7.75 (dd, 1H, J = 7.6, 1.6 Hz, ArH), 8.19 (d, 1H, J = 2.0 Hz, ArH). Anal. ($C_{17}H_{16}N_2O_5S$) C, H, N.

***N*-Methyl-2-(4′-acetoxymethyl-2′-aminophenylthio)benzamide (40).** Amide **39** (0.35 g, 0.97 mmol) was treated with 10% Pd/C (0.35 g) as described for **12**. The desired compound **40** was obtained as an orange oil and used without further purification.

***N*-Methyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamine (41).** Amide **40** (0.22 g, 0.66 mmol) was treated with BH_3−THF (1 M solution in THF) (3.0 mL, 3.0 mmol) as described for **13**. The desired compound **41** was obtained following purification by silica gel flash column chromatography (DCM/MeOH, 9:1) as a yellow oil (59 mg, 32%). ^{1}H NMR ($CDCl_3$, δ): 2.93 (s, 3H, NCH_3), 4.35 (s, 2H, CH_2N), 5.05 (s, 2H, CH_2OH), 7.15 (dd, 1H, J = 8.0, 1.6 Hz, ArH), 7.22 (d, 1H, J = 1.6 Hz, ArH), 7.24 (dd, 1H, J = 7.2, 2.0 Hz, ArH), 7.52 (m, 2H, ArH), 7.74 (dd, 1H, J = 7.2, 2.0 Hz, ArH), 7.81 (d, 1H, J = 8.0 Hz, ArH). Anal. ($C_{15}H_{18}N_2OS$) C, H, N.

Radiochemistry. (1) Radiosynthesis of [^{11}C]-(13). [^{11}C]-Iodomethane, produced from $^{11}CO_2$ as described previously,[21] was swept by a flow of argon gas (25 mL/min) into a solution of **33a** (1.0 mg) in DMF (0.2 mL) at −20 °C. When the radioactivity had peaked, the reaction mixture was heated to 90 °C for 10 min and quenched with HPLC buffer (0.5 mL). The solution was purified by semipreparative HPLC on column A: 50% CH_3CN, 50% H_2O, 6.3 g of $CH_3CO_2NH_4$ (0.082 M), 9 mL/min (retention time (rt) of [^{11}C]-**13** = 14.86 min, rt of **33a** = 7.85 min). The appropriate fractions were collected and condensed via a solid-phase extraction procedure based upon Lemaire's method.[46] An aliquot (0.1 mL) of the formulated solution was used to establish the chemical and radiochemical purity and specific activity of the final solution by analytical HPLC on column B: 70% MeOH, 30% H_2O, 0.1% Et_3N, 1 mL/min (rt of [^{11}C]-**13** = 5.08 min). The radiochemical yield for [^{11}C]-**13** was 24 ± 3% (n = 2). The chemical and radiochemical purity was >99%. [^{11}C]-**14a**, [^{11}C]-**14b**, [^{11}C]-**16**, and [^{11}C]-**20** were prepared in a similar manner with minor adjustments to the HPLC conditions. The radiochemical yields for [^{11}C]-**14a**, [^{11}C]-**14b**, [^{11}C]-**16**, and [^{11}C]-**20** were 30 ± 9% (n = 6), 4 ± 1% (n = 3), 24 ± 1% (n = 6), and 21 ± 6% (n = 6), respectively. Their chemical and radiochemical purities were >99%. Further evidence for the identity of the radiolabeled products was achieved by co-injection with authentic "cold" material on column B.

(2) Solid-Phase Extraction. The 4.5 mL fractions of [^{11}C]-**13** collected from the semipreparative HPLC column were diluted with sodium carbonate solution (6 mL, 12 mg/mL) and combined in one flask. The homogeneous solution was transferred with vacuum, through a Cook line, to a C_{18} Sep Pak (previously activated with ethanol (10 mL) and water (10 mL)) after stirring; the eluate was directed to the waste. After being washed five successive times, four with saline (0.9% NaCl, 10 mL) and one with ethanol (0.5 mL), all being directed to the waste, the [^{11}C]-**13** was eluted with ethanol (1.5 mL) and driven to a sterile empty vial containing 0.9% NaCl solution (3.5 mL). The residue was pushed with argon, through a Millipore filter (pore size 1.0 μm) followed by a smaller one (pore size 0.2 μm), to a 30 mL sterile, empty vial containing 0.9% NaCl solution (10 mL) for log P determinations.

(3) log *P* Measurements. The determination of partition coefficients of radioactive compounds [^{11}C]-**13**, [^{11}C]-**14a**, [^{11}C]-**14b**, [^{11}C]-**16**, and [^{11}C]-**20** between 1-octanol and 0.02 M phosphate buffer at pH 7.4 was performed as reported previously.[47−49]

In Vitro Competition Assays. Competition assays were performed based on methods reported previously.[21,50] Cell membranes from HEK-293 cells stably expressing hSERT or hNET (a gift from Dr. Randy Blakely, Ph.D., Vanderbilt University) and Madin Darby canine kidney cells stably expressing hDAT (a gift from Dr. Gary Rudnick, Yale University) were used in these assays. Cells were grown to confluency

in Dulbecco's Modification of Eagles's Medium containing 10% fetal bovine serum and Geneticin sulfate and then harvested using pH 7.4 phosphate-buffered saline (PBS) containing 0.53 mM ethylenediaminetetracetic acid at 37 °C. Cell pellets were prepared through centrifugation at 2000 rpm for 10 min, the supernatant was decanted, and the pellets were homogenized with a Polytron PT3000 (Brinkman, Littau, Switzerland) at 11 000 rpm for 12 s in 30 vol of PBS. The resulting cell membrane suspensions were centrifuged at 43 000*g* for 10 min; the supernatants were decanted, and the resulting pellets were stored at −70 °C until used in the assays.

Competition assays were performed in 13 mm × 100 mm polystyrene tubes in a 2.0 mL final volume consisting of 1.7 mL of assay buffer, 100 μL of competing ligand in assay buffer, 100 μL of radioligand in assay buffer, and 100 μL of cell membrane suspension (corresponding to 30−70 μg of protein) in assay buffer. Cell membrane pellets were characterized prior to competition assays to determine membrane concentrations that gave optimal signal while not significantly affecting the concentration of the free radioligand. The cell membrane pellets were resuspended in the appropriate volume of assay buffer through brief homogenization using a Polytron PT3000. Competing ligands were assayed in triplicate at 12 concentrations ranging from 10^{-13} to 10^{-5} M. To ensure solubility, the competing ligands were dissolved in 1:1 ethanol/5 mM HCl and then serially diluted in 5 mM HCl.

For SERT assays, the assay buffer consisted of 53 mM Tris buffer, 126 mM NaCl, and 5.3 mM KCl (pH 7.9 at room temperature) and the equilibrium incubation time was 2 h at room temperature. The radioligand used for SERT assays was [^{3}H]citalopram obtained from Dupont NEN (Boston, MA, 3100 GBq/mmol). For NET assays, the assay buffer consisted of 53 mM Tris buffer, 320 mM NaCl, and 5.3 mM KCl (pH 7.4 at 4 °C) and the equilibrium incubation time was 4 h at 4 °C. The radioligand used for NET assays was [^{3}H]nisoxetine obtained from Dupont NEN (3000 GBq/mmol). For the DAT assay, the assay buffer consisted of 42 mM sodium phosphate buffer and 320 mM sucrose (pH 7.4 at room temperature) and the equilibrium incubation time was 1 h at room temperature. The radioligand used for DAT assays was [^{3}H]WIN 35,428 obtained from Dupont NEN (Boston, MA, 84.5 Ci/mmol, 2.0 nM final concentration) or [^{125}I]RTI-55 obtained from Dupont NEN (Boston, MA, 2200 Ci/mmol, 2.0 nM final concentration). All of the assays were initiated by the addition of the cell membrane suspension.

At the end of the incubation, the assays were terminated by the addition of ∼5 mL of assay buffer at 4 °C followed by rapid vacuum filtration with 3 × 5 mL washes with assay buffer at 4 °C through GF/B filters (Whatman, Inc., Clifton, NJ) presoaked in assay buffer containing 0.3% polyethyleneimine. The data from the competition curves were analyzed, and K_i values were calculated using GraphPad Prism software (GraphPad software, San Diego, CA). The reported K_i values are the average of at least two separate assays, each in duplicates, for each compound.

Supporting Information Available: Theoretical and experimental elemental analyses for compounds **10d**−**41**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Sur, C.; Betz, H.; Schloss, P. Immunocytochemical detection of the serotonin transporter in rat brain. *Neuroscience* **1996**, *73*, 217−231.

(2) Tao-Cheng, J. H.; Zhou, F. C. Differential polarization of serotonin transporters in axons versus soma-dendrites: an immunogold electron microscopy study. *Neuroscience* **1999**, *94*, 821−830.

(3) Parent, A.; Descarries, L.; Beaudet, A. Organization of ascending serotonin systems in the adult rat brain. A radioautographic study after intraventribular administration of [^{3}H]5-hydroxytryptamine. *Neuroscience* **1981**, *6*, 115−138.

(4) Steinbusch, H. W. M. Distribution of serotonin-immunoreactivity in the central nervous system of the rat-cell bodies and terminals. *Neuroscience* **1981**, *6*, 557−618.

(5) Laasko, A.; Hietala, J. PET studies of brain monoamine transporters. *Curr. Pharm. Des.* **2000**, *6*, 1611−1623.

(6) Lasne, M. C.; Pike, V. W.; Turton, D. R. The radiosynthesis of [N-methyl-^{11}C]-sertraline. *Int. J. Radiat. Appl. Instrum., Part A* **1989**, *40*, 147−151.

(7) Owens, M. J.; Nemeroff, C. B. The serotonin transporter and depression. *Depression Anxiety* **1998**, *8* , 5−6.

(8) Owens, M. J.; Nemeroff, C. B. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin. Chem.* **1994**, *40*, 288−295.

(9) Lucki, I. The spectrum of behaviors influenced by serotonin. *Biol. Psychiatry* **1998**, *44*, 151−162.

(10) Cash, R.; Raisman, A.; Ploska, Y. High and Low Affinity [^{3}H]-Imipramine Binding Sites in Control and Parkinsonian Brain. *Eur. J. Pharmacol.* **1985**, *117*, 71−80.

(11) Chingaglia, G.; Landwehrmeyer, G.; Probst, A.; Palacios, J. M. Serotonergic Terminal Transporters are Differentially Affected in Parkinson's Disease and Progressive Supranuclear Palsy: An Autoradiographic Study with [^{3}H]Citalopram. *Neuroscience* **1993**, *54*, 691−699.

(12) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. Asymmetric induction in an enammonium-iminium rearrangement. Mechanistic insight via NMR, deuterium labeling, and reaction rate studies. Application to the stereoselective synthesis of pyrroloisoquinoline antidepressants. *J. Am. Chem. Soc.* **1990**, *112*, 3567−3583.

(13) Jagust, W. J.; Eberling, J. L.; Biegon, A.; Taylor, S. E.; Van-Brocklin, H. F.; Jordan, S.; Hanrahan, S. M.; Roberts, J. A.; Brennan, K. M.; Mathis, C. A. Iodine-123−5-iodo-6-nitroquipazine: SPECT radiotracer to image the serotonin transporter. *J. Nucl. Med.* **1996**, *37*, 1207−1214.

(14) Helfenbein, J.; Sandell, J.; Halldin, C.; Chalon, S.; Emond, P.; Okubo, Y.; Chou, Y.-H.; Frangin, Y.; Douziech, L.; Gareau, L.; Swahn C-G.; Besnard, J.-C.; Farde, L.; Guilloteau, D. PET examination of three potent cocaine derivatives as specific radioligands for the serotonin transporter. *Nucl. Med. Biol.* **1999**, *26*, 491−499.

(15) Szabo, Z.; Kao, P. F.; Scheffel, U.; Suehiro, M.; Mathews, W. B.; Ravert, H. T.; Musachio, J. L.; Marenco, S.; Kim, S. E.; Ricaurte, G. A.; Wong, D. F.; Wagner, Jr., H. N.; Dannals, R. F. Positron Emission Tomography imaging of serotonin transporters in the human brain using [^{11}C](+)McN5652. *Synapse* **1995**, *20*, 37−43.

(16) Huang, Y.; Hwang, D.-R.; Narendran, R.; Sudo, Y.; Chatterjee, R.; Bae, S.-A.; Mawlawi, O.; Kegeles, L. S.; Wilson, A. A.; Kung, H. F.; Laruelle, M. Comparative evaluation in nonhuman primates of five PET radiotracers for imaging the serotonin transposters: [^{11}C]McN5652, [^{11}C]ADAM, [^{11}C]DASB, [^{11}C]-DAPA and [^{11}C]AFM. *J. Cereb. Blood Flow. Metab.* **2002**, *22*, 1377−1398.

(17) Blough, B. E.; Abraham, P.; Mills, A. C.; Lewin, A. H.; Boja, J. W.; Scheffel, U.; Kuhar, M. J.; Carroll F. I. 3β-(4-ethyl-3-iodophenyl)nortropane-2-beta-carboxylic acid methyl ester as a high-affinity selective ligand for the serotonin transporter. *J. Med. Chem.* **1997**, *40*, 3861−3864.

(18) Goodman, M. M.; Chen, P.; Kilts, C. D.; Ely, T. D.; Camp, V. M.; Malveaux, E. J.; Votaw, J.; Davis, M.; Owens, M. Fluorine-18 labeled 2β-carbomethoxy-3β-(4′-(2-fluoroisopropenyl)phenyl)-nortropane (FIPPNT) synthesis, characterization and tissue distribution of a potential radioligand for mapping serotonin transporter sites by PET. *Book Abstr. Int. Chem. Congr. Pac. Basin Soc.* **2000**, *1*, 104.

(19) Goodman, M. M.; Chen, P.; Kilts, C. D.; Ely, T.; Davis, M. and Votaw, J. Fluorine-18 Serotonin Transporter Ligands. In *Synthesis and Applications of Isotopically Labelled Compounds*; Pleiss, U., Voges, R., Eds.; Wiley: New York, 2001; pp 362−366.

(20) Goodman, M. M.; Chen, P.; Plisson, C.; Martarello, L.; Galt, J.; Votaw, J. R.; Kilts, C. D.; Malveaux, G.; Camp, V. M.; Shi, B.; Ely, T. D.; Howell, L.; McConathy, J.; Nemeroff, C. B. Synthesis and characterization of iodine-123 labeled 2β-carbomethoxy-3β-(4′-((Z-2-iodoethenyl)phenyl)nortropane. A ligand for in vivo imaging of serotonin transporters by single-photon-emission-tomography. *J. Med. Chem.* **2003**, *46*, 925−935.

(21) Plisson, C.; McConathy, J.; Martarello, L.; Malveaux, E. J.; Camp, V. M.; Williams, L.; Votaw J. R.; Goodman, M. M. Synthesis, Radiosynthesis, and Biological Evaluation of Carbon-11 and Iodine-123 Labeled 2β-Carbomethoxy-3β-[4′-((Z)-2-haloethenyl)phenyl]tropanes: Candidate Radioligands for in Vivo Imaging of the Serotonin Transporter. *J. Med. Chem.* **2004**, *47*, 1122−1135.

(22) Oya, S.; Kung, M.-P.; Acton, P. D.; Mu, M.; Hou, C.; Kung, H. F. A new single-photon emission computed tomography imaging agent for serotonin transporters: [^{123}I]IDAM, 5-iodo-2-((2-((dimethylamino)methyl)phenyl)thio) benzyl alcohol. *J. Med. Chem.* **1999**, *42*, 333−335.

(23) Kung, M.-P.; Hou, C.; Oya, S.; Mu, M.; Acton, P. D.; Kung, H. F. Characterization of [^{123}I]IDAM as a novel single-photon emission tomography tracer for serotonin transporters. *Eur. J. Nucl. Med.* **1999**, *26*, 844−853.
(24) Acton, P. D.; Kung, M.-P.; Mu, M.; Plössl, K.; Hou, C.; Siciliano, M.; Oya, S.; Kung, H. F. Single-photon emission tomography imaging of serotonin transporters in the non-human primate brain with the selective radioligand [^{123}I]IDAM. *Eur. J. Nucl. Med.* **1999**, *26*, 854−861.
(25) Choi, S.-R.; Hou, C.; Oya, S.; Mu, M.; Kung, M.-P.; Siciliano, M.; Acton, P. D.; Kung, H. F. Selective in vitro and in vivo binding of [^{125}I]ADAM to serotonin transporters in rat brain. *Synapse* **2000**, *38*, 403−412.
(26) Oya, S.; Choi, S.-R.; Hou, C.; Mu, M.; Kung, M.-P.; Acton, P. D.; Siciliano, M.; Kung, H. F. 2-((2-((dimethylamino)methyl)phenyl)-thio)-5-iodophenylamine (ADAM): an improved serotonin transporter ligand. *Nucl. Med. Biol.* **2000**, *27*, 249−254.
(27) Acton, P. D.; Choi, S.-R.; Hou, C.; Plössl, K.; Kung, H. F. Quantification of serotonin transporters in nonhuman primates using [^{123}I]IDAM and SPECT. *J. Nucl. Med.* **2001**, *42*, 1556−1562.
(28) Newberg, A. B., MD.; Plössl, K., PhD.; Mozley, P. D., MD.; Stubbs, J. B., PhD.; Wintering, N., MSW.; Udeshi, M., MD.; Alavi, A., MD.; Kauppinen, T., PhD.; Kung, H. F., PhD. Biodistribution and imaging with ^{123}I-ADAM: a serotonin transporter imaging agent. *J. Nucl. Med.* **2004**, *45*, 834−841.
(29) Vercouillie, J.; Tarkiainen, J.; Halldin, C.; Emond, P.; Chalon, S.; Sandell, J.; Langer, O.; Guilloteau, D. Precursor synthesis and radiolabeling of [^{11}C]ADAM: a potential radioligand for the serotonin transporter exploration by PET. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 113−120.
(30) Houle, S.; Ginovart, N.; Hussey, D.; Meyer, J. H.; Wilson, A. A. Imaging the serotonin transporter with positron emission tomography: initial human studies with [^{11}C]DAPP and [^{11}C]-DASB. *Eur. J. Nucl. Med.* **2000**, *27*, 1719−1722.
(31) Emond, P.; Vercouillie, J.; Innis, R.; Chalon, S.; Mavel, S.; Frangin, Y.; Halldin, C.; Besnard, J.-C.; Guilloteau, D. Substituted diphenyl sulfides as selective serotonin transporter ligands: synthesis and in vivo evaluation. *J. Med. Chem.* **2002**, *45*, 1253−1258.
(32) Tarkiainen, J.; Vercouillie, J.; Emond, P.; Sandell, J.; Hiltunen, J.; Frangin, Y.; Guilloteau, D.; Halldin, C. Carbon-11 labeling of MADAM in two different positions: a highly selective PET radioligand for the serotonin transporter. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 1013−1023.
(33) Jarkas, N.; McConathy, J.; Ely, T.; Kilts, C. D.; Votaw, J. R.; Goodman, M. M. Synthesis and radiolabeling of new derivatives of ADAM, potential candidates as SERT imaging agents for PET. *J. Labelled Compd. Radiopharm.* **2001**, *44* , S204−S206.
(34) Huang, Y.; Bae, S.-A.; Zhu, Z.; Guo, N.; Hwang, D.-R.; Laruelle, M. Fluorinated analogues of ADAM as new PET radioligands for the serotonin transporter: synthesis and pharmacological evaluation. *J. Labelled Compd. Radiopharm.* **2001**, *44* (supp. 1), S18−S20.
(35) Huang, Y.; Hwang, D.-R.; Zhu, Z.; Bae, S.-A.; Guo, N.; Sudo, Y.; Kegeles, L. S.; Laruelle, M. Synthesis and pharmacological characterization of a new PET ligand for the serotonin transporter: [^{11}C]5-bromo-2-[2-(dimethylamino- methylphenylsulfanyl)]phenylamine ([^{11}C]DAPA). *Nucl. Med. Biol.* **2002**, *29*, 741−751.
(36) Jarkas, N.; McConathy, J.; Malveaux, E.; Votaw, J. R.; Goodman, M. M. Radiolabeling and *in vivo* characterization of ^{11}C-EADAM: an attractive PET radioligand for serotonin transporters (SERT). *J. Nucl. Med.* **2002**, *43,*164P.
(37) Jarkas, N.; McConathy, J.; Malveaux, E. J.; Williams, L. A.; Votaw, J. R.; Kilts, C. D.; Goodman, M. M. Synthesis, characterization and microPET imaging of serotonin transporters (SERT) with [^{11}C]-HOMADAM: a new diarylsulfide SERT PET imaging agent. *J. Nucl. Med.* **2003**, *44,*148P.
(38) Zhu, Z.; Guo, N.; Narendran, R.; Erritzoe, D.; Ekelund, J.; Hwang, D.-R.; Bae, S-A.; Laruelle, M.; Huang, Y. The new PET imaging agent [^{11}C]AFE is a selective serotonin transporter ligand with fast brain uptake kinetics. *Nucl. Med. Biol.* **2004**, *31*, 983−994.
(39) The thiobenzamide **9a** was obtained from thiosalicylic acid following the procedure described in ref 22.
(40) Ethyl thiosalicylate **9b** was prepared by refluxing thiosalicylic acid in absolute ethanol with concentrated sulfuric acid for 6 days.
(41) Jarkas, N.; McConathy, J.; Votaw, J. R.; Voll, R. J.; Malveaux, E. J.; Camp, V. M.; Williams, L.; Goodman, R. R.; Kilts, C. D.; Goodman, M. M. Synthesis and characterization of EADAM: a selective radioligand for mapping the brain serotonin transporters by positron emission tomography. *Nucl. Med. Biol.* **2005**, *32,* 75−86.
(42) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. The direct orthometalation-Ullmann connection. A new Cu(I)-catalysed variant for the synthesis of substituted diaryl ethers. *J. Org. Chem.* **1999**, *64*, 2986−2987.
(43) Jung, M. E.; Dansereau, M. K. Benzo[H]-1, 6-naphthyridine synthesis via intramolecular Diels−Alder reactions of aryl oxazoles: synthetic approach to 2-bromoleptoclinidinone. *Heterocycles* **1994**, *39*, 767−778.
(44) Middleton, W. J. New fluorinating reagents. Dialkylaminosulfur fluorides. *J. Org. Chem.* **1975**, *40*, 574−578.
(45) Pandey, G.; Bagul, T. D.; Sahoo, A. K. [3+2] Cycloaddition of nonstabilized azomethine ylides. 7. Stereoselective synthesis of epibatidine and analogues. *J. Org. Chem.* **1998**, *63*, 760−768.
(46) Lemaire, C.; Plenevaux, A.; Aerts, J.; Del Fiore, G.; Brihaye, C.; Le Bars, D.; Comar, D.; Luxen, A. Solid phase extraction - an alternative to the use of rotaty evaporators for solvent removal in the rapid formulation of PET radio pharmaceuticals. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 63−75.
(47) Wilson, A. A.; Ginovart, N.; Schmidt, M.; Meyer, J. H.; Threlkeld, P. G.; Sylvain, H. Novel Radiotracers for Imaging the Serotonin Transporters by Positron Emission Tomography: Synthesis, Radiosynthesis, and in Vitro and ex Vivo Evaluation of ^{11}C-Labeled 2-(Phenylthio)araalkylamines. *J. Med. Chem.* **2000**, *43*, 3103−3110.
(48) Wilson, A. A.; DaSilva, J. N.; Houle, S. Facile radiolabeling and purification of 2β-[O-^{11}CH$_3$]-carbomethoxy-3β-aryltropanes: radiotracers for the dopamine transporter. *J. Labelled Compd. Radiopharm.* **1994**, *34*, 759.
(49) Wilson, A. A.; Houle, S. Radiosynthesis of carbon-11 labelled *N*-methyl-2-(arylthio)benzylamines: potential radiotracers for the serotonin reuptake receptor. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 1277−1288.
(50) Owens, M. J.; Morgan, W. N.; Plott, S. J.; Nemeroff, C. B. Neurotransmitter receptor and transporter binding profile of antidepressant and their metabolites. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1305−1322.

JM050079O