Substituted Diphenyl Sulfides as Selective Serotonin Transporter Ligands: Synthesis and In Vitro Evaluation

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A series of diphenyl sulfide derivatives substituted at the 1-, 2′-, and 4′-positions has been synthesized and evaluated for their in vitro affinities at the dopamine, serotonin (SERT), and norepinephrine transporters. The examination of K_i values revealed that most of these derivatives have high affinity and selectivity for the SERT. Moreover, substitutions at these positions differently influence the SERT binding: (i) The nature of the substituent linked at the 1-position critically influences the SERT affinity. (ii) Functions containing heteroatom at the 2′-position afford compounds with high SERT affinity. (iii) The nature of the substituent at the 4′-position slightly influences the SERT affinity whereas steric effect markedly decreases the SERT affinity. From this series, the most SERT selective derivatives (such as **8b**, **8c**, and **8g**) are now evaluated for their potential as positron emission tomography imaging agents when labeled with carbon-11.

Introduction

The serotoninergic neurotransmission plays an important role in the central nervous system and involves the serotonin transporter (SERT), which modulates synaptic serotonin (5-HT) levels. Recent reviews have suggested that alteration of SERT function could be associated with neurological and psychiatric disorders such as Parkinson's and Alzheimer's diseases and depression.[1−4] Moreover, SERT is the site of action of many existing antidepressant drugs. For these reasons, in vivo mapping of the SERT in the living human brain either by positron emission tomography (PET) or by single photon emission computed tomography (SPECT) would be of great value to better understand the physiopathological mechanism of neurodegenerative and mental illness as well as to assess the quantification of SERT occupancy in relation to antidepressant drug treatment. In that aim, the development of highly potent and selective ligands to explore the SERT by scintigraphy has been intensively pursued by many groups. Several classes of compounds have been screened for their SERT affinity, such as phenyl nortropane or quipazine derivatives. In the phenyl nortropane series, although high in vitro SERT affinity and selectivity were obtained for EINT,[5] RTI-364,[6] RTI-330,[6] RTI-357,[6] or LBT-44,[7] 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 to these nortropane analogues, two new derivatives named ZIENT and FIPPNT displayed a high specific binding at the SERT with a low nonspecific accumulation and have been proposed as potential radioligands for SPECT or PET imaging, respectively, of SERT.[8,9] The quipazine structure was also found to be a good framework to design potent SERT ligands. For example, 5-iodo-6-nitroquipazine is highly potent and selective at SERT in vitro and showed promising properties for in vivo mapping of SERT in monkey brain.[10] However, human studies with this ligand have not been reported. More recently, on the basis of a structure described as a novel antidepressant,[11,12] several substituted diphenyl sulfides have been described as potent and selective SERT derivatives (Figure 1). These diphenyl sulfide derivatives (IDAM, ADAM, DAPP, and DASB) have been labeled with I-125 and C-11 and displayed high in vitro and in vivo affinities and selectivities for SERT relative to the dopamine and the norepinephrine transporters (DAT, NET).[13−17] Moreover, preliminary studies with IDAM and ADAM in nonhuman primates[18,19] or with DAPP or DASB in human brains[20] showed that these ligands have promising characteristics for imaging SERT. On the basis of these results and in order to extend the knowledge of the SERT binding site requirements, we report here the synthesis and in vitro properties of new diphenyl sulfide derivatives. Information from these chemical modulations may be useful in the design of new radiopharmaceuticals to explore the SERT in vivo in humans by PET or by SPECT.

Chemistry

All of the compounds tested for their in vitro binding properties were prepared as described in Schemes 1−3. Compounds **3a**−**c** and **4a**−**c** (Scheme 1) were prepared from 2-bromo-5-halogenobenzaldehyde, 2,5-dibromonitrobenzene, or 4-bromo-3-nitrotoluene and *N*,*N*-dimethyl or *N*-methyl-2-thiobenzamide using a previously described procedure.[13,21] The reduction of amide as well as aldehyde functions of compounds **3a**−**c** and **4a**−**c** were achieved using the diborane−tetrahydrofuran (THF) complex to afford **5a**−**c** and **7a**−**c** in 52−85%

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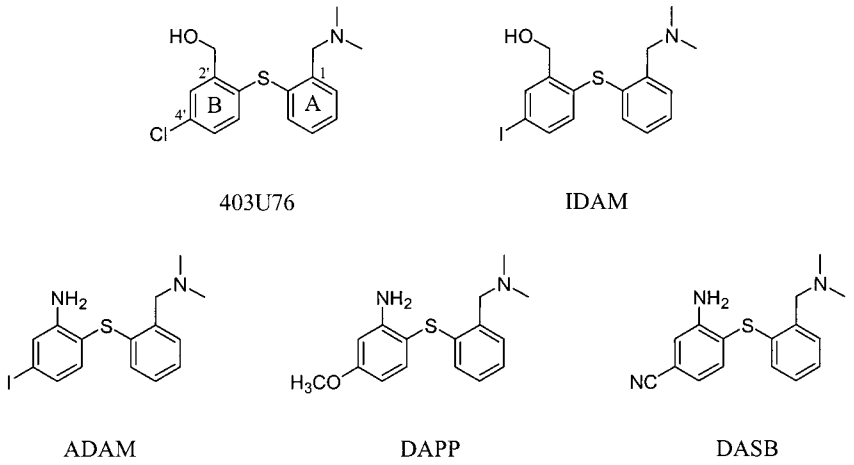
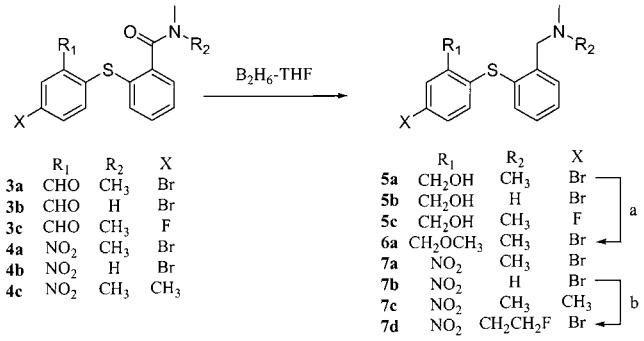


Figure 1. Diphenylsulfide derivatives with high SERT affinity.

Scheme 1[a]

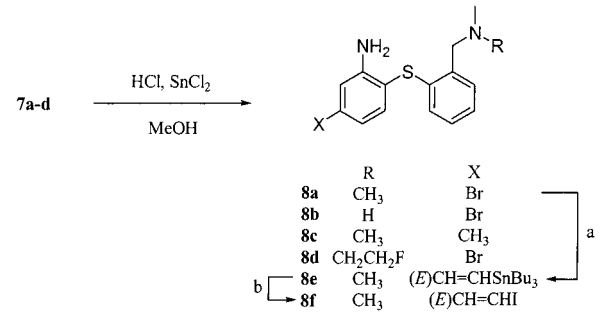


	R_1	R_2	X
3a	CHO	CH_3	Br
3b	CHO	H	Br
3c	CHO	CH_3	F
4a	NO_2	CH_3	Br
4b	NO_2	H	Br
4c	NO_2	CH_3	CH_3

	R_1	R_2	X	
5a	CH_2OH	CH_3	Br	a
5b	CH_2OH	H	Br	
5c	CH_2OH	CH_3	F	
6a	CH_2OCH_3	CH_3	Br	
7a	NO_2	CH_3	Br	
7b	NO_2	H	Br	b
7c	NO_2	CH_3	CH_3	
7d	NO_2	CH_2CH_2F	Br	

[a] Key: (a) NaH/CH_3I; (b) $FCH_2CH_2Br/EtOH/Et_3N$.

Scheme 2[a]



	R	X	
8a	CH_3	Br	a
8b	H	Br	
8c	CH_3	CH_3	
8d	CH_2CH_2F	Br	
8e	CH_3	$(E)CH{=}CHSnBu_3$	b
8f	CH_3	$(E)CH{=}CHI$	

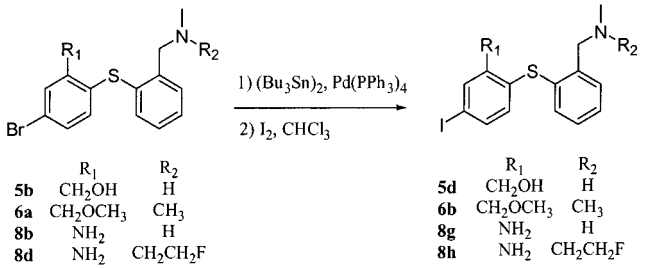
[a] Key: (a) $(E)Bu_3SnHC{=}CHSnBu_3/Pd(PPh_3)_4$; (b) $I_2/CHCl_3$.

yields. *O*-methylation of **5a** by methyl iodide and *N*-alkylation of **7b** by 1-bromo-2-fluoroethane afford **6a** and **7d** in 74 and 46% yields, respectively. Scheme 2 described the reduction of the nitro group of **7a**−**d** by treatment with tin(II) chloride in HCl and MeOH to obtain **8a**−**d** in 66−80% yields. Compound **8f** was obtained by the coupling reaction of **8a** and (*E*)-1,2-bis-(tributylstannyl)ethylene under palladium catalysis as the first step. Compound **8f** was finally prepared by iododestannylation of **8e** using iodine in $CHCl_3$ in 65% yield. The preparation of **5d**, **6b**, **8g**, and **8h** follows a two step sequence in which the bromine atom of **5b**, **6a**, **8b**, and **8d** was exchanged for a tributylstannyl group and finally for an iodide atom in 21−41% yields for the two steps (Scheme 3).

Results and Discussion

403U76 (Figure 1), a diphenyl sulfide substituted by a dimethylaminomethyl group at the 1-position of the aromatic A ring and disubstituted by a hydroxymethyl at the 2′-position and a chlorine at the 4′-position of the aromatic B ring, has been reported as an inhibitor of serotonin uptake.[12] We have modulated these groups in order to extend the knowledge of the SERT binding site requirements, which may be useful for the design of new radiopharmaceuticals to explore the SERT in vivo in humans with PET or SPECT imaging. The affinities for monoamine transporters of the new compounds described here were determined by in vitro competitive binding assays. [^{3}H] paroxetine, [^{3}H] GBR-12935, and [^{3}H] nisoxetine were used as transporter ligands for SERT, DAT, and NET sites, respectively. The results are expressed as inhibition constants (K_i) and are summarized in Table 1.

Scheme 3

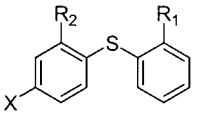


	R_1	R_2
5b	CH_2OH	H
6a	CH_2OCH_3	CH_3
8b	NH_2	H
8d	NH_2	CH_2CH_2F

	R_1	R_2
5d	CH_2OH	H
6b	CH_2OCH_3	CH_3
8g	NH_2	H
8h	NH_2	CH_2CH_2F

The first examination of Table 1 revealed that **3a** and **3c** are the only derivatives of that series with very low affinities for the SERT as well as for the DAT and the NET. These two compounds differ from the other derivatives by two carbonyl functions (aldehyde and amide) to which their low affinities could be attributed. However, Oya et al.[22] showed that **7a** and the *O*-acetylated analogue of compound **5a**, which has a dimethylaminomethyl group at the 1-position, bind with high affinities to the SERT. Moreover, compounds **5a**, **6a**, and **8a** that bear an alcohol, ether, or amine function at the 2′-position also display high SERT affinities. On the basis of these results, it could be assumed that the amide function linked at the 1-position of compounds **3a** and **3c** is responsible for their low SERT affinities since a large range of functional groups such as ester, alcohol, ether, nitro, or amino could be introduced at the 2′-position without affecting the SERT affinity when a dimethylaminomethyl group is linked at the 1-position. The modulation of the dimethylaminomethyl group at the 1-position, replacing one methyl by a hydrogen

Table 1. K_i Values at the SERT, DAT, and NET of Substituted Diphenyl Sulfides



compds[a]	R_1	R_2	X	K_i values (nM) SERT	DAT	NET
3a	$CON(CH_3)_2$	CHO	Br	>1000	>1000	>1000
3c	$CON(CH_3)_2$	CHO	F	695 ± 172	>1000	>1000
5a[13]	$CH_2N(CH_3)_2$	CH_2OH	Br	1.92 ± 0.42	950 ± 350	5.80 ± 1.93
5c	$CH_2N(CH_3)_2$	CH_2OH	F	7.96 ± 2.43	339 ± 121	28.4 ± 4.3
5d	CH_2NHCH_3	CH_2OH	I	0.98 ± 0.33	760 ± 214	12.8 ± 2.3
6a	$CH_2N(CH_3)_2$	CH_2OCH_3	Br	2.75 ± 0.24	>1000	326 ± 76
6b[22]	$CH_2N(CH_3)_2$	CH_2OCH_3	I	2.50 ± 0.26	172 ± 64	212 ± 46
ADAM[14]	$CH_2N(CH_3)_2$	NH_2	I	0.4 ± 0.12	>1000	683 ± 143
8a[22]	$CH_2N(CH_3)_2$	NH_2	Br	2.23 ± 0.42	171 ± 77	107 ± 32
8b	CH_2NHCH_3	NH_2	Br	1.49 ± 0.28	171 ± 77	107 ± 32
8c	$CH_2N(CH_3)_2$	NH_2	CH_3	1.65 ± 0.10	>1000	325 ± 108
8f	$CH_2N(CH_3)_2$	NH_2	(*E*)-CH=CHI	53.3 ± 5.8	>1000	80.2 ± 23.3
8g[31]	CH_2NHCH_3	NH_2	I	1.25 ± 0.01	818 ± 207	714 ± 184
8h	$CH_2NCH_3CH_2CH_2F$	NH_2	I	19.3 ± 1.9	>1000	>1000

[a] Other affinity values using different experimental conditions are described in quoted references.

or a fluoroethyl group, has been undertaken. Regarding the 2′-hydroxymethyl series, compound **5d** retains a high SERT affinity (0.98 nM) when compared to compound **5a**,**c** (1.92 and 7.96 nM). Similar results were also obtained in the 2′-amino series, with high SERT affinities for compounds **8a** and ADAM (2.23 and 0.40 nM, respectively) and their corresponding *N*-desmethylated analogues **8b** and **8g** (1.49 and 1.25 nM). However, the introduction of a fluoroethyl group at the nitrogen (**8h**) reduces SERT affinity (19 nM) when compared to compound **8g** or ADAM. Even though the decrease in SERT affinity could be attributed to the increase of steric effect brought by the fluoroethyl group, the reduction of the nitrogen atom basicity by the fluorine atom could also affect the SERT binding. Regardless of the causes, these results confirm that the substituent linked at that part of the molecule critically influences SERT binding. Subsequent substitutions at the 2′- and 4′-positions have been undertaken on *N*,*N*-dimethylaminomethyl derivatives.

The *N*,*N*-dimethylaminomethyl-4′-bromo or 4′-iodo derivatives with a hydroxymethyl (**5a**), a methoxymethyl (**6a**,**b**), or an amino function (**8a**, ADAM) at the 2′-position displayed high SERT binding affinities ranging from 1.9 to 2.8 nM and low affinities for DAT ranging from 171 to more than 1000 nM. High SERT affinities of compounds **5a**, **6a**,**b**, **8a**, and ADAM suggest that the heteroatom link at the 2′-position is critical for the SERT binding given that Oya et al.[22] reported that the pyridinyl analogue of **8a** (in which the 2′-amino-4′-bromophenyl was replaced with a 4′-bromopyridin-2-yl group) showed a weak SERT affinity. Furthermore, the substituent at the 2′-position is implicated in the SERT selectivity of these compounds, as compound **5a**,**d** has a high NET affinity (5.80 and 12.80 nM) whereas moderate to low NET affinities were obtained for compounds **8a** and **6a** (107 and 326 nM).

To evaluate the influence on monoamine transporter affinity of the substituent linked at the 4′-position, K_i values of 2′-amino, 2′-hydroxymethyl, or 2′-methoxymethyl derivatives were examined. Changing the fluorine atom of compound **5c** to a bromine atom (**5a**) or the bromine atom of compounds **6a** and **8a**,**b** to an iodine atom (**6b**, ADAM, **8g**) has weak to no influence on SERT binding affinity. Moreover, the replacement of the iodine atom of ADAM by a methyl group (**8c**) produced high SERT affinity (1.65 nM). These results are in agreement with those published earlier describing that the substitution of the iodine atom of ADAM by a trifluoromethyl, a chlorine, a methoxy, or a cyano group affords compounds with nano- to subnanomolar affinities for the SERT.[15] On the basis of these results, it could be assumed that the nature of the substituent linked at the 4′-position of the molecule has relatively little effect on SERT binding. However, the steric effect at that part of the structure seems to greatly influence the binding potency of such derivatives since compound **8f**, with a trans iodovinyl group, displayed a low SERT affinity (53.4 nM).

In conclusion, chemical modifications of diphenyl sulfide derivatives at the 1-, 2′-, and 4′-positions have been realized. Examination of in vitro affinities to monoamine transporters showed that (i) the substituent at the 1-position is critical for SERT binding and significantly influences SERT affinity; (ii) the SERT binding site tolerates functions containing a heteroatom (hydroxymethyl, methoxymethyl, amino) at the 2′-position of diphenyl sulfide and can yield compounds with high SERT affinities; and (iii) the nature of the substituent linked at the 4′-position slightly influences the SERT affinity whereas steric effect markedly decreases the SERT affinity.

From this series, the most selective SERT derivatives such as compounds **6a** and **8c**,**g** have been selected for further biological evaluation. As a first step of these investigations, compound **8c**, also named MADAM, has been labeled with tritium for more detailed in vitro characterization and with carbon-11 for PET investigations. [^{3}H]-MADAM displayed in vitro a K_d value of 59.6 pM with a B_{max} of 543 fmol/mg protein (rat cortical membranes).[23] Moreover, preliminary in vivo PET imaging in a monkey showed that [^{11}C]-MADAM had a rapid and high specific accumulation in brain regions rich in SERT, with a thalamus to cerebellum uptake ratio of 2.[24,25] We are now working on the full in vivo

characterization of this compound to evaluate its potential as a PET ligand for SERT imaging in human subjects.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on a Brüker DPX Advance 200 spectrometer (200 MHz for ^{1}H, 50.3 MHz for ^{13}C). $CDCl_3$ was used as the solvent; chemical shifts are expressed in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were obtained on a CG-MS Hewlett-Packard 5989A spectrometer (electronic impact at 70 eV). The thin-layer chromatographic analyses were performed using Merck 60F-254 silica gel plates. Flash chromatography was used for routine purification of reaction products using silica gel (230−400 mesh). Visualization was accomplished under UV or in an iodine chamber. All chemicals and solvents were of commercial quality and were purified following standard procedures. Elemental analyses of new compounds were within ±0.4% of theoretical values.

Chemistry. Synthesis of Compounds 5a−c and 7a−c: General Procedure. To a solution of compounds **3a**−**c** and **4a**−**c** (8 mmol) in THF (20 mL) under a nitrogen atmosphere was added drop by drop diborane−THF (1M, 20 mL) at 0 °C. The mixture was heated to reflux for 5 h, stirred at room temperature overnight, and quenched with concentrated HCl (1 mL). The residue was then dissolved in water (20 mL), basified with NaOH (to pH 10), and extracted with $CHCl_3$ (3 × 20 mL). After the solvent was evaporated, the crude product was purified by flash chromatography (EtOAc/petroleum ether/Et_3N: 4/5/1 for *N*,*N*-dimethyl derivatives and EtOAc/MeOH/Et_3N: 8/1/1 for *N*-methyl derivatives).

***N*,*N*-Dimethyl-2-(4′-bromo-2′-hydroxymethylphenylthio)benzylamine (5a).** Yield = 54%; yellow oil. ^{1}H NMR: δ 2.29 (s, 6H), 3.54 (s, 2H), 4.69 (s, 2H), 6.94−6.98 (m, 1H), 7.06−7.14 (m, 2H), 7.21−7.26 (m, 2H), 7.36 (dd, 1H, ^3J = 8.3 Hz, ^4J = 2.0 Hz), 7.50 (d, 1H, ^4J = 2.0 Hz). ^{13}C NMR: δ 45.6 (2C), 62.4, 62.9, 123.1, 127.1, 128.9, 131.1, 131.3, 131.4, 132.3, 133.4, 136.3, 136.4, 138.3, 145.5. MS: *m*/*z* = 353 (M^+, 11), 351 (M^+, 11), 293 (12), 291 (15), 227 (25), 197 (21), 165 (22), 164 (20), 132 (26), 58 (62), 46 (100), 42 (27). Anal. ($C_{16}H_{18}BrNOS$) C, H, N.

***N*-Methyl-2-(4′-bromo-2′-hydroxymethylphenylthio)benzylamine (5b).** Yield = 52%; yellow oil. ^{1}H NMR: δ 2.36 (s, 3H), 3.01 (s, 1H), 3.75 (s, 2H), 4.50 (s, 2H), 6.97−7.22 (m, 5H), 7.26 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.1 Hz), 7.57 (d, 1H, ^4J = 2.1 Hz). ^{13}C NMR: δ 35.9, 54.0, 61.8, 122.4, 128.2, 128.9, 130.6, 131.0, 131.1, 132.0, 132.5, 133.6, 134.0, 139.8, 144.8. Anal. ($C_{15}H_{16}BrNOS$) C, H, N.

***N*,*N*-Dimethyl-2-(4′-fluoro-2′-hydroxymethylphenylthio)benzylamine (5c).** Yield = 55%; orange oil. ^{1}H NMR: δ 2.35 (s, 6H), 3.58 (s, 2H), 4.59 (s, 2H), 6.91−7.32 (m, 6H), 7.57 (dd, 1H, ^3J = 8.4 Hz, ^3J = 5.7 Hz). ^{13}C NMR: δ 45.5 (2C), 62.2, 62.7, 115.1 (d, ^2J = 21.0 Hz), 115.9 (d, ^2J = 23 Hz), 126.4, 127.1, 128.7, 129.6, 131.0, 137.5 (2C), 137.6, 147.3 (d, ^3J = 7 Hz), 163.7 (d, ^1J = 248.6 Hz). MS: *m*/*z* = 291 (M^+, 79), 231 (68), 215 (98), 132 (67), 91 (48), 58 (100), 46 (68), 42 (45). Anal. ($C_{16}H_{18}FNOS$) C, H, N.

***N*,*N*-Dimethyl-2-(4′-bromo-2′-nitrophenylthio)benzylamine (7a).** Yield = 61%; yellow oil. ^{1}H NMR: δ 2.21 (s, 6H), 3.54 (s, 2H), 6.60 (d, 1H, ^3J = 8.7 Hz), 7.39 (td, 1H, ^3J = 7.4 Hz, ^4J = 1.4 Hz), 7.43 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.2 Hz), 7.54 (td, 1H, ^3J = 7.4 Hz, ^4J = 1.4 Hz), 7.57 (dd, 1H, ^3J = 7.4 Hz, ^4J = 1.4 Hz), 7.70 (dd, 1H, ^3J = 7.4 Hz, ^4J = 1.4 Hz), 8.40 (d, 1H, ^4J = 2.2 Hz). ^{13}C NMR: δ 45.8 (2C), 61.7, 112.0, 128.8, 129.1, 130.0, 130.3, 131.2, 131.3, 136.6, 137.6, 139.1, 144.4, 145.7. MS: *m*/*z* = 368 (M^+, 3), 366 (M^+, 3), 277 (19), 275 (18), 58 (100). Anal. ($C_{15}H_{15}BrN_2O_2S$) C, H, N.

***N*-Methyl-2-(4′-bromo-2′-nitrophenylthio)benzylamine (7b).** Yield = 60%; yellow oil. ^{1}H NMR: δ 1.47 (s broad, 1H), 2.33 (s, 3H), 3.74 (s, 2H), 6.50 (d, 1H, ^3J = 8.7 Hz), 7.27−7.56 (m, 5H), 8.33 (d, 1H, ^4J = 2.1 Hz). ^{13}C NMR: δ 32.2, 49.3, 119.1, 129.4, 131.3, 131.8, 132.3, 132.5, 135.7, 137.0, 137.5, 138.4, 144.8 145.6. MS: *m*/*z* = 354 (M^+, 1), 352 (M^+, 1), 319 (23), 317 (22), 277 (29), 275 (27), 152 (27), 150 (33), 44 (100), 42 (71). Anal. ($C_{14}H_{13}BrN_2O_2S$) C, H, N.

***N*,*N*-Dimethyl-2-(4′-methyl-2′-nitrophenylthio)benzylamine (7c).** Yield = 85%; orange oil. ^{1}H NMR: δ 2.23 (s, 6H), 2.40 (s, 3H), 3.56 (s, 2H), 6.63 (d, 1H, ^3J = 8.3 Hz), 7.16 (dd, 1H, ^3J = 8.3 Hz, ^4J = 2.0 Hz), 7.38 (td, 1H, ^3J = 7.4 Hz, ^4J = 1.5 Hz), 7.50 (td, 1H, ^3J = 7.4 Hz, ^4J = 1.5 Hz), 7.56 (dd, 1H, ^3J = 7.4 Hz, ^4J = 1.4 Hz), 7.69 (dd, 1H, ^3J = 7.4 Hz, ^4J = 1.4 Hz), 8.08 (d, 1H, ^4J = 2.0 Hz). ^{13}C NMR: δ 20.9, 45.8 (2C), 61.6, 126.3, 128.7, 128.8, 130.6, 130.7, 131.2, 134.9, 135.8, 135.9, 137.4, 144.1, 145.6. MS: *m*/*z* = 302 (M^+, 12), 285 (42), 211 (75), 194 (21), 58 (100), 42 (25). Anal. ($C_{16}H_{18}N_2O_2S$) C, H, N.

***N*,*N*-Dimethyl-2-(4′-bromo-2′-methoxymethylphenylthio)benzylamine (6a).** To a solution of compound **5a** (290 mg, 0.82 mmol) in 4 mL of dimethylformamide were added at 0 °C NaH (29 mg, 1.21 mmol) and CH_3I (156 mg, 1.1 mmol). The mixture was stirred for 3 h at room temperature, treated with water (20 mL), and extracted with $CHCl_3$ (3 × 10 mL). The organic layers were dried and evaporated, and the residue was purified by flash chromatography (Et_2O/Et_3N: 9/1) to obtain compound **6a** in 74% yield as a yellow oil. ^{1}H NMR: δ 2.20 (s, 6H), 3.35 (s, 3H), 3.47 (s, 2H), 4.44 (s, 2H), 6.94 (dd, 1H, ^3J = 7.3 Hz, ^4J = 1.6 Hz), 6.98 (d, 1H, ^3J = 8.4 Hz), 7.07 (td, 1H, ^3J = 7.3 Hz, ^4J = 1.6 Hz), 7.16 (td, 1H, ^3J = 7.3 Hz, ^4J = 1.6 Hz), 7.25 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.2 Hz), 7.34 (dd, 1H, ^3J = 7.3 Hz, ^4J = 1.6 Hz), 7.60 (d, 1H, ^4J = 2.0 Hz). ^{13}C NMR: δ 45.8 (2C), 59.1, 62.5, 72.0, 122.3, 127.4, 128.4, 130.7, 131.2, 131.4, 131.6, 133.3, 134.5, 135.7, 139.8, 141.9. MS: *m*/*z* = 352 (12), 350 (12), 290 (31), 288 (29), 165 (24), 164 (23), 132 (32), 126 (35), 58 (100), 45 (70), 44 (28), 42 (48). Anal. ($C_{17}H_{20}BrNOS$) C, H, N.

***N*-(2-Fluoroethyl),*N*-methyl-2-(4′-bromo-2′-nitrophenylthio)benzylamine (7d).** A solution of compound **7b** (354 mg, 1 mmol), EtOH (10 mL), Et_3N (140 μL), and 1-bromo-2-fluoroethane (1.3 mmol) was heated at 70 °C for 16 h. After it was cooled at room temperature, the solvent was removed, and the residue was purified by flash chromatography (AcOEt/Et_3N: 9/1) to give compound **7d** in 46% yield as an orange oil. ^{1}H NMR: δ 2.26 (s, 3H), 2.74 (td, 2H, ^3J = 27.2 Hz, ^3J = 5.0 Hz), 3.71 (s, 2H), 4.52 (td, 2H, ^2J = 47.6 Hz, ^3J = 5.0 Hz), 6.60 (d, 1H, ^3J = 8.7 Hz), 7.37−7.46 (m, 2H), 7.51−7.61 (m, 2H), 7.73 (d, 1H, ^3J = 6.9 Hz), 8.42 (d, 1H, ^4J = 2.2 Hz). ^{13}C NMR: δ 45.8, 57.5 (d, ^2J = 20.1 Hz), 60.2, 82.8 (d, ^1J = 168.1 Hz), 118.0, 128.8, 129.2, 130.0, 130.3, 131.2, 131.4, 136.6, 137.7, 139.0, 144.3, 145.7. MS: *m*/*z* = 383 (12), 381 (12), 277 (25), 275 (25), 243 (32), 90 (46), 44 (76), 42 (100). Anal. ($C_{16}H_{16}BrFN_2O_2S$) C, H, N.

Synthesis of Compounds 8a−d: General Procedure. To a solution of compound **7a**−**d** (4.11 mmol), concentrated HCl (15.2 mL) and MeOH (30.5 mL) were added below 10 °C $SnCl_2$ (3.05 g, 16 mmol). The reaction mixture was stirred at room temperature overnight, treated with water (75 mL), basified with NaOH (to pH 10), and extracted with AcOEt (3 × 50 mL). After the solvent was evaporated, the residue was purified by flash chromatography.

***N*,*N*-Dimethyl-2-(2′-amino-4′-bromophenylthio)benzylamine (8a).** Flash chromatography (EtOAc/petroleum ether/Et_3N: 5/4.5/0.5); yield = 79%; orange oil. ^{1}H NMR: δ 2.25 (s, 6H), 3.53 (s, 2H), 4.68 (s broad, 2H), 6.70−6.81 (m, 2H), 6.85−6.90 (m, 1H), 7.04−7.10 (m, 2H), 7.18−7.23 (m, 1H), 7.40 (d, 1H, ^3J = 5.7 Hz). ^{13}C NMR: δ 45.7 (2C), 62.9, 114.9, 118.1, 121.3, 125.2, 126.1, 128.5, 128.6, 130.9, 137.0, 137.4, 139.1, 150.7. MS: *m*/*z* = 338 (M^+, 9), 336 (M^+, 9), 212 (36), 165 (100), 164 (54), 134 (45), 58 (67), 44 (38). Anal. ($C_{15}H_{17}BrN_2S$) C, H, N.

***N*-Methyl-2-(2′-amino-4′-bromophenylthio)benzylamine (8b).** Flash chromatography (EtOAc/MeOH/Et_3N: 8/1/1); yield = 66%; orange oil. ^{1}H NMR: δ 1.43 (s broad, 1H), 2.44 (s, 3H), 3.94 (s, 2H), 4.46 (s broad, 2H), 6.76−6.84 (m, 3H), 7.03−7.07 (m, 2H), 7.20−7.25 (m, 2H). ^{13}C NMR: δ 36.6, 54.5, 114.0, 118.2, 121.8, 125.3, 126.3, 127.7, 128.4, 129.9, 135.6, 138.1, 138.8, 150.4. MS: *m*/*z* = 324 (M^+, 4), 322 (M^+,

4), 212 (19), 152 (11), 151 (42), 150 (26), 120 (100), 118 (25), 44 (29). Anal. ($C_{14}H_{15}BrN_2S$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-methylphenylthio)benzylamine (8c).** Flash chromatography (EtOAc/petroleum ether/ Et_3N: 4.5/5/0.5); yield = 80%; yellow oil. ^{1}H NMR: δ 2.34 (s, 6H), 2.36 (s, 3H), 3.62 (s, 2H), 4.44 (s broad, 2H), 6.60−6.65 (m, 2H), 6.91 (dd, 1H, ^3J = 7.3 Hz, ^4J = 1.6 Hz), 7.07−7.16 (m, 2H), 7.27−7.31 (m, 1H), 8.41 (d, 1H, ^3J = 8.3 Hz). ^{13}C NMR: δ 22.0, 45.8 (2C), 62.8, 112.2, 116.4, 120.0, 125.5, 127.6, 128.4, 130.6, 136.9, 138.0, 138.2, 141.7, 149.7. MS: *m*/*z* = 272 (M^+, 24), 165 (100), 164 (57), 150 (48), 134 (44), 132 (32), 58 (57), 44 (40). Anal. ($C_{16}H_{20}N_2S$) C, H, N.

***N*-(2-Fluoroethyl),*N*-methyl-2-(2′-amino-4′-bromophenylthio)benzylamine (8d).** Flash chromatography (EtOAc/MeOH/Et_3N: 5/4.5/0.5); yield = 57%; brown oil. ^{1}H NMR: δ 2.39 (s, 3H), 2.90 (td, 2H, ^3J = 27.4 Hz, ^3J = 5.0 Hz), 3.53 (s, 2H), 4.66 (s, 2H), 4.68 (td, 2H, ^2J = 47.6 Hz, ^3J = 5.0 Hz), 6.85−7.01 (m, 3H), 7.12−7.20 (m, 2H), 7.27−7.41 (m, 2H). ^{13}C NMR: δ 42.7, 57.5 (d, ^2J = 20.0 Hz), 61.3, 82.8 (d, ^1J = 167.6 Hz), 115.0, 118.1, 121.5, 125.1, 126.1, 128.5, 128.6, 130.8, 136.9, 137.2, 139.0, 145.7. MS: *m*/*z* = 370 (M^+, 18), 368 (M^+, 18), 212 (100), 165 (39), 115 (45), 91 (39). Anal. ($C_{16}H_{18}BrFN_2S$) C, H, N.

***N,N*-Dimethyl-2-(2′-amino-4′-(*E*)-tri-*n*-butylstannylvinylphenylthio)benzylamine (8e).** Under an argon atmosphere, a solution of compound **8a** (500 mg, 1.48 mmol), (*E*)-1,2-Bis(tri-*n*-butylstannyl)ethylene (1.43 g, 2.36 mmol), and 60 mg of $Pd(PPh_3)_4$ in 6 mL of Et_3N was heated at 90 °C for 4 h. After it was cooled, the solvent was evaporated, and the residue was purified by flash chromatography (Et_2O/petroleum ether/ Et_3N: 50/50/5) to afford compound **7e** in 75% yield as a brown oil. ^{1}H NMR: δ 0.94−1.10 (m, 15H), 1.37−1.51 (m, 6H), 1.46−1.63 (m, 6H), 2.37 (s, 6H), 3.65 (s, 2H), 4.54 (s broad, 2H), 6.75−7.02 (m, 5H), 7.11−7.17 (m, 2H), 7.27−7.35 (m, 1H), 7.37 (d, 1H, ^3J = 7.9 Hz). ^{13}C NMR: δ 10.1, 14.2, 27.8, 29.6, 45.7, 62.8, 113.1, 115.1, 116.7, 125.6, 127.9, 128.3, 130.6, 131.3, 137.2, 137.8, 138.0, 141.7, 146.1, 149.5.

***N,N*-Dimethyl-2-(2′-amino-4′-(*E*)-iodovinylphenylthio)benzylamine (8f).** Compound **8f** was obtained from compound **8e** (251 mg, 4.4 mmol) by treatment with a solution of iodine in chloroform (0.1 M) at 0 °C until the color persisted. The solvent was removed, and the crude product was purified by flash chromatography (AcOEt/petroleum ether/ Et_3N: 50/50/5) to give compound **8f** in 65% yield as an orange oil. ^{1}H NMR: δ 2.35 (s, 6H), 3.62 (s, 2H), 4.62 (s broad, 2H), 6.63 (d, 1H, ^4J = 1.8 Hz), 6.71 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.8 Hz), 6.87 (d, 1H, $^3J_{trans}$=14.9 Hz), 6.94−7.00 (m, 1H), 7.08−7.18 (m, 2H), 7.25−7.32 (m, 1H), 7.38 (d, 1H, $^3J_{trans}$=14.9 Hz), 7.12 (d, 1H, ^3J = 7.9 Hz). ^{13}C NMR: δ 45.7 (2C), 62.9, 78.2, 112.9, 116.3, 116.4, 126.0, 128.4, 128.5, 130.8, 137.2, 137.5, 138.0, 140.3, 145.1, 149.5. MS: *m*/*z* = 410 (M^+, 6), 165 (100), 164 (41), 58 (43), 44 (38). Anal. ($C_{17}H_{19}IN_2S$) C, H, N.

Synthesis of Compounds 5d, 6b, and 8g,h: General Procedure. Under an argon atmosphere, a solution of compound **5b**, **6a**, **8b**, or **8d** (0.77 mmol), Et_3N (6 mL), hexabutylditin (2.4 mL), and $Pd(PPh_3)_4$ (80 mg) was heated at 100 °C for 24 h. After it was cooled at room temperature. the solvent was evaporated, and the residue was purified by flash chromatography. Stannylated derivatives were diluted in $CHCl_3$ (38 mL) and treated with a solution of iodine in $CHCl_3$ (0.1 M) until the color persisted to afford after purification by flash chromatography compounds **5d**, **6b**, and **8g**,**h**.

***N*-Methyl-2-(2-hydroxymethyl-4-iodophenylthio)benzylamine (5d).** Yield = 21%; yellow oil; flash chromatography (AcOEt/MeOH/ Et_3N: 8/1/1). ^{1}H NMR: δ 2.31 (s, 3H), 3.45 (s, 1H), 3.72 (s, 2H), 4.48 (s, 2H), 6.76 (d, 1H, ^3J = 8.2 Hz), 7.00−7.28 (m, 4H), 7.54 (dd, 1H, ^3J = 8.2 Hz, ^4J = 2.0 Hz), 7.76 (d, 1H, ^4J = 2.0 Hz). ^{13}C NMR: δ 36.1, 54.2, 62.2, 93.9, 128.2, 129.0, 130.7, 132.8, 133.5, 134.1 (2C), 137.4 (2C), 140.1, 144.5. MS: *m*/*z* = 385 (M^+, 8), 263 (31), 262 (69), 197 (26), 150 (29), 118 (56), 44 (86), 42 (100). Anal. ($C_{15}H_{16}INOS$) C, H, N.

***N,N*-Dimethyl-2-(4-iodo-2-methoxymethylphenylthio)benzylamine (6b).** Yield = 48%; yellow oil; flash chromatography (Et_2O/petroleum ether/ Et_3N: 7/3/1). ^{1}H NMR: δ 2.30 (s, 6H), 3.45 (s, 3H), 3.57 (s, 2H), 4.54 (s, 2H), 6.91 (d, 1H, ^3J = 8.2 Hz), 7.09 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.7 Hz), 7.18 (td, 1H, ^3J = 7.2 Hz, ^4J = 1.7 Hz), 7.27 (td, 1H, ^3J = 7.2 Hz, ^4J = 1.7 Hz), 7.46 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.7 Hz), 7.53 (dd, 1H, ^3J = 8.2 Hz, ^4J = 2.1 Hz), 7.89 (d, 1H, ^4J = 2.1 Hz). ^{13}C NMR: δ 45.8 (2C), 59.1, 62.5, 71.2, 93.5, 127.6, 128.4, 130.7, 132.0, 134.3, 134.5, 135.3, 137.2, 137.4, 140.1, 141.6. MS: *m*/*z* = 413 (M^+, 8), 290 (31), 398 (22), 336 (21), 209 (59), 165 (29), 164 (22), 132 (30), 126 (52, 58 (100), 45 (70), 44 (32). Anal. ($C_{17}H_{20}INOS$) C, H, N.

***N*-Methyl-2-(2-amino-4-iodophenylthio)benzylamine (8g).** Yield = 44%; brown oil; flash chromatography (AcOEt/MeOH/Et_3N: 8/1/1). ^{1}H NMR: δ 1.65 (s broad, 1H), 2.44 (s, 3H), 3.84 (s, 2H), 4.40 (s broad, 2H), 6.77−6.81 (m, 1H), 6.96−7.10 (m, 5H), 7.20−7.27 (m, 1H). ^{13}C NMR: δ 36.5, 54.5, 97.3, 114.9, 124.2, 126.3, 127.8, 127.9, 128.5, 130.0, 135.5, 138.0, 138.8, 150.3. MS: *m*/*z* = 370 (M^+, 6), 212 (19), 152 (10), 151 (40), 150 (25), 120 (100), 118 (22), 44 (26). Anal. ($C_{14}H_{15}IN_2S$) C, H, N

***N*-(2-Fluoroethyl),*N*-methyl-2-(2-amino-4-iodophenylthio)benzylamine (8h).** Yield = 41%; brown oil; flash chromatography (AcOEt/MeOH/Et_3N: 70/30/5). ^{1}H NMR: δ 2.39 (s, 3H), 2.89 (td, 2H, ^3J = 27.5 Hz, ^3J = 5.0 Hz), 3.76 (s, 2H), 4.60 (s, 2H), 4.67 (td, 2H, ^2J = 47.5 Hz, ^3J = 5.0 Hz), 6.95−7.00 (m, 1H), 7.05−7.23 (m, 5H), 7.30−7.34 (m, 1H). ^{13}C NMR: δ 42.7, 57.5 (d, ^2J = 19.2 Hz), 61.3, 82.8 (d, ^1J = 167.6 Hz), 97.2, 115.8, 124.1, 126.1, 127.5, 128.5, 128.6, 130.8, 136.8, 137.2, 139.0, 145.7. MS: *m*/*z* = 416 (M^+, 1), 213 (34), 121 (53), 197 (42), 164 (100), 150 (33), 91 (32), 90 (41), 44 (72), 42 (82). Anal. ($C_{16}H_{18}FIN_2S$) C, H, N.

Transporter Affinity Assays. Radioligand binding assays for the SERT, DAT, and NET were performed as previously detailed[26,27] by the NIMH Psychoactive Drug Screening Program. Screening determinations and inhibitory constants (K_i) were determined on membrane preparation from cells expressing transporters using [^{3}H] paroxetine (K_D around 0.15 nM),[28] [^{3}H] GBR 12935 (K_D around 5 nM),[29] and [^{3}H] nisoxetine (K_D around 0.70 nM)[30] for SERT, DAT, and NET, respectively, as reference ligands. For screening purposes, 10 μM of each compound (dissolved in 10% dimethyl sulfoxide) was incubated with the appropriate transporter preparation, and percent inhibition was determined for duplicate determinations, each performed in duplicate. When >50% inhibition of specific binding was measured, K_i determinations were then measured by competition binding assays in which concentrations from 0.1 to 100 000 nM were incubated in duplicate. For each K_i value, the data represent the mean ± standard deviation of computer-derived estimates for $N = 4$ separate determinations.

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