# Radiosynthesis of σ Receptor Ligands for Positron Emission Tomography: $^{11}C$- and $^{18}F$-Labeled Guanidines

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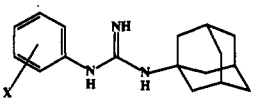
A series of analogues of the potent and selective σ receptor ligand 1,3-ditolylguanidine (DTG) were synthesized and demonstrated to have high affinity for the σ receptor as measured by in vitro [$^3$H]DTG displacement studies using guinea pig brain tissue. Three of these 1-aryl-3-(1-adamantyl)guanidines were radiolabeled—two with carbon-11 and one with fluorine-18. Radiochemical yields and specific activities were sufficient for these radiotracers to be used in positron emission tomography imaging of the haloperidol-sensitive σ receptor.

Typical dopamine $D_2$ antipsychotic drugs have many shortcomings that include a spectrum of side effects, most seriously tardive dyskinesia, and lack of efficacy on the negative symptoms of schizophrenia. New atypical neuroleptics have been sought which overcome these deficiencies with a few entering clinical trials.[1] Many such neuroleptics of diverse chemical classes bind avidly to σ receptors in brain tissue[2,3] and it has been suggested that psychotomimetic benzomorphans, such as SKF 10,047, act through the σ receptor.[4] Additionally, a relationship between the binding ability of cocaine analogues to σ receptors and their ability to induce psychosis has been observed.[5] This, and other evidence, has led to speculation that certain types of psychosis may be treated with σ-selective antagonists.[1,6] Spurred by the promise of new insights into psychosis and movement disorders, and a new class of antipsychotic drugs, the haloperidol-sensitive σ receptor has been the focus of intense scrutiny. Despite this recent attention, the functional role of the σ receptor remains controversial, due in part to the use of unselective and/or low affinity ligands.[7] In the periphery, high concentrations of σ receptors are concentrated in the endocrine system,[8] the immune system,[9] and in hepatic tissue.[10] In addition strongly enhanced binding of σ ligands has been reported in certain types of tumors compared with nontumor tissue,[11] raising the possibility of σ radiotracer ligands as tumor-imaging agents.

1,3-Ditolylguanidine (DTG) and (+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine ((+)-PPP) were the first two ligands shown to bind with high affinity and selectivity to the σ receptor.[12,13] From our perspective DTG is important as a prototype or template for the design of analogues which may be labeled with imaging radionuclides, for use as σ receptor radiotracers in positron emission tomography (PET) or single photon emission computed tomography (SPECT). Localization and quantification of σ receptors using PET or SPECT could help to elucidate the role of the σ receptor. A comparison of the distribution, concentration, and affinity of σ receptors in normals, psychotic patients, and experienced drug users could help to elucidate the mechanism of action of atypical neuroleptics and the relationship between σ receptors and psychotic individuals.[14]

Numerous analogues of DTG have been synthesized[15] and among the most potent inhibitors of [$^3$H]DTG are some 1-adamantyl cogeners. These compounds are also the most potent among a heterogeneous series of σ ligands in an in vitro bioassay.[16] They were identified as potential

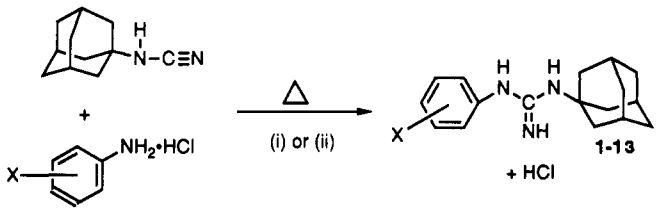
**Table I.** Properties of 1-Aryl-3-(1-adamantyl)guanidines



| compd | substituent (X) | mp, °C | synthesis method[a] | $IC_{50}$ (nM) vs [$^3$H]DTG |
|---|---|---|---|---|
| 1 | 2-$CH_3O$ | 98–104 | B | 17 ± 2 |
| 2 | 3-$CH_3O$ | 150–151 | B | 7 ± 1 |
| 3 | 4-$CH_3O$ | 180–183 | B | 10 ± 1 |
| 4 | 2-$CH_3$, 4-$CH_3O$ | 142–145 | B | 7 ± 1 |
| 5 | 2-F | 132–134 | A | 8 ± 1 |
| 6 | 3-F | 220–224 dec[b] | A | 13 ± 1 |
| 7 | 4-F | 153–156 | A | 9 ± 1 |
| 8 | 2-$CH_3$, 4-F | 157–160 | A | 3.2 ± 0.8 |
| 9 | 4-OH | 265–266 dec[c] | C | ND[d] |
| 10 | 2-$CH_3$, 4-OH | >240 dec[c] | C | ND |
| 11 | 2-I | 189–192 | A | 6.2 ± 1 |
| 12 | 3-I | 150–152 | A, B | 8 ± 1 |
| 13 | 4-I | 204–206 | A, B | 2.8[e] |
| haloperidol | | | | 5 ± 1 |
| DTG | | | | 28 ± 1 |
| (+)-PPP | | | | 76 ● 5 |

[a] See methods section for details. [b] HCl salt. [c] Hemisulfate salt. [d] Not determined. [e] $K_D$ of the $^{125}$I-labeled guanidine.[15]

**Scheme I.** Synthesis of 1-Aryl-3-(1-adamantyl)guanidines




(1) Deutsch, S. I.; Weizman, A.; Goldman, M. E.; Morihasa, J. M. *Clinical Neuropharmacol.* **1988**, *11*, 105.
(2) Itzak, Y. *Life Sci.* **1988**, *42*, 745.
(3) Largent, B.; Wikström, H.; Snowman, A.; Synder, S. *Eur. J. Pharmacol.* **1988**, *155*, 345.
(4) Tam, S. W.; Cook, L. *Proc. Natl. Acad. Sci. U.S.A* **1984**, *81*, 5618.
(5) Sharkey, J.; Glen, K. A.; Wolfe, S.; Kuhar, M. J. *Eur. J. Pharmacol.* **1988**, *149*, 171.
(6) Snyder, S. H.; Largent, B. L. *J. Neuropsychol.* **1989**, *1*, 7.
(7) Chavkin, C. TIPS *Trends Pharmacol. Sci.* **1990**, *11*, 213.
(8) Wolfe, S. A., Jr.; Culp, S. G.; De Souza, E. B. *Endocrinology (Baltimore)* **1989**, *124*, 1160.
(9) Wolfe, S. A., Jr.; Kulsakdinun, C.; Battaglia, G.; Jaffe, J. H.; De Souza, E. B. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1114.
(10) Ross, S. B. *Pharmacol. Toxicol.* **1990**, *67*, 93.

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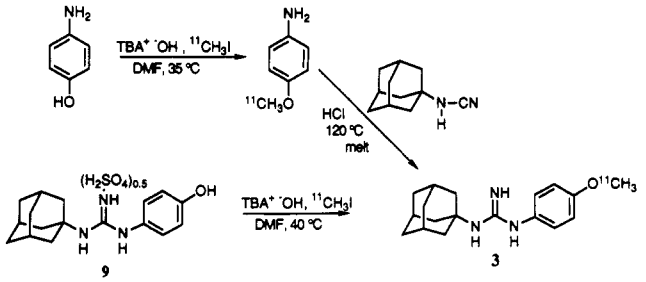
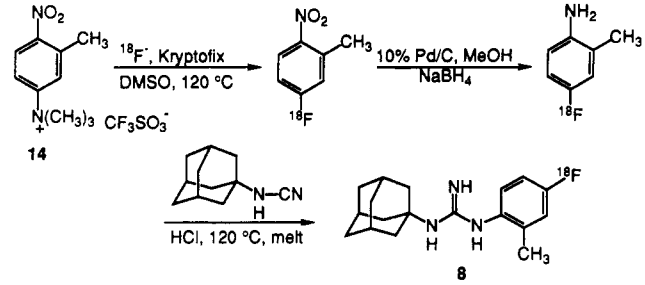
**Scheme II.** Two Methods of Radiosynthesis of [$^{11}$C]-3




**Scheme III.** Radiosynthesis of [$^{18}$F]-8




radiotracers since it was demonstrated that the binding affinity of these compounds is tolerant of many types of substituents on the phenyl ring. We report here the syntheses of a series of adamantyl DTG analogues amenable to radiolabeling, their in vitro binding affinity for the $\sigma$ receptor, and the radiosyntheses of three of the most promising guanidines with $^{11}$C and $^{18}$F.

## Chemistry

A series of 1-aryl-3-(1-adamantyl)guanidines **1–13** (Table I, Scheme I) were synthesized by the acid-catalyzed addition of substituted anilines to 1-adamantylcyanamide,[17] which is readily prepared from 1-adamantylamine and cyanogen bromide.[18] The reactions were carried out in refluxing acetonitrile (method A) or, when reduced solubility led to slow reaction rates, in a melt (methods B and C). Isolated yields of analytically pure products after recrystallization ranged from 55 to 90%. As our objectives lay toward labeling with imaging radionuclides, iodine, methoxy, and fluorine substituents were targeted for the future introduction of $^{123}$I, $^{11}$C, and $^{18}$F, respectively.

Compounds **9** and **10**, containing phenol substituents, were required as precursors for the radiosyntheses of [$^{11}$C]-**3** and [$^{11}$C]-**4**, respectively. They proved to be unstable and despite much effort could not be isolated as free bases; however their salts proved to be manageable with a shelf-life of over 9 months at room temperature. 2-Nitro-5-(trimethylammonio)toluene trifluoromethanesulfonate (**14**), the starting material in the synthesis of [$^{18}$F]-**8**, was prepared in two steps from 5-fluoro-2-nitrotoluene via 5-(dimethylamino)-2-nitrotoluene in an overall yield of 65%.

## Binding Studies

To determine their affinity for the haloperdol-sensitive $\sigma$ receptor, competitive in vitro binding assays on the substituted guanidines were performed against [$^3$H]DTG and homogenized guinea pig whole brain. The results are displayed in Table I. For comparison, the $IC_{50}$s of the established $\sigma$ ligands haloperidol, DTG, and (+)-PPP are also shown. All substituted guanidines tested were more potent than DTG itself in displacing [$^3$H]DTG ($K_D$ = 28 nM),[13] their $IC_{50}$s ranging from 3.2 to 17 nM. Reputedly the highest affinity ligand for the $\sigma$ receptor is haloperidol, which has reported $K_D$s of between 0.3 and 2.8 nM in a variety of human and animal tissues.[20-23] In this context, several of these guanidines are among the most potent $\sigma$ receptor ligands which have been synthesized to date. The high affinity displayed by the iodinated cogeners **11–13** suggest that when labeled with $^{125}$I,[19] they will be useful pharmacological tools for investigation of the $\sigma$ receptor.

## Radiosynthesis

Three of the more potent compounds (**3**, **4**, and **8**) were chosen as candidates for radiolabeling with $^{11}$C and $^{18}$F. Because initial attempts to isolate the phenolic precursor required for a one-step radiosynthesis of [$^{11}$C]-**3** were unsuccessful (vide supra), a two-step method was devised (Scheme II). [$^{11}$C]Iodomethane was trapped in a solution of *p*-aminophenol in DMF at −70 °C. Addition of 1 equiv of tetrabutylammonium hydroxide and warming effected selective alkylation of the phenolate oxygen (<2% of [$^{11}$C]-*p*-(methylamino)phenol was detected by HPLC). Coupling of [$^{11}$C]-*p*-anisidine with 1-adamantylcyanamide was induced as a melt in the presence of hydrochloric acid at 120 °C since the reaction in solution required more than 4 h and was not concomitant with the half-life of carbon-11. Purification of the reaction mixture by semipreparative HPLC and formulation gave radiochemically pure [$^{11}$C]-**3**. Average synthesis time from end-of-bombardment (EOB), radiochemical yield from [$^{11}$C]iodomethane, and specific activity at end-of-synthesis (EOS) were 32 min, 12.4%, and 1160 mCi/$\mu$mol, respectively.

The one-step radiosynthesis of [$^{11}$C]-**3** is also depicted in Scheme II. A solution of the phenolate anion of **9** was freshly prepared, prior to [$^{11}$C]iodomethane production and trapping, by addition of tetrabutylammonium hydroxide (2 equiv) to the guanidinium hemisulfate salt **9** in DMF. This is a similar approach to the method used to prepare [$^{11}$C]raclopride[24] labeled in the methoxy position. After HPLC purification and formulation, radiochemically pure [$^{11}$C]-**3** was obtained in 17% average radiochemical yield from [$^{11}$C]iodomethane 20 min after EOB, at an average specific activity of 1240 mCi/$\mu$mol. The one-step radiosynthesis of [$^{11}$C]-**4** was accomplished, with the hemisulfate salt of **10** as precursor, in a similar fashion. Radiochemical yields were 16% on average with an average specific activity of 1300 mCi/$\mu$mol.

(11) Thomas, G. E.; Szücs, M.; Mamone, J. Y.; Bem, W. T.; Rush, M. D.; Johnson, F. E.; Coscia, C. J. *Life Sci.* **1990**, *46*, 1279.
(12) Largent, B. L.; Gundlach, A. L.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 5618.
(13) Weber, E.; Sonders, M.; Quarum, M.; McLean, S.; Pou, S.; Keana, J. F. W. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8784.
(14) Junien, J. L.; Leonard, B. E. *Clin. Neuropharm.* **1989**, *12*, 353.
(15) Scherz, M. W.; Fialeix, M.; Fischer, J. B.; Reddy, N. L.; Server, A. C.; Sonders, M. S.; Tester, B. C.; Weber, E.; Wong, S. T.; Keana, J. *J. Med. Chem.* **1990**, *33*, 2421.
(16) Campbell, B. G.; Scherz, M. W.; Keana, J.; Weber, E. *J. Neurosci.* **1989**, *9*, 3380.
(17) Adams, J.; Teal, P.; Sonders, M.; Tester, B.; Esherick, J.; Scherz, M.; Keana, J.; Weber, E. *Eur. J. Pharmacol.* **1987**, *142*, 61.
(18) Geluk, H.; Schut, J.; Schlatman, J. *J. Med Chem* **1969**, *12*, 712.
(19) Wilson, A. A.; Scheffel, U.; Stathis, M.; Dannals, R. F.; Ravert, H. T.; Wagner, H. N., Jr. *J. Nucl. Med.* **1990**, *31*, P376.
(20) Wolfe, S., Jr.; Culp, S.; De Souza, E. *Endocrinology* **1989**, *124*, 1160.
(21) Su, T.; Schell, S.; Ford-Rice, F.; London E. *Eur. J. Pharmacol.* **1988**, *148*, 467.
(22) Wolfe, S., Jr.; Kulsakdinun, C.; Battaglia, G.; Jaffe, J.; De Souza, E. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1114.
(23) Weissman, A. D.; Su, T.-P.; Hedreen, J. C.; London, E. D. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 29.
(24) Ehrin, E.; Gawell, L.; Högberg, T.; de Paulis, T.; Ström, P. *J. Labelled Compd. Radiopharm.* **1987**, *24*, 931.

The two-step radiosynthesis of [$^{11}$C]-3 steered us toward the sequence outlined in Scheme III depicting the radiosynthesis of 8 labeled with $^{18}$F. The precursor trifluoromethanesulfonate 14 was a logical choice for a number of reasons. The nitro group has two purposes, activating the aromatic ring toward nucleophilic substitution[25] and serving as a masked amino group. Trimethylammonium salts are efficient nucleofuges, are selectively displaced by [$^{18}$F]fluoride anion in the presence of a nitro group,[26] and can attenuate purification problems.[27,28]

Reaction of 14 with anhydrous [$^{18}$F]fluoride in the presence of Kryptofix 2.2.2 and potassium carbonate in DMSO resulted in 60–70% incorporation of radioactivity, forming 5-([$^{18}$F]fluoro)-2-nitrotoluene. Other solvents, including DMF, acetonitrile, and THF gave inferior results. Since DMSO was not compatible with the next reductive step, the reaction mixture was applied onto a $C_{18}$ Sep-pak and washed with water to remove DMSO. In addition, the $C_{18}$ Sep-pak was washed with dilute aqueous hydrochloric acid to remove the kryptofix which was found to interfere with the coupling step (vide infra). Upon elution of the product with methanol, reduction was effected with sodium borohydride in the presence of 10% palladium or charcoal.[29] This reaction was rapid at ambient temperature when greater than 2 mg of catalyst was used but irreversible adsorption of labeled aniline 15 was significant (>20%). Using one mg or less of catalyst at reflux resulted in complete reduction in 5 min with less than 10% losses attributable to adsorption by the catalyst.

Following another $C_{18}$ Sep-pak workup, [$^{18}$F]-15 was reacted with 1-adamantylcyanamide in a similar fashion to that described above during the two-step synthesis of [$^{11}$C]-3. Upon HPLC purification and formulation, radiochemically pure [$^{18}$F]-8 was obtained in an overall yield of 7–12% (EOS) in a synthesis time of 65–70 min. HPLC analysis showed less than 10% of other chemical impurities and gave specific activities (EOS) of 600–950 mCi/μmol. Prior to the development of this method, the direct displacement of the nitro group in 1-(4-nitrophenyl)-3-(1-adamantyl)guanidine by $^{18}F^-$ was attempted as this is the most direct route to [$^{18}$F]-8. As expected for an unactivated system no [$^{18}$F]-8 was formed even under forcing conditions (165 °C, 60 min, DMSO).

## Conclusions

We have witnessed extensive efforts during the past 10 years to localize and quantify the dopamine $D_2$ receptor in the living human brain by positron emission tomography.[30-32] Much of this work has been spurred by the integral role that dopamine and the dopamine receptor are believed to play in psychosis. Until now, little attention has been devoted to the development of σ receptor imaging radiotracers despite a growing appreciation of the role played by the σ receptor in psychosis and movement disorders.[7,33]

In this work a number of potential tomographic imaging radiotracers, based on the DTG model, have been identified. Three guanidines, which display high affinity for the σ receptor, have been labeled in good yields with $^{18}$F and $^{11}$C at the high specific activities required for neuroreceptor investigations. These radiotracers may be useful in imaging the distribution of σ receptors in man using PET and are currently being evaluated as such in rodent models in vivo. As demonstrated by Scherz et al.[15] and here, binding affinity for the σ receptor is tolerant of a variety of substituents, providing much scope in the future design of radiopharmaceuticals for neuroreceptor investigations.

## Experimental Section

NMR spectra were obtained on an IBM NR/80 using $(CH_3)_4Si$ as an internal standard. DMF was stirred overnight with BaO, then distilled under reduced pressure from BaO. DMSO was distilled from basic alumina (activity grade I) under reduced pressure and stored over 3-Å molecular sieves. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. All new compounds gave satisfactory analyses (C, H, N ± 0.4%) unless noted otherwise and had appropriate spectral (NMR, IR) characteristics. Purification and analyses of radioactive mixtures by HPLC were performed with a previously described system.[34] The HPLC columns used were either (A) Alltech Econosil $C_{18}$ (250 mm × 10mm) or (B) Alltech Econosil $C_{18}$ (250 mm × 4.6 mm). Peak areas were measured with Hewlett-Packard 3390A recording integrators. Isolated radiochemical yields were determined with a dose-calibrator (Capintec CRC-12). All formulated radiochemical preparations tested sterile and pyrogen-free by standard methods.

**Substituted-Aniline Hydrochloride Salts.** All anilines (commercially available) were dissolved in ether and treated with ethereal hydrochloric acid. The precipitated salts were collected and recrystallized from ethanolic acetone.

**Synthesis of 1-Aryl-3-(1-adamantyl)guanidines. Method A.** A mixture of 1-adamantylcyanamide (100 mg, 0.57 mmol) and a substituted aniline hydrochloride (0.62 mmol) in acetonitrile (5 mL) was stirred under reflux for 6–72 h. Upon cooling the reaction mixture was extracted between aqueous $Na_2CO_3$ (4 N) and 50/50 ether/dichloromethane. The organic layer was washed with water, dried ($Na_2SO_4$), filtered, and the solvents were removed. The residue was recrystallized from 50% aqueous ethanol and the product isolated by vacuum filtration.

**Method B.** A finely ground mixture of 1-adamantylcyanamide (200 mg, 1.14 mmol) and substituted-aniline hydrochloride (1.24 mmol) in a Reacti-vial (Pierce) were heated to 150 °C for 1 h. The mixture was then vortexed and heated for a further 45 min and cooled. Workup was as described in method A.

**Method C** was as in method B but with a different workup. The vial contents were dissolved in warm ethanol/3% aqueous sulfuric acid (50/50) and passed through a column of anion-exchange resin (Bio-Rad AG MP-1) equilibrated with the same mixture. Removal of the ethanol precipitated a solid which was collected and recrystallized from ethanol/5% aqueous sulfuric acid (50/50). Treatment with charcoal and a second recrystallization from ethanol/1% aqueous sulfuric acid (50/50) afforded the product. Two of the fluorinated guanidines, 5 and 7, did not give satisfactory elemental analyses. 5 ($C_{17}H_{22}N_3F$) Anal. Calcd: C, 71.05; H, 7.72; N 14.62. Found: C, 71.43; H, 7.66; N, 13.96. 7 ($C_{17}H_{22}N_3F$) Anal. Calcd: 71.05; H, 7.72; N, 14.62. Found: C, 71.70, H, 8.42; N, 13.95.

**1-Adamantylcyanamide** was prepared by a known procedure from 1-adamantylamine and cyanogen bromide:[18] mp 148–149 °C (lit.[18] mp 150–151 °C).

(25) Attinà, M.; Cacace, F.; Wolfe, A. P. *J. Labelled Compd. Radiopharm.* **1983**, *20*, 501.
(26) Haka, M. S.; Kilbourn, M. R.; Watkins, G. L.; Tooronigian, S. A. *J. Labelled Compd. Radiopharm.* **1989**, *27*, 823.
(27) Wilson, A. A.; Dannals, R. F.; Ravert, H. T.; Wagner, H. N., Jr. *J. Labelled Compds. Radiopharm.* **1990**, *28*, 1190.
(28) Haka, M. S.; Kilbourn, M. R. *J. Labelled Compd. Radiopharm.* **1990**, *28*, 793.
(29) Feliu, A. L. *J. Labelled. Compd. Radiopharm.* **1988**, *25*, 1245.
(30) Mazière, B.; Mazière, M. *Eur. J. Nucl. Med.* **1990**, *16*, 817.
(31) Fowler, J. S.; Wolf, A. P. *Positron Emitter-Labeled Compounds: Priorities and Problems*; Phelps, M.; Mazziotta, J. Schelbert, H., Eds.; Raven Press: New York, 1986; pp 391.
(32) Wagner, H. N., Jr.; Burns, H. D.; Dannals, R. F.; Wong, D. F.; Långström, B.; Duelfer, T.; Frost, J. J.; Ravert, H. T.; Links, J. M.; Rosenbloom, S. B.; Lukas, S. E.; Kramer, A. V.; Kuhar, M. J. *Science* **1983**, *221*, 1264.
(33) Hoffman, D. W. *Am. J. Psychiatry* **1990**, *147*, 1093.
(34) Dannals, R. F.; Ravert, H. T.; Frost, J. J.; Wilson, A. A.; Burns, H. D.; Wagner, H. N., Jr. *Int. J. Appl. Radiat. Isot.* **1985**, *36*, 303.

**5-(Dimethylamino)-2-nitrotoluene.** A mixture of 5-fluoro-2-nitrotoluene (5.7 g, 36.9 mmol), dimethylamine hydrochloride (5 g, 61.3 mmol), $K_2CO_3$ (5 g, 36.2 mmol), water (10 mL), and DMSO (25 mL) was stirred under argon at 90 °C for 1 h then at ambient temperature for 72 h. The mixture was partitioned between aqueous $K_2CO_3$ (1 N, 50 mL) and ether/chloroform (4:1, 50 mL) and the organic layer washed with water, dried ($Na_2SO_4$), and filtered. Removal of the solvent gave a yellow solid which was recrystallized from chloroform/hexane to give fine yellow needles (6.53 g, 98.3%): mp 79–80 °C.

**2-Nitro-5-(trimethylammonio)toluene Trifluoromethanesulfonate (14).** A solution of 5-(dimethylamino)-2-nitrotoluene (2.0 g, 11.1 mmol) in dichloromethane (100 mL) was stirred under argon while methyl trifluoromethanesulfonate (2.18 g, 13.3 mmol) was added slowly by syringe. The solution was heated to reflux for 16 h, then cooled, and ether (150 mL) added. The pale orange precipitate was collected, washed rigourously with ether (to ensure the removal of trace amounts of 5-fluoro-2-nitrotoluene, which would result in a decrease in the specific activity of [$^{18}$F]-8) and recrystallized from acetonitrile/dichloromethane to give a white powder (2.47 g, 67.8%); mp 151–154 °C.

**1-[4-([$^{11}$C]Methoxy)phenyl]-3-(1-adamantyl)guanidine (3). Two-Step Method.** [$^{11}$C]$CH_3I$, produced as previously described,[34,35] was swept by a stream of nitrogen into a solution of *p*-aminophenol (0.5 mg, recrystallized from ethanol/acetone and sublimed (80 °C, 0.05 mmHg)) in DMF (100 μL) at −78 °C. Tetrabutylammonium hydroxide (5 μL, 1 M in methanol) was added and the solution warmed to 35 °C for 1 min. A solution of 1-adamantylcyanamide (3 mg) in acetonitrile (250 μL) and aqueous hydrochloric acid (5 μL, 2 N) was added. Solvents were removed at 120 °C by a stream of argon and the residue was heated at 120 °C for 7 min. Upon cooling, the residue was taken up in 400 μL of HPLC buffer and purified by semipreparative HPLC using column A (60% $CH_3CN$/40% $H_2O$ containing 0.1 N $NH_4HCO_2$, 10 mL/min, $k'_{product}$ = 4.7). The desired fraction was collected and evaporated to dryness, and the residue taken up in 7 mL of sterile saline. This was passed through a sterile 0.22-μm filter into a sterile, pyrogen-free bottle and sterile aqueous sodium bicarbonate (3 mL, 8.4%) was added. The radiochemical purity and specific activity of the final solution was determined by analytical HPLC using column B; (60% $CH_3CN$/40% $H_2O$ containing 0.1 N $NH_4HCO_2$, 5 mL/min, $k'_{product}$ = 3.6).

**1-[4-([$^{11}$C]Methoxy)phenyl]-3-(1-adamantyl)guanidine (3). One-Step Method.** [$^{11}$C]$CH_3I$ as swept by a steam of nitrogen gas into a freshly prepared blue solution of 1-(4-hydroxyphenyl)-3-(1-adamantyl)guanidine (9, 1.5 mg, hemisulfate) and tetrabutylammonium hydroxide (6 μL, 1.0 M in methanol) in DMF (200 μL) cooled to −78 °C. Upon heating the reaction mixture to 40 °C for 2 min, HPLC buffer (400 μL) was added, and the mixture was purified by semipreparative HPLC as described above.

**1-[4-([$^{11}$C]Methoxy)-2-methylphenyl-3-(1-adamantyl)-guanidine (4)** was prepared and purified by the same one-step procedure as described above using 10 (hemisulfate) as precursor. Results were very similar.

**5-([$^{18}$F]Fluoro)-2-nitrotoluene.** [$^{18}$F]Fluoride was produced by the $^{18}$O(p,n) reaction on >95% atom [$^{18}$O]$H_2O$ using a Scanditronix MC-16F biomedical cyclotron. The [$^{18}$O]$H_2O$ was separated from the [$^{18}$F]fluoride with Dowex 1-X8 anion-exchange resin.[36] The [$^{18}$F]fluoride was eluted from the column with aqueous potassium carbonate (2.3 mg/0.3 mL) into a glass Reacti-vial containing Kryptofix 2.2.2 (13 mg) and evaporated to dryness at 120 °C azeotropically with acetonitrile. A solution of 14 (2.0 mg) in DMSO (0.35 mL) was added and heated to 120 °C for 5 min in the sealed vial. Upon cooling and dilution with water (5 mL), the mixture was passed through a $C_{18}$ Sep-pak, followed by 5 mL of methanol/water (1:9) used to rinse the Reacti-vial, 10 mL of 0.1 N aqueous HCl, and 10 mL of water. The product was eluted with 1.5 mL of methanol into a test tube containing 10% palladium on charcoal (0.8–1.0 mg).

**4-([$^{18}$F]Fluoro)-2-methylaniline.** The methanolic solution of 5-([$^{18}$F]fluoro)-2-nitrotoluene containing 10% palladium on charcoal was treated with freshly prepared sodium borohydride solution (10 mg in 0.5 mL of water) and heated to reflux for 5 min. The mixture was taken up into water (8.5 mL) and passed through a $C_{18}$ Sep-pak; the Sep-pak was washed with water (10 mL) and dried with a stream of argon for 1 min. The labeled aniline was eluted into a Reacti-vial containing 1-adamantylcyanamide (3–4 mg) with acetonitrile (3 mL) containing aqueous HCl (15 μL, 2 N).

**1-[4-([$^{18}$F]-Fluoro)-2-methylphenyl]-3-(1-adamantyl)-guanidine (8).** The acetonitrile was removed by a stream of argon, the residue heated to 120 °C for 12 min, then taken up in HPLC buffer (1.5 mL). Semipreparative HPLC purification was performed using column A (60% $CH_3CN$/40% $H_2O$ containing 0.1 N $NH_4HCO_2$, 10 mL, min, $k'_{product}$ = 5.0). Upon evaporation of the collected HPLC fraction, the residue was taken up in 7 mL of sterile saline and passed through a sterile 0.22-μm filter into a sterile, pyrogen-free bottle when sterile aqueous sodium bicarbonate (3 mL, 8.4%) was added. The radiochemical purity and specific activity of the final solution were determined by analytical HPLC using column B (60% $CH_3CN$/40% $H_2O$ containing 0.1 N $NH_4HCO_2$; 4 mL/min; $k'_{product}$ = 4.0).

**Binding Studies.** Binding assays were performed according to the procedures previously described.[13] Briefly, frozen guinea pig brain membrane homogenates were thawed and diluted in 50 mM Tris HCl, pH 7.4, at a concentration of 1 mg of protein/mL. All other solutions were made in the same buffer. To 100 μL of buffer containing ca. 1.4 pmol of [$^3$H]DTG (46 Ci/mmol), 800 μL of brain homogenate, and 100 μL of drug standard was added buffer (to define total binding) or 100 μM haloperidol (to define nonspecific binding). Tubes were incubated at room temperature for ≥90 min, diluted with 4 mL of buffer, and rapidly vacuum filtered through glass-fiber sheets (#32, Schleicher & Schuell) with a 48-well Brandel cell harvester. Filters were washed twice more with 5 mL of buffer after which they were dissolved in Cytoscint ES (ICN Biomedicals) and the radioactivity measured by liquid scintillation counting. Adamantyl guanidine cogeners were typically dissolved in methanol to make a 10 mM solution, which was then serially diluted with buffer. Standard curves were generated by 10 drug dilutions (tubes in triplicate) ranging between 100 pM and 10 μM (final concentration). Assays were repeated three times.

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(35) Dannals, R. F.; Ravert, H. T.; Wilson, A. A.; Wagner, H. N., Jr. *Appl. Radiat. Isot. Int. J. Appl. Instrum. Part A* **1986**, *37*, 433.

(36) Schlyer, D. J.; Bastos, M. A.; Alexoff, D.; Wolf, A. P. *Appl. Radiat. Isot. Int. J. Radiat. Appl. Instrum. Part A* **1990**, *41*, 531.