(4-[^{18}F]Fluoro-3-iodobenzyl)guanidine, a Potential MIBG Analogue for Positron Emission Tomography

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The aims of this investigation were to develop a no-carrier-added (nca) synthesis of (4-[^{18}F]-fluoro-3-iodobenzyl)guanidine ([^{18}F]FIBG) and to evaluate its potential as an MIBG analogue useful for positron emission tomography. [^{18}F]FIBG was prepared in four steps starting from 4-cyano-2-iodo-*N,N,N*-trimethylanilinium trifluoromethanesulfonate in 5% decay-corrected radiochemical yield in a total synthesis time of 130 min. The specific activity was more than 1500 Ci per mmol. *In vitro* binding studies showed that the percent binding of [^{18}F]FIBG to SK-N-SH human neuroblastoma cells remained constant over a 3-log activity range and was similar to that of nca [^{131}I]MIBG. Specific and high uptake of FIBG was also seen in mouse heart and adrenals. The *in vitro* and *in vivo* properties of [^{18}F]FIBG suggest that this compound may be a useful positron-emitting analogue of MIBG.

Introduction

Radioiodinated (*m*-iodobenzyl)guanidine (MIBG), an analogue of the neuron-blocking agent guanethedine, was developed originally as an adrenomedullary radiopharmaceutical.[1,2] Subsequently, MIBG has been used in the diagnosis and therapy of various neuroendocrine tumors[3–6] and to study abnormalities of the heart.[7–9] For imaging, both planar scintigraphy and single photon emission computed tomography (SPECT) have been used in combination with [^{131}I/^{123}I]MIBG.[10,11] Planar scintigraphy is not ideal for identifying lesions because it is incapable of separating overlying and underlying planes of activity from the region of interest.[12] The advantages of SPECT with [^{123}I]MIBG over planar scintigraphy using [^{131}I]MIBG have been demonstrated by a number of investigators.[13,14] While tomographic imaging can be achieved with SPECT, positron emission tomography (PET) permits more rigorous attenuation correction, resulting in more accurate quantitative capabilities. PET is a functional imaging modality that can probe altered biochemical pathways and in some cases can be used to assess metabolic levels quantitatively.[15]

The development of an MIBG analogue labeled with a positron emitting nuclide such as ^{18}F or ^{124}I has been recommended.[16] Several approaches are being investigated for combining the distribution properties of MIBG with the imaging advantages of PET. Preliminary reports describing the synthesis of [^{124}I]MIBG[12,17] and ^{11}C-labeled benzylguanidine[18] have appeared. Recently, the synthesis and preliminary evaluation of (3-[^{76}Br]bromobenzyl)guanidine (MBBG)[19,20] have been reported. Iodine-124 and ^{76}Br are not ideal nuclides for PET. The presence of several high-energy γ rays in the decay of ^{124}I, which are in cascade with its positron emissions, could interfere with the ability to perform quantitative PET studies. The high energy of the positrons from ^{76}Br would probably impose severe limitations on the dose that could be administered to patients. Furthermore, these nuclides are not routinely available. Fluorine-18, on the other hand, is an attractive nuclide for use in PET because of its more favorable nuclear decay characteristics and routine availability. (*p*-[^{18}F]Fluorobenzyl)guanidine ([^{18}F]PFBG) or, more likely, (4-[^{18}F]fluoro-3-iodobenzyl)guanidine ([^{18}F]FIBG) has been suggested to be a potential MIBG analogue for positron emission tomography.[1] The preparation and preliminary evaluation of (3-[^{18}F]fluorobenzyl)-guanidine ([^{18}F]MFBG)[21,22] and [^{18}F]PFBG[21] have recently been reported; however, compared to MIBG, the specific binding to SK-N-SH human neuroblastoma cells and the myocardial uptake in mice of [^{18}F]MFBG and [^{18}F]PFBG were significantly lower.[21]

The less than ideal properties of MFBG and PFBG could be related to the lower lipophilicity of these compounds as a result of the absence of iodine in their structures. Since fluorine is a bioisostere of aromatic hydrogen,[1] it was hypothesized that FIBG should have a lipophilicity similar to MIBG. Another impetus for the preparation of this compound is the possibility of making its radioiodinated analogue. An imaging study with [^{18}F]FIBG could be used to predict dosimetry for a subsequent therapy study using [^{131}I]FIBG. In this paper, a synthesis for [^{18}F]FIBG and its *in vitro* and *in vivo* evaluation are described. The results suggest that FIBG could be an excellent analogue of MIBG.

Results and Discussion

Chemistry. The synthetic route to prepare the unlabeled FIBG is depicted in Scheme 1. Commercially available *p*-aminobenzonitrile was iodinated with iodine and 30% hydrogen peroxide[23] to obtain **1** in 53% yield. An alternate method[24] using chlorobenzene as solvent was investigated, but it was not as efficient. Conversion of **1** to **3** was performed using two methods. In the first method, **1** was diazotized and treated with fluoboric acid to isolate the diazonium tetrafluoroborate, **2**, in 33% yield. Pyrolysis of **2** in 3:1 (v/v) mixture of xylene and 1,4-dioxane gave **3** in 13% isolated yield. In the second method, **1** was directly converted to **2** using nitrosonium tetrafluoroborate,[25] and **2** was *in situ* pyrolyzed in 1,2-dichlorobenzene to yield **3** in 25% yield. The procedure of choice for the conversion of **1** to **3** is the second

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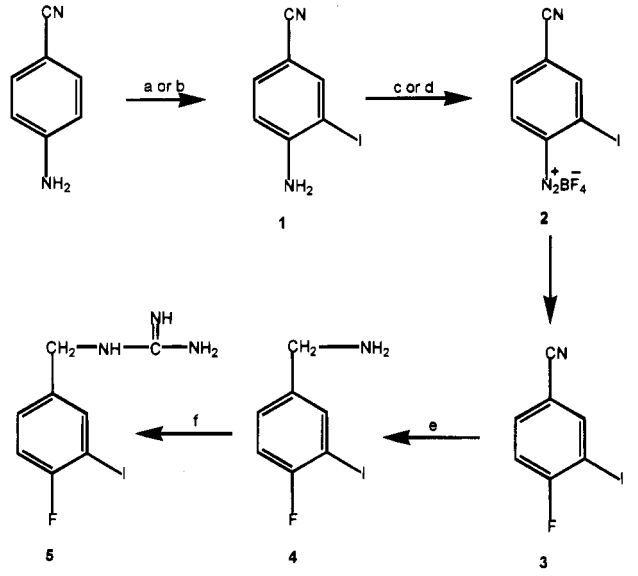
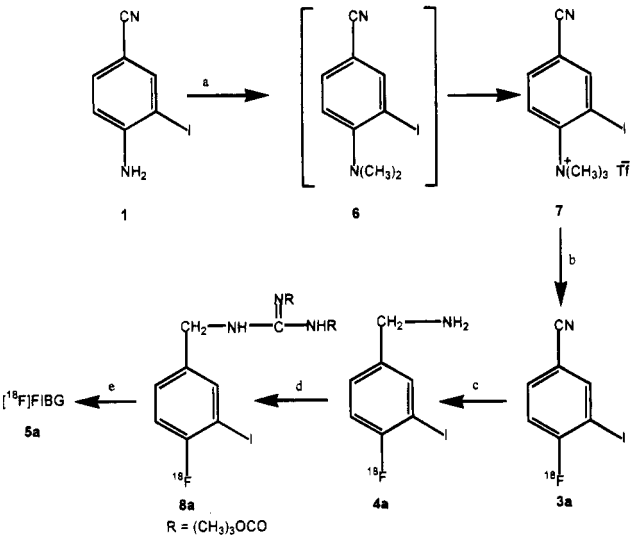
Scheme 1[a]



[a] (a) H_2O_2, I_2, MeOH; (b) H_2O_2, I_2, chlorobenzene; (c) (i) sodium nitrite, HCl; (ii) fluoboric acid; (iii) heat, xylene:dioxane (3:1); (d) (i) nitrosonium tetrafluoroborate, methylene chloride; (ii) heat, 1,2-dichlorobenzene; (e) BH_3·THF, THF; (f) cyanamide, 100 °C.

Scheme 2[a]



[a] (a) methyl triflate, methylene chloride; (b) [^{18}F]fluoride, kryptofix, DMSO; (c) sodium borohydride/iodine/THF; (d) *N,N'*-bis(*tert*-butyloxycarbonyl)thiourea, mercuric chloride, DMF; (e) trifluoroacetic acid.

method, as the former gave only less than 5% overall yield. The fluoro derivative **3** was reduced to **4** using BH_3·THF complex in 50% isolated yield. Finally, **4** was reacted with cyanamide, under conditions used to prepare MIBG,[26] to obtain FIBG (**5**) in 28% yield. It was characterized by NMR, high-resolution mass spectrometry, infrared spectrometry, and elemental analysis.

The above method cannot be adapted to prepare the nca [^{18}F]FIBG because in the conversion of **2** to **3** (Baltz–Scheiman reaction), only a maximum 25% of the activity will be incorporated into **3**. Furthermore, this results in a product with substantial amounts of carrier. The method we used is shown in Scheme 2. The preparation of the key intermediate, the quaternary salt **7**, was problematic. Trimethylammonium triflates are generally obtained by the simple treatment of a primary amine or its methyl derivatives with excess of methyl trifluoromethanesulfonate. For example, 4-(*N,N*-dimethylamino)benzaldehyde could be exhaustively methylated to its quaternary salt with methyl trifluoromethanesulfonate in good yields.[27,28] However, **1** remained unchanged under this condition. The problem is 2-fold. First, amine **1** is not very nucleophilic due to the presence of the electron-withdrawing groups, iodine and cyano, at *ortho* and *para* positions, respectively. Second, there is a steric hindrance due to the presence of bulky iodine at the *ortho* position. Sterically hindered organic bases, of base strength greater than that of the reactant amines, have been utilized to achieve quaternization of a wide variety of amines.[29] The reaction of **1** with methyl triflate was repeated using 2 molar equiv of either 1,2,2,6,6-pentamethylpiperidine or di-*n*-propylaniline. While a considerable amount of the starting material was converted to the dimethylated derivative **6**, no quaternary salt could be isolated. Recently, 2,6-di-*tert*-butyl-4-methylpyridine has been used to convert *p*-nitroaniline to its quaternary salt.[28] Using this base in the reaction, it was possible to prepare **7** in about 28% isolated yield.

The quaternary salt **7** was converted to **3a** using [^{18}F]-fluoride and Kryptofix in DMSO. About 50% of the ^{18}F activity used could be incorporated into **3a** when the reaction was conducted at 55–60 °C. The radiofluorination yield increased with increasing temperature; however, the proportion of **3a** (t_R = 12–13 min using eluent A) decreased concomittantly. This is due to the formation of the deiodinated byproduct, 4-[^{18}F]fluorobenzonitrile (t_R = 8–10 min using eluent A; corresponds with that of an authentic sample of 4-fluorobenzonitrile). It is not clear whether deiodination occurred before or after fluorination; however, the latter possibility is supported by the fact that **3** underwent deiodination, as evidenced by TLC, even when stored at 4 °C.

Initially, borane–tetrahydofuran was used for the reduction of **3a** to **4a**. The reduction *per se* was not efficient; substantial amount of deiodination was also observed. A number of reducing agents such as borane methyl sulfide,[30] Al–$NiCl_2$·$6H_2O$–THF,[31] and sodium (acyloxy)borohydride,[32] which are expected to reduce the nitrile functionality chemoselectively without affecting carbon–halogen bonds, did not deliver the expected results. The major problem was deiodination. Sodium borohydride/iodine system has been used to reduce nitriles to amines.[33] It was reasoned that the presence of iodine in the reaction medium may prevent deiodination. Use of this reducing system produced the expected product in 40–60% radiochemical yield, and the deiodination was decreased. Initially, consistent yields were not obtained. Assuming this to be due to the adventitious moisture, a large excess of sodium borohydride was employed in subsequent reactions, and this resulted in reproducible yields. A problem with this reaction is the formation of a large amount of a byproduct (presumably 4-iodo-1-butanol[33]). However, most of this could be removed by extractive workup.

Adaptation of conditions, used to prepare **5** from **4**, to convert **4a** to **5a** gave less than 5% radiochemical yield. Additionally, due to the higher temperature used, deiodination was observed. Thus, it was necessary to use alternate, milder conditions for this reaction. Re-

cently, newer reagents such as urethane-protected 1-guanylpyrazole[34] and *N,N'*-bis(*tert*-butyloxycarbonyl)-thiourea[35] have been used to prepare guanidines in good yields under milder conditions. Use of either the Boc- or CBZ-protected 1-guanylpyrazole to convert **4** to the urethane-protected derivative of **5** (**8**) was not successful, nor did we succeed in preparing **8**/**8a** from **4**/**4a** using the di-Boc-thiourea. Presumably, this is due to the weak nucleophilicity of **4**/**4a** because of the presence in these compounds of highly electronegative fluorine as well as iodine in the same ring. Parenthetically, preparation of guanidines from amines containing a [18F]fluorophenyl moiety has been reported[21,36] to proceed readily. Indeed, higher reaction temperatures could be used in these cases because of the absence of an iodine in the benzene ring. Interestingly, amines that are highly deactivated, either sterically or electronically, could be converted to the guanidine derivatives using *N,N'*-bis(*tert*-butyloxycarbonyl)thiourea in the presence of mercuric chloride.[37,38] Simple deprotection of the Boc protecting group with trifluoroacetic acid treatment delivered the required guanidine in good yields. Encouraged by this, we treated **4a** with *N,N'*-bis(*tert*-butyloxycarbonyl)thiourea in DMF, in the presence of mercuric chloride and triethylamine, and the resultant product was treated with trifluoroacetic acid. On HPLC, 50–60% of the injected activity was associated with a peak corresponding to the t_R (18–20 min) of FIBG. Thus, the synthetic reactions that were very dependable for macrosyntheses were not of value for radiosynthetic transformations.

The total synthesis time for converting the [18F]-fluoride activity to the final [18F]FIBG dose was about 130 min, and the overall decay-corrected radiochemical yield was 5%. About 2–2.2 mCi of product could be obtained from 100 mCi of [18F]fluoride activity. The chemistry would need to be further improved, possibly in tandem with automation, if frequent clinical use of this tracer were to be contemplated. No chemical or radiochemical impurities have been detected in the HPLC trace. The limit of detection of FIBG is 1 nmol. On the basis of this, the specific activity of the final preparation was estimated to be more than 1500 Ci per mmol.

Lipophilicity. As mentioned before, other investigators from our laboratory have reported on the synthesis and evaluation of (*p*-[18F]fluorobenzyl) and (*m*- [18F]-fluorobenzyl)guanidines.[21] With respect to specific binding to SK-N-SH human neuroblastoma cells *in vitro* and to the mouse myocardial uptake *in vivo*, these agents were inferior to MIBG. One possible explanation may be the reduction in the lipophilicities of these compounds when fluorine was substituted for iodine. To address this issue, we measured the lipophilicities of various benzylguanidines by two methods. The logarithms of retention factors for MFBG, PFBG, MIBG, and FIBG were −0.05 ± 0.01, −0.03 ± 0.01, 0.28 ± 0.03, and 0.31 ± 0.01, respectively. The octanol/water partition coefficients for FIBG and MIBG were 0.33 ± 0.02 and 0.31 ± 0.02, respectively, and the difference was statistically significant (paired *t* test, $p < 0.005$). Thus, both methods showed that FIBG is slightly more lipophilic than MIBG, and the HPLC results indicated that both MIBG and FIBG are much more lipophilic than the (*m*-fluorobenzyl) and (*p*-fluorobenzyl)guanidines. As one would expect, lipophilicity increases with the size of the halogen. The astatinated analogue of MIBG, (*m*-[211At]-astatobenzyl)guanidine ([211At]MABG),[39] is more lipophilic than MIBG. The octanol/water partition coefficient of MABG was 0.36 ± 0.02 in comparison to 0.31 ± 0.01 for nca [131I]MIBG, determined by a paired-label experiment as in the case of [18F]FIBG and nca [125I]-MIBG.

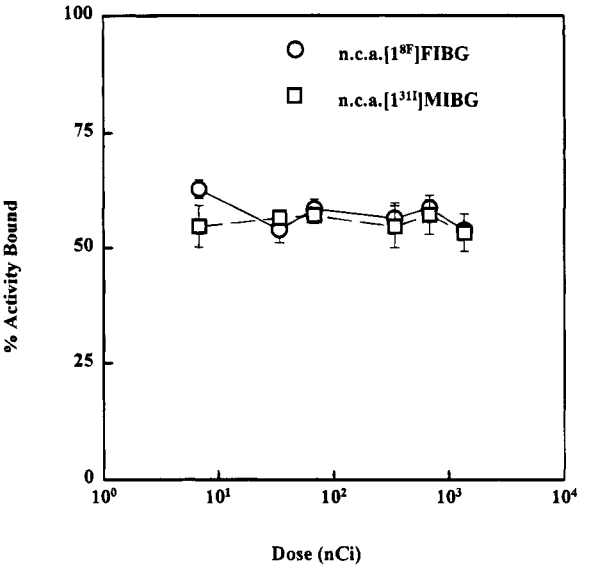


Figure 1. Binding of nca [18F]FIBG and nca [131I]MIBG to SK-N-SH human neuroblastoma cells.

***In Vitro* Binding Studies.** In order to determine whether the introduction of fluorine into the MIBG structure substantially altered its biological behavior, *in vitro* binding studies of [18F]FIBG were performed using SK-N-SH human neuroblastoma cells. The nonspecific binding for both tracers determined by preincubating the cells with 50 μM desipramine was less than 1%. The dose-dependent binding of [18F]FIBG to SK-N-SH cells is shown in Figure 1. Also shown in Figure 1 are data for nca [131I]MIBG obtained from an assay conducted in parallel. Over a 3-log range of activity, the percent of activity bound for both tracers remained almost constant and was 53–63%, suggesting that the binding of both [18F]FIBG and [131I]MIBG to SK-N-SH cells was similar. At the 7 nCi dose, the percent of [18F]-FIBG bound was higher than that of [131I]MIBG, and the difference was statistically significant ($p < 0.05$) by an independent Student *t* test. [18F]FIBG binding was slightly higher than that of [131I]MIBG at the remaining doses except the 34 nCi dose; however, the differences in all of these cases were not statistically significant.

The results were also similar to that observed earlier with (*m*-[211At]astatobenzyl)guanidine ([211At]MABG).[39] In contrast, the specific binding of [18F]PFBG and [18F]-MFBG was substantially lower than that for [131I]-MIBG[21] (34.5 ± 3.5% and 26.5 ± 1.1%, respectively, for [18F]MFBG and [18F]PFBG in comparison to 55.4 ± 0.5% for [131I]MIBG prepared by exchange method), suggesting that the presence of iodine (or another larger halogen) in the structure and presumably, higher lipophilicity, is necessary to retain maximum specific binding of (halobenzyl)guanidines to this uptake-1 targeted cell line.

Concentration-Dependent Inhibition of [18F]-FIBG and nca [125I]MIBG Uptake in SK-N-SH Cells

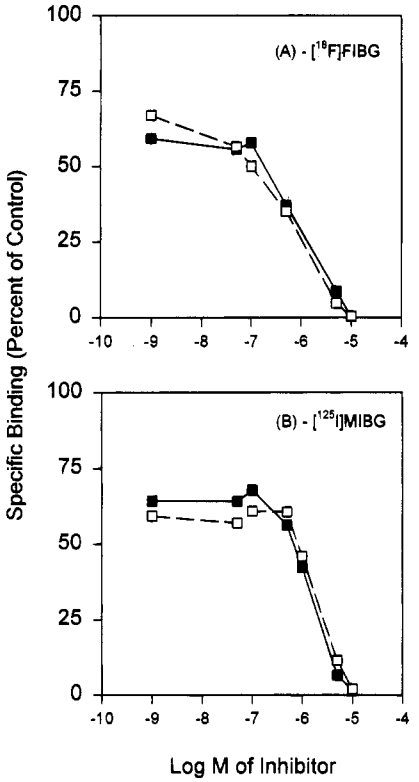


Figure 2. Inhibition of (A) [^{18}F]FIBG and (B) nca [^{125}I]MIBG binding to SK-N-SH cells by graded concentrations of unlabeled FIBG (■) and MIBG (□).

by Carrier MIBG and FIBG. The uptake of [^{18}F]-FIBG and nca [^{125}I]MIBG were found to be sensitive to competition by unlabeled analogues (Figure 2). The inhibition pattern of FIBG and MIBG was identical for both tracers. For [^{18}F]FIBG inhibition, the IC_{50} were approximately 125 and 200 nM, respectively, for MIBG and FIBG. In the case of [^{125}I]MIBG, these values were 980 and 630 nM. An IC_{50} value of about 200 nM was reported for the inhibition of uptake of [^{125}I]MIBG in this cell line by unlabeled MIBG.[40] The difference in IC_{50} values measured for [^{125}I]MIBG may be related to at least two factors. First, a no-carrier-added preparation was used in the current study, while tracer prepared by isotopic exchange method was used previously.[40] And second, the percentage binding of MIBG varies with different passage numbers of SK-N-SH cells,[41] and thus it is possible that IC_{50} may also depend on the cell passage number.

Uptake in Innervated Tissues in Mice. To further establish that FIBG is a true analogue of MIBG, the tissue distribution of [^{18}F]FIBG was studied in mice. As shown in Table 1, high uptake (% ID/g) of [^{18}F]FIBG was seen in heart and adrenals (18.2 ± 2.9%, 19.5 ± 2.7%, and 18.3 ± 0.9% in heart and 21.3 ± 2.4%, 19.2 ± 3.9%, and 19.7 ± 2.7% in adrenals at 1, 2, and 4 h, respectively). These values are comparable to those reported for nca [^{131}I]MIBG, nca [^{123}I]MIBG, and [^{211}At]-MABG.[39,42,43] In comparison, the myocardial uptake of [^{18}F]PFBG at 1 h (9.7 ± 2.2% ID/g) and 4 h (5.9 ± 0.8% ID/g) and that of [^{18}F]MFBG at 4 h (10.5 ± 1.7% ID/g) were considerably less.[21] The adrenal uptake at 1 h for these agents was also less compared with [^{18}F]FIBG (about 70–75%), although the small size of this tissue in the mouse makes comparisons between groups of questionable utility. These data also suggest that it is advantageous to have iodine present in the structure to obtain optimal *in vitro* binding and target tissue uptake. Differences in lipophilicity likely contribute to the fact that the tissue distribution of [^{18}F]FIBG is different from that of [^{18}F]PFBG and [^{18}F]MFBG.

Table 1. Tissue Distribution of nca [^{18}F]FIBG in Normal Mice

	% ID/g[a]		
tissue	1 h[b]	2 h[b]	4 h[c]
liver	10.5 ± 0.6	9.2 ± 1.1	6.8 ± 0.7
spleen	3.8 ± 0.5	3.7 ± 0.5	3.2 ± 0.2
lungs	9.7 ± 2.8	5.5 ± 1.0	4.0 ± 1.2
heart[d]	18.2 ± 2.9	19.5 ± 2.7	18.3 ± 0.9
kidney	2.6 ± 0.2	2.3 ± 0.2	1.9 ± 0.3
stomach	3.0 ± 0.6	2.4 ± 0.5	1.9 ± 0.7
sm. int.	5.5 ± 0.6	4.3 ± 0.5	3.0 ± 0.4
lg. int.	3.8 ± 0.4	4.5 ± 0.8	3.8 ± 0.5
thyroid	1.8 ± 0.3	1.9 ± 0.3	1.5 ± 0.7
muscle	1.7 ± 0.2	1.7 ± 0.3	1.5 ± 0.2
bone	1.1 ± 0.1	0.9 ± 0.1	0.7 ± 0.4
blood	0.9 ± 0.1	0.7 ± 0.1	0.4 ± 0.0
brain	0.1 ± 0.0	0.1 ± 0.1	0.2 ± 0.1
adrenals[d]	21.3 ± 2.4	19.2 ± 3.9	19.7 ± 2.7

[a] Percent injected dose per gram of tissue; mean ± SD ($n = 5$). [b] $n = 10$. [c] $n = 5$. [d] The adrenal and heart uptake (% ID/g) of [^{18}F]MFBG and [^{18}F]PFBG at 1 and 4 h are as follows (from ref 19). [^{18}F]MFBG: heart, 21.0 ± 2.6% and 10.5 ± 1.7%, respectively, at 1 and 4 h; adrenals, 13.9 ± 1.0% and 23.8 ± 5.0%, respectively, at 1 and 4 h. [^{18}F]PFBG: heart, 9.7 ± 2.2% and 5.9 ± 0.8%, respectively, at 1 and 4 h; adrenals, 15.3 ± 3.8% and 20.3 ± 4.8%, respectively, at 1 and 4 h.

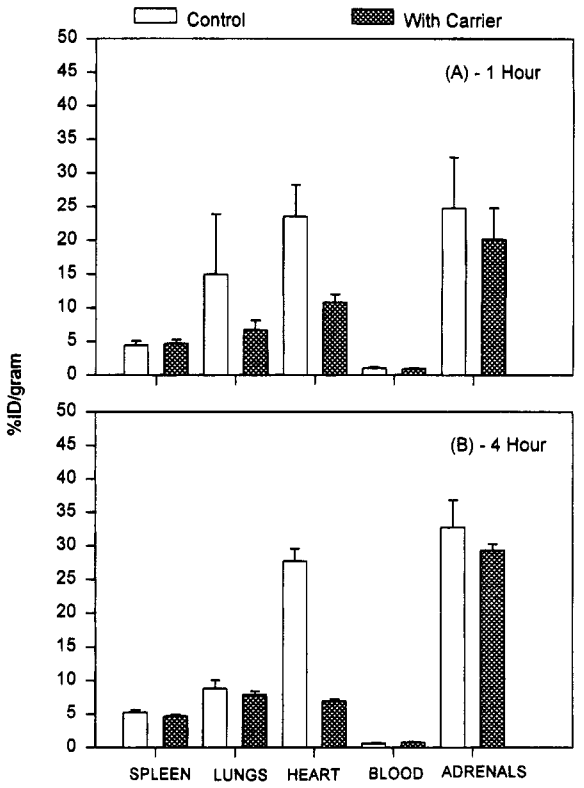


Figure 3. Effect of carrier FIBG on the mouse tissue uptake of [^{18}F]FIBG at (A) 1 h and (B) 4 h postinjection.

As shown in Figure 3, co-injection of unlabeled FIBG resulted in substantial reduction in the mouse myocardial uptake of [^{18}F]FIBG. At 1 h after administration, heart uptake was reduced to 10.8 ± 1.2% ID/g, which was less than 50% of the control value (23.5 ± 4.7% ID/g; $p < 0.005$). At 4 h postinjection, the uptake was only 25% of the control value ($p < 0.0005$). Saturability of myocardial uptake of [^{123}I]MIBG by carrier has been

demonstrated in rats.[44] At 1 h the lung uptake was reduced significantly, an observation also seen with MIBG in rats.[44] Although there was a reduction in the adrenal uptake both at 1 and 4 h, the differences were not statistically significant. With [131I]MIBG, difference in mouse adrenal uptake was seen as early as 1 h between nca preparation and exchange preparation and the difference became more significant with time.[42] On the other hand, with the 123I analogue, the difference was apparent only at 4 h.[43] Due to the shorter half-life of 18F, the adrenal uptake of [18F]FIBG could not be determined at extended time points.

Conclusion. [18F]FIBG could be prepared in good yields and high specific activities in a time equivalent to about 1 half-life of 18F. Both *in vitro* binding studies to SK-N-SH human neuroblastoma cells and *in vivo* tissue distribution studies indicate that [18F]FIBG could be an excellent analogue of MIBG for use in PET imaging of various neuroendocrine tumors as well as heart abnormalities.

Experimental Section

General. All chemicals were purchased from Aldrich Chemical Co. except as noted. Desipramine (DMI) and norepinephrine (arterenol) were obtained from Sigma. Sodium [131I]iodide in 0.1 N NaOH was supplied by DuPont-New England Nuclear (North Billerica, MA). No-carrier-added [125I]-MIBG was prepared using an identical procedure reported[42,43] for labeling with 131I and 123I, and its specific activity was at least 1200 Ci per mmol. [211At]MABG and carrier MIBG, MFBG, and PFBG were prepared as reported before.[21,39,42] The human neuroblastoma cell line SK-N-SH[45] was purchased from American Type Culture Collection (Rockville, MD). The incubation medium (JRH Biosciences, Lenexa, KS) was made by mixing 440 mL of RPMI 1640, 50 mL of Serum Plus, 5 mL of penicillin-G/streptomycin (5000 units of penicillin and 5000 μg of streptomycin in 1 mL), and 5 mL of glutamine (200 mM in saline). The cells were grown at 37 °C in a humidified incubator with 5% CO_2.

Melting points were determined on a Fisher Johns apparatus and were uncorrected. High-pressure liquid chromatography (HPLC) was performed using two LKB Model 2150 pumps, an LKB Model 2152 control system, an LKB Model 2138 fixed-wavelength UV detector, and a Beckman Model 170 radioisotope detector. Peak analysis was performed using a Nelson Analytical software package on an IBM computer. Reverse-phase chromatography was used to identify and determine the purity of various intermediates and to purify the final product. A Waters μ-Bondapak C18 (10 μm, 3.9 × 300 mm) column was used and eluted with (A) 110:89:1 (v/v/v) methanol:water:acetic acid at a flow rate of 0.5 mL/min (for 4-fluorobenzonitrile and **3**/**3a**) or (B) 80:20 (v/v) 0.2 M ammonium dihydrogen phosphate:tetrahydrofuran at a flow rate of 0.8 mL/min. NMR spectra were obtained on a General Electric Midfield GN-300 spectrometer. Proton chemical shifts were reported in δ units, and tetramethylsilane was used as an internal reference (δ = 0). Infrared spectra were acquired on a BOMEM MB-100 variable-resolution FTIR spectrophotometer. Mass spectra were obtained on a ZAB-E high-resolution mass spectrometer (VG, Manchester, England), a Hewlett-Packard GC/MS/DS Model HP-5988A instrument, or on a JEOL SX-102 high-resolution mass spectrometer. Elemental analyses were provided by Oneida Research Services (Whitesboro, NY).

4-Amino-3-iodobenzonitrile (1). *p*-Aminobenzonitrile (2.4 g; 20 mmol) was dissolved in a minimum volume of methanol in a 250 mL round-bottom flask. A solution of iodine (3.05 g; 12 mmol) and hydrogen peroxide (2 mL; 30% w/v) in about 25 mL of methanol was added, and the mixture was stirred for 4–5 h at room temperature. Methanol was removed from this mixture by rotary evaporation, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with sodium bisulfite solution, dried with anhydrous sodium sulfate, and evaporated. The residual crude solid was purified by silica gel chromatography using 25% (v/v) ethyl acetate in hexane to yield 2.6 g (53%) of a solid: mp 94–97 °C; ^{1}H-NMR ($CDCl_3$) 4.64 (br s, 2H, NH_2), 6.71 (d, 1H), 7.4 (m, 1H), 7.9 (d, 1H); MS (CI, NH_3) *m/z* 262 (base peak, $(M + NH_4)^+$), 245 (MH^+), 136 ($(M + NH_4 - I)^+$), 119 ($(MH - I)^+$).

4-Fluoro-3-iodobenzonitrile (3). Method A. To a cold (0–2 °C) suspension of 4-amino-3-iodobenzonitrile (976 mg; 4 mmol) in 8 mL of 15% (w/v) HCl was added gradually 4 mL of an aqueous solution of sodium nitrite (380 mg in 4.75 mL). To the resultant clear solution was added 24 mL of 48% (w/v) fluoboric acid. The bright yellow crystalline precipitate formed was filtered through a fritted-disk funnel, washed with cold water, and dried in a vacuum desiccator at room temperature to yield 452 mg (33%) of **2**: mp 148–151 °C; IR (KBr) 3264, 2227, 1592, 1509, 1455, 1249, 1166, and 827 cm^{-1}.

The diazonium salt, **2** (300 mg, 0.87 mmol), was taken in 50 mL of 3:1 (v/v) xylene:dioxane, and the mixture was refluxed for 40–45 min. The solvent was removed from the cooled reaction mixture by rotary evaporation using a vacuum pump. The residual oil was purified by silica gel chromatography using 15% (v/v) ethyl acetate in hexane to obtain 232 mg of an oil. This was further purified by preparative silica gel thick layer chromatography using the same solvent to obtain 28 mg (13%) of **3**.

Method B. To a cold suspension of nitrosonium tetrafluoroborate (858 mg; 7.3 mmol) in 67 mL of Sure Seal methylene chloride was added 4-amino-3-iodobenzonitrile (1.63 g; 6.7 mmol) portionwise. The bright yellow suspension was stirred on ice for 4 h. The methylene chloride was removed by rotary evaporation, 134 mL of 1,2-dichlorobenzene was added to the residue, and the mixture was refluxed for 6 h. The majority of the dichlorobenzene was removed from the mixture by passing through a large column of silica gel and eluting with hexane. The product was subsequently eluted from the column with ethyl acetate and further purified by column chromatography using a hexane-to-ethyl acetate gradient. Evaporation of solvents from fractions containing the desired product gave 410 mg (25%) of white solid: mp 53–54 °C; ^{1}H-NMR ($CDCl_3$) 7.17 (t, 1H), 7.65 (m, 1H), 8.07 (d, 1H); MS (CI, NH_3) *m/z* 265 ($(M + NH_4)^+$), 247 (MH^+), 229, 121.

4-Fluoro-3-iodobenzylamine Hydrochloride (4). Three hundred and eighty two milligrams (1.55 mmol) of 4-fluoro-3-iodobenzonitrile was added to a dry, two-necked flask fitted with a reflux condenser and septa. To this, under argon atmosphere, was added 3 mL of THF (dried over lithium aluminum hydride or benzophenone ketyl) using a glass syringe. To the above stirred solution was added dropwise 5–6 mL of 1 M BH_3·THF in THF. After the initial reaction subsided, the entire assembly was transferred to an oil bath, and the reaction mixture was refluxed for 5–6 h. Excess BH_3·THF was quenched by the careful addition of ethanol to the cooled reaction mixture. Most of the THF and ethanol were removed by rotary evaporation at room temperature. The residue was partitioned between ethyl acetate and water, and the aqueous layer was further extracted with ethyl acetate. The combined ethyl acetate layer was washed with brine, dried, and evaporated to obtain a brown oil. This oil was dissolved in dry ether, and to the resultant solution was added excess 1 N ethereal HCl with stirring. The precipitate thus formed was filtered, washed with ether, and dried in a vacuum desiccator to obtain 221 mg (50%) of a granular solid: mp 218–220 °C; ^{1}H-NMR (CD_3OD) 4.08 (s, 2H), 7.20 (t, 1H), 7.48 (m, 1H), 8.42 (m, 1H); MS (CI, NH_3) *m/z* 252 (MH^+), 235, 126.

(4-Fluoro-3-iodobenzyl)guanidine Hemisulfate (5). To 184 mg (0.64 mmol) of (4-fluoro-3-iodobenzyl)amine hydrochloride was added 43 mg (1 mmol) of cyanamide in a 5 mL pear-shaped flask. The dry mixture was heated for 4 h at 100 °C in an oil bath. The melt was dissolved in 0.32 mL of distilled water, and a solution of potassium bicarbonate (66.2 mg; 1 equiv) in water (0.26 mL) was added to it. The precipitate formed was filtered and recrystallized from 0.2 M sulfuric acid. The white granular precipitate was dried in a vacuum desiccator: yield 60 mg (28%); mp 192–193 °C; IR (KBr) 3353, 3156, 1691, 1640, 1489, 1096, 626 cm^{-1}; ^{1}H-NMR

(CD_3OD) 4.35 (s, 2H), 7.12 (t, 1H), 7.38 (m, 1H), 7.77 (m, 1H); MS (EI) *m/z* 293 (M^+; free base), 276, 250, 235, 166; HRMS calcd for $C_8H_{10}FIN_3$ (MH+) *m/z* 292.982 53, found 292.982 40. Anal. ($C_8H_9FIN_3 \cdot {}^1/_2H_2SO_4 \cdot {}^1/_2H_2O$) N; C: calcd, 27.37; found, 27.19; H: calcd, 3.16; found 3.29.

4-Cyano-2-iodo-*N,N,N*-trimethylanilinium Trifluoromethanesulfonate (7). In an argon-purged 200 mL round-bottom flask were dissolved 938 mg (3.84 mmol) of 4-amino-3-iodobenzonitrile and 1.62 g (7.9 mmol) of 2,5-di-*tert*-butyl-4-methylpyridine in 55 mL of Sure Seal methylene chloride. To this solution was added 1 mL (8.8 mmol) of methyl trifluoromethanesulfonate dropwise, and the mixture was stirred at room temperature. After 4 h, an additional 1 mL of methyl trifluoromethanesulfonate was added, and the reaction mixture was stirred at room temperature for 50 h. The precipitate formed was filtered through a fritted-disk funnel, and the solvent was evaporated from the filtrate by rotary evaporation. The residue was subjected to silica gel chromatography using a 10% to 100% (v/v) ethyl acetate in hexane gradient. This yielded 207 mg of 4-(*N,N*-dimethylamino)-3-iodobenzonitrile (6): ^{1}H-NMR (CD_3CN) 2.82 (s, 6H), 7.13 (d, 1H), 7.66 (m, 1H), 8.16 (d, 1H); IR (KBr) 2942, 2791, 2223, 1587, 1492, 1136, 944, and 826 cm^{-1}. The column was further eluted with 800 mL of methanol. The first 400 mL of the methanol eluate was discarded. Evaporation of methanol from the remaining solution resulted in a sticky solid that was purified repeatedly by the following method. The solid was taken in acetone, and any remaining insolubles (presumably the salt of the pyridine derivative) were filtered off. The filtrate was concentrated and reprecipitated with ether. This process yielded 310 mg (28%) of a pale yellow, free-flowing solid (a second crop of 70 mg was also obtained): mp 203–206 °C; IR (KBr) 3122, 3045, 2244, 1261, 1161, 1023, 937 cm^{-1}; ^{1}H-NMR (CD_3CN) 3.79 (s, 9H), 7.99 (m, 2H), 8.66 (m, 1H); MS (FAB) *m/z* 287 (M^+), 161 ($MH - I)^+$; HRMS calcd for $C_{10}H_{12}IN_2$ (M^+) *m/z* 287.00453, found 287.00440.

***N,N'*-Bis(*tert*-butyloxycarbonyl)-*N''*-(4-fluoro-3-iodobenzyl)guanidine (8).** To a 5 mL, dry, argon-purged pear-shaped flask was added 27.1 mg (0.1 mmol) of mercuric chloride, 28.6 mg (0.1 mmol) of **4**, 27.4 mg (0.1 mmol) of *N,N'*-(di-*tert*-butyloxycarbonyl)thiourea,[35] 14 μL (0.1 mmol) of triethylamine, and 500 μL of Sure Seal DMF. The mixture was stirred for 5 h at room temperature under an argon atmosphere. The reaction mixture was dissolved in ethyl acetate (10 mL), and the ethyl acetate solution was washed with brine twice and dried with sodium sulfate. The residue, after removal of ethyl acetate, was purified by thick layer chromatography using 20% (v/v) ethyl acetate in hexane to obtain 27 mg (57%) of an oil which turned to a waxy solid: mp 107–109 °C; ^{1}H-NMR ($CDCl_3$) 1.49 (s, 9H), 1.52 (s, 9H), 4.56 (d, 2H), 7.02 (t, 1H), 7.72 (m, 1H), 8.58 (m, 1H); MS (FAB) m/z 494 (MH^+), 438, 382, 364, 338, 256, 235. Its identity was further confirmed by its conversion (demonstrated by silica gel TLC) to (4-fluoro-3-iodobenzyl)guanidine on treatment with trifluoroacetic acid.

(4-[^{18}F]Fluoro-3-iodobenzyl)guanidine (5a). [^{18}F]Fluoride ion was produced using the $^{18}O(p,n)^{18}F$ reaction by irradiating [^{18}O]H_2O in a small volume (300 μL) silver target.[46] The activity was delivered to a solution of Kryptofix (Fluka; 10 mg in 1 mL of CH_3CN) and potassium carbonate (1 mg in 5 μL water) in a glass tube and then evaporated in an automated drying unit. The dried activity was resolubilized in 100–200 μL of dry DMSO. This solution containing the fluoride activity (50–100 mCi) was transferred to a 5 mL Reacti vial containing about 0.5–1.0 mg of the quaternary salt, **7**. The vial was capped tightly and heated at 50–55 °C in an oil bath for 10 min. The vial was cooled in an ice bath, and the contents were diluted with 5 mL of water and passed through an activated C18 Sep Pak (Millipore, Milford, MA) cartridge. The cartridge was further washed with water and purged with argon to remove most of the moisture. The desired compound, 4-[^{18}F]fluoro-3-iodobenzonitrile, in 50% decay-corrected yield, was eluted from the cartridge using 2 × 2 mL of methylene chloride. The pooled methylene chloride solution was dried with sodium sulfate and passed through a Silica Sep Pak cartridge, and the activity was eluted again with methylene chloride.

The combined methylene chloride solution was evaporated to a small volume in a rotary evaporator and tranferred to a 1 mL Reacti vial and evaporated further using argon (due to the extreme volatility of the product, about 20% of the activity is lost during argon evaporation). The activity was redissolved in 50 μL of Sure Seal THF, and 5–10 mg of sodium borohydride was added to the solution. A solution of iodine in THF (25 μL of 12.5 mg/100 μL) was added dropwise to the above mixture. The vial was capped and heated in an oil bath maintained at 50–55 °C for 10 min. During this period, 25 μL aliquots of the above iodine solution were added until the iodine was no longer consumed (generally a total of 100–125 μL of the solution was needed). Under these conditions, about 50–60% of the activity is converted to 4-[^{18}F]fluoro-3-iodobenzylamine (t_R = 10–11 min using eluent B; 4-fluorobenzylamine had a t_R of 5–6 min). The supernatant THF solution was carefully withdrawn and added to 1 mL of cold 6 N HCl. The small amount of activity sticking to the solid residue was further extracted with 2 × 100 μL of THF, and the extract was also added to the above. The HCl solution was warmed for 1–2 min and extracted with 3 × 1 mL of ethyl acetate. The aqueous layer was made basic by adding 1–1.2 mL of cold 6 N NaOH. The required activity was extracted with 3 × 1 mL of ethyl acetate. The combined ethyl acetate solution was washed with 1 mL of brine, dried with sodium sulfate, and evaporated to a small volume in a rotary evaporator. The activity was then transferred to a 1 mL Reacti vial, and the remaining ethyl acetate was evaporated off with an argon stream.

To the above 4-[^{18}F]fluoro-3-iodobenzylamine activity was added 5 μL (3 μmol) each of a DMF solution of mercuric chloride, *N,N'*-bis(*tert*-butyloxycarbonyl)thiourea, and triethylamine. The vial was capped, vortexed, and kept at room temperature for 5–8 min. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted further with 0.5 mL of ethyl acetate. The combined ethyl acetate solution was washed once with brine, dried, and evaporated in a rotary evaporator to a small volume. This was taken into a $^1/_2$ dram vial and further evaporated to dryness using argon. To the residue was added 200 μL of trifluoroacetic acid, and the mixture was heated at 50–55 °C for 5–8 min. A precipitate was formed on addition of trifluoroacetic acid. The mixture was filtered through a 0.2 μm Teflon syringe filter, and the filter was further washed with 100 μL of trifluoroacetic acid. Trifluoroacetic acid was evaporated from the filtrate, and the residue was taken into a HPLC syringe with the help of methanol. The activity was purified by reverse-phase HPLC (t_R = 18–20 min using eluent B; PFBG had a t_R of 6–7 min). For biological evaluations, the HPLC fractions containing the activity were desalted using a C18 Sep Pak and reconstituted in an appropriate buffer as reported before for radioiodinated MIBG and [^{211}At]MABG.[39,42,43]

Lipophilicity Measurements. The relative lipophilicities of benzylguanidines were measured using two techniques. In the first technique reverse-phase HPLC was utilized.[47] The retention times of MFBG, PFBG, MIBG, and FIBG were determined using a Waters μ-Bondapak C18 (10 μm, 3.9 × 300 mm) column with 1% acetic acid in 60:40 (v/v) water:methanol as the eluent at a flow rate of 1 mL/min. From these values, the logarithms of retention factors[48] were calculated. In the second technique, the partition coefficient of [^{125}I]MIBG and [^{18}F]FIBG between octanol and water were measured in a paired-label experiment. A protocol reported in the literature[49] was utilized. Octanol and water were presatuarated with the other. A few nanocuries of nca [^{125}I]MIBG and 2–3 μCi of [^{18}F]-FIBG were added to 2 mL of water followed by 2 mL of octanol in triplicate. The mixture was vortexed thoroughly and centrifuged at 2500 rpm in a Beckman Model TJ-6 centrifuge for 10 min to separate phases. Duplicate aliquots (50 μL) of both phases were counted for ^{125}I and ^{18}F activity using a dual label counting program on the γ counter. The aqueous phases were repartitioned against an equal volume of fresh octanol, and the distribution of activity in each phase was determined as above. This process was repeated five times to ensure

constancy of partition coefficient values. The partition coefficient was calculated by dividing the counts in the octanol layer by the counts in the water layer.

Binding of nca [18F]FIBG to Human Neuroblastoma SK-N-SH Cells. The cells were seeded into 24-well plates (4×10^5 cells in 500 μL medium/well) and incubated for 24 h in a 37 °C/5% CO_2 humidified atmosphere. Cells were incubated with 6.8–1360 nCi of [18F]FIBG for 2 h at room temperature. A parallel experiment was conducted using nca [131I]MIBG under identical conditions. The medium was removed at the end of 2 h incubation, and the cells were washed twice with phosphate-buffered saline. The cells were solubilized by incubation with 500 μL of 0.5 N NaOH for 30 min at room temperature and then removed with cotton swabs. The cell-bound activity was counted along with input standards using the γ counter. Each measurement was performed in triplicate.

Inhibition of [18F]FIBG and [125I]MIBG Binding to SK-N-SH Cells by FIBG and MIBG. A solution containing about 1 μCi of [18F]FIBG or 0.1 μCi of nca [125I]MIBG and various concentrations of FIBG and MIBG were added in triplicates to 4×10^5 cells per well in a final volume of 500 μL in 24-well plates. The cells were incubated for 2 h at 37 °C, and the cell-bound activity determined as described above. Nonspecific binding was determined by preincubating cells with 1 μM desipramine for 30 min. Specific binding, expressed as percentage of control, was plotted against the concentration of the inhibitor.

Tissue Distribution in Mice. Normal, BALB/c mice, weighing 26–29 g, were injected via the tail vein with 4 μCi of nca [18F]FIBG. Groups of five mice were killed at 1, 2, and 4 h postinjection using halothane. The mice were dissected and the tissues of interest were isolated. The tissues were washed with saline, blot-dried, weighed, and counted in a γ counter for 18F activity. The results were expressed as % ID/g, the percentage of injected dose per gram of tissue. Experiments were also performed to determine the effect of carrier FIBG on the tissue uptake of [18F]FIBG. A group of five mice was co-injected with carrier FIBG (25 μg per mouse; about 1 mg/kg body weight) and 5–10 μCi of [18F]FIBG via the tail vein. The control group of five mice received the same dose of labeled FIBG. The tissue uptake in both groups was determined at 1 and 4 h postinjection.

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