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RADIOSYNTHESIS OF NO-CARRIER-ADDED N-(4-DIPROPYL AMINOBUTYL)-4-[^{125}I]-IODOBENZAMIDE, A PROMISING TRACER FOR THE DETECTION OF MELANOMA

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SUMMARY

N-(4-dipropylaminobutyl)-4-iodobenzamide was recently developed in our laboratory as a potentially improved imaging agent for metastatic melanoma. Our purpose was to seek an efficient route to the labelling of this tracer with iodine-125 at a carrier free level.Three different approaches were explored : Wallach triazene reaction, nucleophilic exchange of bromide for iodide, iododestannylation. The most suitable method appeared to be the electrophilic radio-iododestannylation of the tributyl-stannyl precursor using no-carrier added sodium [^{125}I] iodide oxidized with chloramine T. The exchange between iodine-125 and the leaving group occured in 15 min at room temperature. A chemically and radiochemically pure product was obtained after reverse phase HPLC purification, with a radiolabeling yield of about 75 %.

Keywords : melanoma tracer, [^{125}I] Iodobenzamide, Iododestannylation

INTRODUCTION

Due to the aggressive nature of melanoma, the early detection of the primary disease and of the invasive metastatic process is of paramount importance to greatly enhance the chances of successful therapy. Previous work conducted in our laboratory established N-(2-diethylaminoethyl)-4-iodobenzamide (BZA ; Figure 1) as a suitable agent for melanoma scintigraphy (1,2) : [^{125}I]-BZA showed selective uptake in mice tumor models, murine B16 and human melanotic melanoma (3) ; further investigation in humans with [^{123}I]-BZA led to a diagnostic sensitivity of 81 % and a specificity of 87 % (4).

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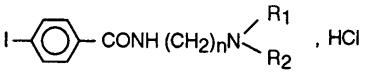


BZA : n = 2 ; $R_1 = R_2 = C_2H_5$

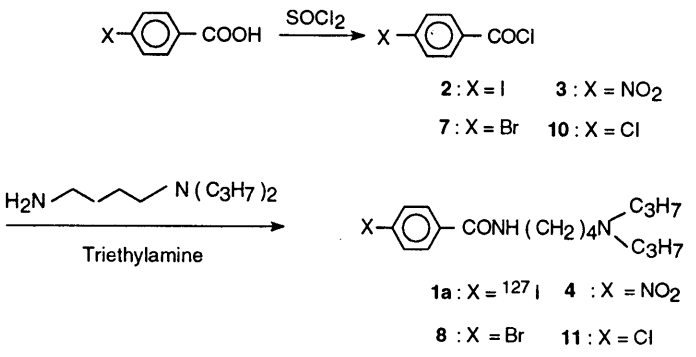
1 : n = 4 ; $R_1 = R_2 = n\,C_3H_7$. (**1a** : ^{127}I ; **1b** : ^{125}I)

Figure 1

However, as the best tumoral definition was obtained only 24 h after injection, the routine clinical use of [^{123}I] BZA may be limited given the 13. 2 h half-life of the expensive iodine radionuclide. Therefore, for economic reasons and to improve dosimetry, we attempted to synthesize other derivatives able to provide quality images sooner after injection (5). We are currently undertaking the study of new benzamide analogs systematically obtained from BZA by the variation of the N-terminal substituents and the length of the methylene chain (6). For biological evaluation, each compound is labelled with ^{125}I using an isotopic exchange reaction. The radiohalogenation technique does not allow the obtaining of carrier free products. Comparative biodistribution analysis is carried out in mice with subcutaneously transplanted B16 melanoma. Among the benzamides investigated so far, N-(4-dipropylaminobutyl)-4-iodobenzamide **1** (Figure 1) showed excellent melanoma/non-target tissue ratios associated with high melanoma affinity after 3 hrs injection. Based on these promising animal results, the evaluation in man seemed of a great interest and in this aim the preparation of no-carrier-added iodine-123 benzamide **1** became necessary. In this paper we present a comparison of three different synthetic approaches that we explored to optimize the synthesis : the triazene method, non-isotopic exchange of bromine with radioiodine, and iododestannylation. For convenience and economy the longer lived ^{125}I was chosen as isotope for the development work.

RESULTS AND DISCUSSION

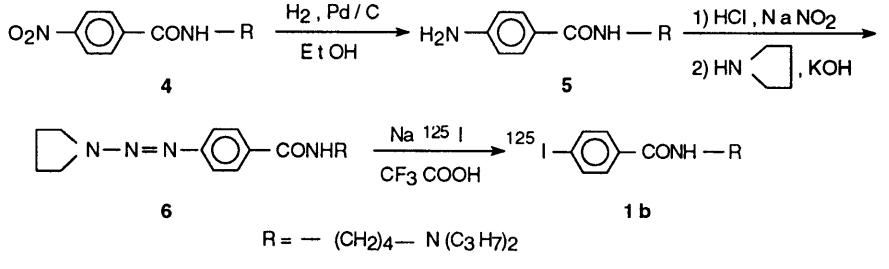
The non radioactive reference compound **1a** was conveniently prepared in two steps from 4-iodobenzoic acid using standard reaction conditions as shown in scheme 1 : transformation of the acid to the corresponding acid chloride **2** and coupling with 4-amino-N,N-dipropylbutylamine gave the desired benzamide in good yield after purification by low pressure liquid chromatography.



Scheme 1

The identity of **1a** was based on its ^1H NMR spectrum where the signals were consistent with the expected structure. It was used as an authentic standard in the TLC and HPLC analyses to identify and confirm the product of interest.

Our first approach to carrier free radioiodinated benzamide **1b** was by the Wallach triazene reaction. This method involves the use of a triazenyl precursor which undergoes nucleophilic radioiodine substitution when decomposed by acids in the presence of the radioiodide ion (7). The triazene **6** was prepared by the following sequence of reactions (scheme 2) : catalytic hydrogenation of the 4-nitrosubstituted benzamide **4** gave the corresponding amino compound **5**. The latter was transformed into its diazonium chloride with nitrous acid generated in situ, then addition of an excess of pyrrolidine gave the expected triazene **6** in 83 % yield. This substance could be used for iodination without purification as indicated by TLC and analytical HPLC ; it was identified by its ^1H NMR spectrum.

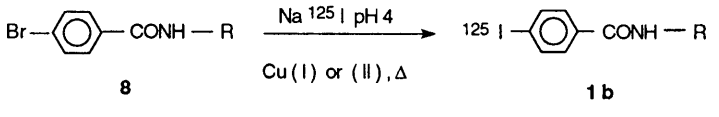


Scheme 2

According to the literature, the conversion of triazenes to radioiodinated products depends greatly on the choice of acid, solvent and reaction time. Optimum conditions determined for one compound are not general for other analogs (8). So preliminary non-radioactive experiments were performed under various conditions : acetonitrile or ethanol as solvent, hydrochloric or trifluoroacetic acid, reaction times : 15 min, 30 min, or 60 min, at room temperature. The best yield (60 %) of iodobenzamide was obtained when the reaction was

carried out in ethanol in the presence of CF_3CO_2H and left at room temperature for 30 min. Based on this information about the reaction conditions, the radioiodination was attempted using n.c.a Na ^{125}I. After separation by semi-preparative HPLC, the required **1b** was isolated in only 18-20 % yield. Such low yields for the preparation of radioiodinated compounds in n.c.a labeling conditions have been reported in the literature (9,10). The reasons are not clear but the amount of Na ^{125}I is very small with respect to the triazene intermediate and this may lead to the predominant formation of side substances. In fact, HPLC analysis of the crude reaction mixture using UV detection indicated the presence of several non-identified by-products. So, in spite of the fact that the aryl triazene **6** is a stable precursor, easily prepared and easily separated from the expected radiotracer, the present triazene method to prepare **1b** at high specific activity is unsatisfactory.

The second method explored was the non-isotopic exchange reaction starting from the brominated benzamide **8** (scheme 3). The latter was dissolved in citrate buffer at pH 4 and heated at 150°C for 1 h in the presence of n.c.a. Na ^{125}I and copper sulfate or chloride used as a catalyst (5).



8 **1b**

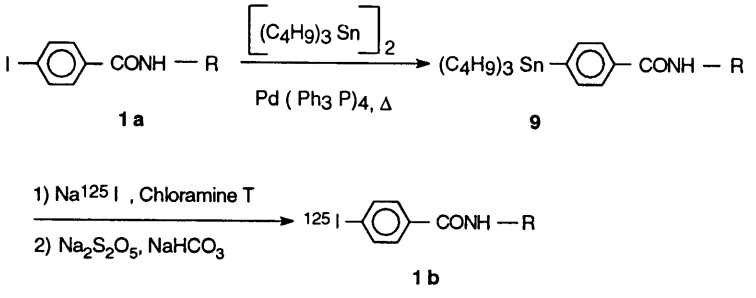
R = — $(CH_2)_4$ — $N(C_3H_7)_2$

Scheme 3

The initial radiochemical purity of **1b** was in the range 81-93 % (n = 4) as determined by radio-TLC analysis, the rest of the radioactivity representing mostly free [^{125}I] iodide. Purification was achieved by using semi-preparative HPLC with sequential UV and radioactivity detection. Free radioiodide was eluted with the solvent front, 4-bromobenzamide after 25.1 min and 4-[^{125}I] iodobenzamide after 29.6 min. The radiochemical yield was approximately 75 %. The quality control of the purified **1b** by analytical HPLC analysis showed > 98 % radiochemical purity but UV detection indicated the presence of a small amount of starting material **8**. With the HPLC column and mobile phase used, the difference between the retention time of the bromo and iodobenzamides was not sufficient to allow their total separation. Further studies will hopefully optimize the chromatographic parameters.

The third approach involved was electrophilic iododestannylation. In recent years, many studies at incorporating radioiodine into aromatic compounds have been carried out using

organo-metallic intermediates (11). Of these derivatives, the organostannanes have been particularly attractive due to their broad reactivity with radiohalogens (12-14). Based on these considerations, p-tri-n-butylstannyl benzamide **9** was prepared as described in scheme 4 : treatment of **1a** with excess hexabutylditin for 24 h in refluxing toluene in the presence of tetrakis (triphenylphosphine) palladium (0) as catalyst, afforded the required precursor.



Scheme 4

It was purified by silica column chromatography and isolated (80 %) as a clear yellow oil. The material was shown by ^{1}H NMR, analytical HPLC and TLC analyses, to be free of **1a** which if present could lower the specific activity of the final radiolabeled tracer. Radioiodination of **9** was accomplished by treatment with no-carrier-added sodium [^{125}I] iodide at acidic pH (ethanolic hydrochloric or acetic acid) and oxidized with chloramine T trihydrate (scheme 4). After standing for 15 min at room temperature, a good incorporation of ^{125}I was achieved (between 74 % and 83 %, n = 7) as controlled by radio-TLC analysis. The mixture was then quenched with aqueous sodium metabisulfite and purified by semi-preparative HPLC. The separation using a reverse silica phase column was facilitated by the fact that the main components of the reaction mixture were the highly polar oxidant and unreacted radioiodide which eluted in the solvent peak, the labeled product (R_t = 10.1 min) and the highly lipophilic tributyl stannyl precursor which eluted much later than **1b** (R_t = 18.6 min). Thus the required radiotracer could be isolated with a specific activity of the same order as the starting material sodium [^{125}I] iodide. The mean radiolabelling efficiency was in the 70 to 75 % range and the radiochemical purity was > 98 % as determined by HPLC analysis. However, when the radioiododestannylation was performed in dilute hydrochloric acid, formation of small amounts of the chlorine substituted analog **11** could be observed using UV detection. No trace of **11** was detectable when the iodination was performed using acetic acid.

In conclusion, our aim was to develop an efficient procedure for labelling N-(4-dipropylaminobutyl)-4-iodobenzamide, a promising melanoma tracer, with ^{125}I at carrier free level. The wallach triazene reaction led to low radiochemical yield. The Cu (I or II) catalyzed nucleophilic exchange of bromide for iodide provided high incorporation of ^{125}I ; however the disadvantage of using this pathway was the difficulty of obtaining the labelled product free of precursor after HPLC purification. Experimentally the radioidodestannylation of the corresponding 4-(tri-n butyltin) benzamide was found to be the most suitable method because of the rapid reaction time at room temperature, good radiochemical yield and excellent product purity. This technique will be used for the synthesis of [^{123}I] benzamide with the aim of evaluating this novel melanoma imaging agent in humans.

EXPERIMENTAL

General : Reagents for organic synthesis were purchased from Aldrich Chemical Company and used without further purification. All solvents were of analytical grade and were used directly. Melting points were determined with a Kofler apparatus and are reported uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at 200 MHz on a Bruker AM 200 spectrometer ; chemical shifs (δ) are reported in parts per million relative to the internal tetramethylsilane standard in the following order : multiplicity (s, d, t, q, br, for singlet, doublet, triplet, quartet and broad respectively), number of protons, proton assignment ; exchange with D_2O was used, when necessary, to identify NH protons. ^{13}C NMR spectra are reported using chloroform as the reference signal (77.0 ppm). Silica gel 60 (Chromagel , 230-400 mesh, SDS) or Aluminium oxide type 507 C neutral (100-125 mesh, Fluka) were used for low-pressure liquid column chromatography. Analytical thin layer chromatography (TLC) was carried out on pre-coated silica gel or neutral aluminium oxide plates (Merck 60 F 254, 0.2 mm thick) subsequently visualized under UV light (254 nm) and by exposure to iodine vapor. The radioactive spots were scanned with a Berthold LB 2832 linear analyzer. Two high performance liquid chromatography (HPLC) systems were used :
The HPLC purification (system A) was performed on a Shimadzu system (LC 6A pump, SCL 6B controller, CR_5A integrator) ; the semi-preparative column packed with Kromasil 100 Å 13 µm (300 x 10.5 mm) was connected in series with a Shimadzu SPD 6AV UV spectrophotometer and a Raytest steffi gamma detector. The flow rate was 5 ml/min with different isocratic or continuous elution gradient of water/methanol 0.2% NH_4OH as indicated later. The HPLC analytical system (system B) consisted of a Chromatem 380 model

equipped with two pumps and a solvent programmer (Altex, Touzart and Matignon, Paris). An analytical column (250 x 4.6 mm) packed with Kromasil C18 5 µm was connected to a UV spectrophotometer (Pye Unicam, Ltd, Cambridge) and a flow-on-line radioactive detector (Flow one A_{200} Radiomatic, Canberra, Australia). The flow rate was 1.5 ml/min with different elution systems of water/methanol 0.2 % NH_4OH. For the two systems A and B, the following mobile phases, expressed as volume/volume ratios, were used : program a : 73/27 ; program b : 75/25 ; program c : elution gradient from 80/20 to 100 during 10 min. The ^{125}I-labelled compound was identified by TLC (Rf) and HPLC (Rt) comparisons with the corresponding unlabelled authentic sample. Sodium [^{125}I] iodide was supplied by CIS Bio-international as a no-carrier-added solution in reductant-free aqueous NaOH.

N-(4-dipropylaminobutyl)-4-iodobenzamide, **1a**

A solution of 4-iodobenzoic acid (2 g, 7.5 mmol) in CH_2Cl_2 (25 ml) was treated with $SOCl_2$ (2.5 ml) and a catalytic amount of DMF. The reaction mixture was refluxed for 3 hr and the solvent was removed under reduced pressure. The crude acid chloride **2** thus obtained was dissolved in CH_2Cl_2 (20 ml) and treated dropwise with 4-amino-N,N-dipropylbutylamine (1.3 g, 7.5 mmol) in CH_2Cl_2 (10 ml) and triethylamine (1 ml, 7.5 mmol). The mixture was stirred at room temperature overnight and then concentrated in vacuo. The residue was taken up in 2 % $NaHCO_3$ (20 ml) and extracted with CH_2Cl_2 (3 x 30 ml). The organic solution was dried over $MgSO_4$, filtered and rotary evaporated. The crude mixture of products was purified by column chromatography on neutral alumina and the elution with ethyl acetate/methanol 95: 5 afforded **1a** as a white solid (1.8 g, 60 %). m.p. 70°C, ^1H NMR ($CDCl_3$) δ : 0.84 (t, 6H, **CH**3), 1.43 (m, 4H,**CH**$_2$ CH_3), 1,62 (m, 4 H, CH_2 **CH**$_2$ **CH**$_2$ CH_2), 2.38 (m, 6H, N(**CH**$_2$)$_3$), 3.46 (q, 2H, NH **CH**$_2$; t after D_2O addn), 7.0 (br s, 1 H, **NH**, exc. D_2O), 7.46-7.79 (dd, 4H, aromatic) ; ^{13}C NMR . ($CDCl_3$) δ : 11.92 (**CH**$_3$)), 19.71 (**CH**$_2$CH$_3$), 25.0 (**CH**$_2$**CH**$_2$N), 27.51 (NH **CH**$_2$**CH**$_2$), 40.06 (**NHCH**$_2$), 53.56 (**CH**$_2$N(C_3H_7)$_2$), 56.09 (**NCH**$_2$**CH**$_2$**CH**$_3$), 97.90, 128.58, 134.48, 137.54 (aromatic carbons), 166.78 (**CO**) ; TLC (Al_2O_3) ethyl acetate/methanol (95 : 5) Rf = 0.56 ; HPLC (system B, U V detection) program a : R_t = 25.4 min, program b : R_t = 11 min, program c : R_t = 6.8 min.

N-(4-dipropylaminobutyl)-4-nitrobenzamide, **4**.

A solution of 4-nitrobenzoylchloride **3** (1.85 g, 10 mmol) in CH_2Cl_2 (30 ml) was treated with 4-amino-N,N-dipropylbutylamine (1.72 g, 10 mmol) in CH_2Cl_2 (20 ml) followed by triethylamine (1.35 ml, 10 mmol), and the mixture was stirred at room temperature overnight. After the same treatment as described above for **1a**, the pure benzamide **4** was obtained as a

white solid (2.18 g, 68 %). ^{1}H NMR ($CDCl_3$) δ : 0.95 (t, 6H, CH_3), 1.60 (m, 8H, CH_2CH_3 and CH_2 CH_2 CH_2 CH_2) , 2.78 (m, 6H, $N(CH_2)_3$, 3,54 (q, 2H, $NHCH_2$; t after D_2O addn) , 8.25 (m, 5 H, NH and aromatic) ; T LC (Al_2O_3) ethyl acetate/pentane (80 :20) Rf = 0.34.

N-(4-dipropylaminobutyl)-4-aminobenzamide, **5**

A suspension of **4** (2.18 g, 6.8 mmol) and 10 % palladium on charcoal (0.3 g) in ethanol (150 ml) was hydrogenated for 1 hr at room temperature. The catalyst was removed by filtration through Celite. The solvent was evaporated to give crude **5** as a light-yellow oil (1.78 g, 90 %) which was used for the next step without purification. ^{1}H NMR (CD Cl_3) δ : 0.90 (t, 6H, CH_3), 1.62 (m, 8H, CH_2 CH_3 and CH_2 CH_2 CH_2 CH_2), 2.61 (m, 6 H, N $(CH_2)_3$, 3.44 (q, 2H, $NHCH_2$; t after D_2O addn) , 4.05 (s, 2H, NH_2, exc. D_2O), 6.75-7.66 (dd, 4H, aromatic), 6.80 (br s, 1H, NH, exc. D_2O) ; TLC (SiO_2) $MeOH/H_2O/NH_4OH$ (80 : 15 : 5) Rf = 0.73

N-(4-dipropylaminobutyl)-4-pyrrolidinotriazenylbenzamide, **6**.

A suspension of **5** (0.9 g, 3.09 mmol) in 5 ml of water and 2 ml of concentrated HCl was heated at 40°C until dissolved. The mixture was cooled to 0°C with vigorous stirring and then sodium nitrite (0.28 g, 4.06 mmol) dissolved in 1 ml of water was added over a period of 10 min. Stirring was continued for 15 min at 0°C and pyrrolidine (0.4 ml, 4.8 mmol) was added dropwise followed by 0.6 ml KOH. The reaction mixture was kept at room temperature for 1 hr and then extracted with CH_2Cl_2 (3 x 30 ml). Combined extracts were dried ($MgSO_4$) and the evaporation of the solvent gave **6** as a pure white solid (0.96 mg, 83 %). m.p. 88°C ; ^{1}H NMR ($CDCl_3$) δ : 0.87 (t, 6H, CH_3), 1.52 (m, 6H, CH_2 CH_3 and $NHCH_2CH_2CH_2$), 1.63 (m, 2H, $NHCH_2CH_2$), 2.04 (m, 4H, CH_2 pyrrol), 2.47 (m, 6H, N $(CH_2)_3$), 3.45 (q, 2H, $NHCH_2$, t after D_2O addn), 3.76 (s, 4H, CH_2 pyrrol), 6.80 (br s, 1H, NH, exc. D_2O), 7.40-7.78 (dd, 4H, aromatic) ; ^{13}C NMR ($CDCl_3$) δ : 11.67 (CH_3), 19.18 (CH_2CH_3), 23.58 (CH_2CH_2N), 24.03 (CH_2 pyrrol), 27.32 ($NHCH_2CH_2$), 39.53 ($NHCH_2$), 53.31 ($CH_2N(C_3H_7)2$), 55.62 ($NCH_2CH_2CH_3$ and CH_2 pyrrol) ; 119.98, 127.75, 130.00, 153.85 (aromatic carbons), 167.30 (CO) ; TLC (Al_2O_3) ethylacetate Rf = 0.22 ; HPLC (system B, U V detection, program a) : Rt = 16.3 min.

N-(4-dipropylaminobutyl)-4-bromobenzamide, **8**.

A solution of 4-bromobenzoylchloride **7** (0.44 g, 2 mmol) in CH_2Cl_2 (10 ml) was treated with 4-amino-N,N-dipropylbutylamine (0.34 g, 2 mmol) in CH_2Cl_2 (5 ml) and triethylamine (0.28 ml, 2 mmol). After the same treatment as for **1a** and **4**, the pure benzamide **8** was obtained as a white solid (0.5 g, 70 %). m.p. 56°C ; ^{1}H NMR ($CDCl_3$) δ : 0.92 (t, 6H, CH_3), 1.45 (m, 4H, CH_2 CH_3) , 1.59 (m, 4H, CH_2 CH_2 CH_2 CH_2) , 2.36 (m, 6H, $N(CH_2)_3$), 3,44 (q, 2H, $NHCH_2$,

t, after D_2O addn),7.00 (br s, 1H, NH, exc. D_2O), 7.62 (m, 4H, aromatic) ; ^{13}C NMR ($CDCl_3$) δ : 11.45 (CH_3) , 17.98 (CH_2CH_3), 22.74 (CH_2,CH_2N), 26.62 ($NHCH_2CH_2$), 38.86 ($NHCH_2$), 52.77 (CH_2N ($C_3H_7)_2$), 54.79 ($NCH_2CH_2CH_3$) ; 125.74, 128.89, 131.44, 133.38 (aromatic carbons), 166.63 (CO) ; TLC (Al_2O_3) ethylacetate/methanol (98:2) Rf = 0.63 ; HPLC (system B, U V detection, program b) : R_t = 11.5 min.

N-(4-dipropylaminobutyl)-4-(tri-n-butylstannyl) benzamide, **9**

To a solution of iodobenzamide **1a** (0.60 g, 1.49 mmol) in dry toluene (20 ml) was added hexabutylditin (1.49 g, 2.61 mmol) and a catalytic amount of tetrakis (triphenyl phosphine) palladium. The mixture was stirred at reflux temperature for 24 hr under an argon atmosphere. The black precipitate that formed as the reaction progressed was removed by filtration through Celite and toluene was evaporated under reduced pressure. The residue was purified by silica column chromatography eluting with 1 % ethanolic dichloromethane to give the tributylstannyl benzamide **9** as a yellow oil (0.67 g, 80 %). ^1H NMR ($CDCl_3$) δ : 1.06 (t, 15 H, CH_3) , 1.22 (t, 6H, CH_2Sn), 1.33 (m, 8H, $CH_2CH_2CH_2Sn$ and CH_2CH_3), 1.37 (m, 8H, CH_2 CH_2 CH_2 Sn and CH_2CH_3), 1.47 (m, 4H, CH_2 CH_2 CH_2 CH_2), 2.52 (m, 6H, N (CH_2)$_3$), 3.50 (q, 2H, $NHCH_2$, t after D_2O addn), 6.95 (br s, 1H, NH, exc D_2O), 7.50-774 (dd, 4 H aromatic); ^{13}C NMR ($CDCl_3$) ; δ : 9.53 (CH_3 (CH_2)$_3$Sn), 11.63 (CH_3), 13.52 (CH_3CH_2 (CH_2)2 Sn), 18.91 (CH_2CH_3), 23.71 (CH_2CH_2N), 27.19 ($CH_3CH_2CH_2CH_2Sn$), 28.93 (CH_2Sn), 29.58 ($NHCH_2CH_2$), 39.32 ($NHCH_2$), 53.26 (CH_2 $N(C_3H_7)_2$), 55.46 (NCH_2 CH_2 CH_3), 126.00, 134.12, 136.37, 146;78 (aromatic carbons), 167.87 (CO) ; TLC (SiO2) dichloromethane/ethanol (95 :5) Rf = 0.51 ; HPLC (system B, U V detection, program c) : R_t = 14.9 min.

N-(4-dipropylaminobutyl)-4-[^{125}I]-iodobenzamide 1b

a) Synthesis from the triazene **6**

A solution of compound **6** (1 mg, 2.7 μmol) in ethanol (100 μl) was treated at 0°C with CF_3CO_2H (10 μl) and immediatly transferred to sodium [^{125}I] iodide (10 μl, 500 μCi, 18.5 MBq). After standing for 30 min at room temperature with intermittent shaking, the reaction mixture was made basic by the addition of 0.1 N $NaHCO_3$ and purified by HPLC (system A, program a ; simultaneous UV and gamma radioactivity detection ; **1b** : R_t = 31.2 min ; **6** : R_t = 23.5 min) to provide **1b** in 18-20 % radiochemical yield. Determination of chemical and radiochemical purities was performed by analytical HPLC (system A, program a). Radioactive tracer co-migrated with non-radioactive standard **1a** and showed chemical and radiochemical purities > 95 %.

b) Synthesis by nucleophilic halogen exchange

A solution of the bromoprecursor **11** (1 mg, 2.8 µmol) in 0.05 M citrate buffer pH4 (200 µl) was added to sodium [^{125}I] iodide (10 µl, 500 µCi, 18.5 MBq). followed by anhydrous copper sulfate (0.33 mg) in water (100 µl) and the reaction mixture was heated at 150°C in a sealed vial for 90 min. After cooling, the residue was diluted in water (100 µl) and 0.1 N $NaHCO_3$ was added to basic pH. The material was injected onto HPLC semi-preparative column (system A, program b ; **1b** : Rt = 29.6 min ; **11** : Rt = 25.1 min). The expected radioiodotracer was obtained in 75-80 % radiochemical yield with radiochemical purity > 95 % (system B, program b), U V detection showed the presence of a small amount of **11** in the final solution.

c) Synthesis by electrophilic iododestannylation

A solution of the tri-n-butylstannyl precursor **9** (1.5 mg, 2.65 µmol) in ethanol containing glacial acetic acid (100 µl ; 90 : 10 v/v) was added to sodium [^{125}I] iodide (10 µl, 500 µCi, 18.5 MBq), followed by chloramine T trihydrate (0.5 mg ; 1.78 µmol) in H_2O (20 µl). The reaction vial was capped, vigorously shaken for 30 sec. and allowed to stand at room temperature. After 15 min, a solution of $Na_2S_2O_5$ (1.2 mg, 6.3 µmol) in water (50 µl) was added and the mixture was made basic by the addition of 0.1 N $NaHCO_3$. Purification by reverse phase HPLC (system A, programm c ; **1b** : Rt = 10.1 min ; **9** : Rt = 18.6 min) led to the desired radiotracer with 70-75 % radiochemical yield and chemical and radiochemical final purities > 95 % (system B, program c).

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