[^{125}I]*N*-(4-Dipropylaminobutyl)-4-iodobenzamide

[^{125}I]BZ18

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Chemical name:	[^{125}I]*N*-(4-Dipropylaminobutyl)-4-iodobenzamide	
Abbreviated name:	[^{125}I]BZ18	
Synonym:		
Agent Category:	Compounds	
Target:	Melanin	
Target Category:	Others	
Method of detection:	Single-photon emission computed tomography (SPECT), planar imaging	
Source of signal / contrast:	^{125}I	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals	Chemical structure is not available.

Background

[PubMed]

Radioiodinated *N*-(4-dipropylaminobutyl)-4-iodobenzamide, abbreviated as [^{125}I]BZ18, is a benzamide (BZA) derivative that was synthesized for melanin-targeted radionuclide imaging and therapy of melanoma (1, 2).

BZA derivatives represent a versatile class of aromatic compounds that possess a common structure element of Ph-CONH$(CH_2)_mNR_2$ (m = 1, 2) and exhibit comparable properties, including high and specific binding with melanin in melanoma cells and

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melanocytes (3-5). Some of these compounds, such as *N*-(2-diethylaminoethyl)-4-[^{123}I]iodobenzamide ([^{123}I]BZA) and [^{123}I]-*N*-(2-diethylaminoethyl)-2-iodobenzamide ([^{123}I]BZA2), have been successfully evaluated in melanoma patients, showing high sensitivity and selectivity in the detection of melanoma and its metastasis (6-9).

The promising results with [^{123}I]BZA have prompted great efforts from several groups in screening BZA analogs (2, 3, 10). Among them is a group of investigators in France who synthesized a series of BZA derivatives *via* structure-activity studies (1, 6, 11, 12). On the basis of the structure of the lead agent [^{123}I]BZA, they synthesized a group of spermidine BZA derivatives by replacing the diethylaminoethyl moiety in the BZA structure with a triamine (spermidine). Spermidine BZA derivatives exhibit high affinity for melanin comparable to that of [^{123}I]BZA; however, these compounds exhibit less accumulation in tumors than [^{123}I]BZA in animal models of melanoma (13). More recently, the investigators generated a class of heteroaromatic BZA analogs by incorporating the heteroaromatic structure in place of the benzene moiety to take advantage of the polycyclic aromatic compounds that display a strong affinity for melanin while keeping the lipophilic side chain (14). The heteroaromatic analogs, [^{125}I]5a through [^{125}I]5I, showed high specific and long-lasting uptake in the melanoma, which is favorable for both imaging and therapy (14). At the same time, the investigators also identified a group of quinoxaline analogs; the radioiodinated derivative 3 (ICF01012) is one of these compounds, which show the most favorable pharmacokinetic properties for radionuclide therapy (12, 15). The rapid and specific tumor uptake of quinoxaline compounds also suggests that they are potentially valuable for radionuclide imaging. For radiofluorination, ICF01012 was modified by incorporating 2- or 6-fluoropyridine in the *N*,*N*-diethylethylenediamine framework of ICF01012 (16). This strategy allows nucleophilic heteroaromatic radiofluorination of corresponding halogeno- or nitro-precursors without the need for an additional electron-withdrawing substituent in the aromatic ring. Fluoropyridine was introduced on the tertiary amine either directly or in combination with various linkers, which resulted in a group of amide tracers, such as the agents [^{125}I]56 and [^{18}F]44 (compound 56 is the dihydrochloride salt of 44) (16). These derivatives showed favorable properties for combined radionuclide imaging (^{18}F, ^{125}I) and therapy (^{131}I) of melanoma using a single chemical structure. The following is a list of some representative agents that were synthesized and tested by the investigators from the group in France.

BZA derivatives: [$^{125/123}$I]BZA, [^{125}I]BZA2, [^{125}I]BZ18, and [^{125}I]5a through [^{125}I]5l; and quinoxaline derivatives: [$^{125/131}$I]ICF01012 (or [$^{125/131}$I]3), [^{125}I]56, and [^{18}F]44.

This chapter summarizes the data of imaging studies obtained with [^{125}I]BZ18 (1, 2).

Related Resource Links:

Melanin-targeted imaging agents in MICAD

Benzamide derivatives in PubChemBenzamide derivatives in clinical trials in ClinicalTrials.gov

Synthesis

[PubMed]

BZ18 was synthesized by the reaction of 4-diethylaminobutylamine and 4-iodobenzoyl chloride (1, 2). Labarre et al. labeled BZ18 by electrophilic radio-iododestannylation of the tributyl stannyl precursor using no-carrier-added [^{125}I]NaI. From different synthetic batches of [^{125}I]BZ18, the yields of iodination were in the range of 50%–60%, with a radiochemical purity of >99% and a high specific activity of 180 GBq/mg (4.86 Ci/mg) (1).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Binding of [^{125}I]BZ18 to melanin was measured after incubation of [^{125}I]BZ18 with synthetic tyrosine-melanin in water (1). Scatchard plot analysis indicated two classes of binding sites, one with a high association constant ($K_1 = 5.7 \times 10^7$ M-1), and a second one with a lower association constant ($K_2 = 4.2 \times 10^5$ M-1).

Radiotoxicity was studied with a method of B16F0 clonogenic survival in different conditions of exposure (1). Results showed that the unlabeled BZ18 ($2 \times 10-5$ M) was not cytotoxic. On the contrary, [^{125}I]BZ18 induced cytotoxicity that was radioactivity-dependent, and the toxic effect was complete with 2.2 MBq (0.059 mCi) per well. The cytotoxicity was also dependent on incubation time for a given radioactive concentration (data not shown).

Animal Studies

Rodents

[PubMed]

Labarre et al. investigated the biodistribution of [^{125}I]BZ18 in mouse (1). Whether the animals were pretreated with Lugol's iodine solution to block thyroid uptake was not reported.

In male C57Bl6 mice bearing B16F0 murine melanoma ($n = 3$ mice), the tumor uptake of [^{125}I]BZ18 after injection of 0.37 MBq/$10-7$ mol (0.01 mCi/$10-7$ mol) was ~10% injected dose per gram of tissue (ID/g) between 1 h and 3 h, and remained at 3.2% ID/g at 72 h after injection. Low radioactive levels were observed in blood, muscle, and brain. [^{125}I]BZ18 was washed out from almost all of the organs except for tumor and uvea at 6 h after injection, giving high tumor/nontarget organ ratios.

The effect of [^{125}I]BZ18 concentration on its biodistribution was assessed with a fixed dose of 0.37 MBq (0.01 mCi) [^{125}I]BZ18 but at different concentrations ranging from $10-11$ to $10-6$ mol per mouse ($n = 30$ mice). The radioactivity in the melanoma and uvea

did not differ for each time point at any of the doses studied. However, the radioactivity in the liver increased with increased concentration at 3 h after injection.

Other Non-Primate Mammals

[PubMed]

Labarre et al. also investigated the biodistribution of [^{125}I]BZ18 in sheep models of melanoma (1). Whether the animals were pretreated with Lugol's iodine solution to block thyroid uptake was not reported.

The sheep models of tumors were generated by inoculating the cells of murine B16F0, human SK amelanotic melanoma, Malme melanotic melanoma, and LS174T human colonic carcinoma at different sites (n = 11 sheep). Sheep were euthanized at different time points. After injection of 14 MBq (0.38 mCi) [^{125}I]BZ18, radioactivity was detected in all tumors and organs examined from day 1 to day 3. On day 6 after injection, radioactivity in SK melanoma and LS174T colonic carcinoma became undetectable. On days 9 and 12 after injection, only blood, Malme melanoma, B16 melanoma, lymph nodes, and uveal tract showed detectable radioactivity. In more detail, a high uptake in B16 melanoma (0.0214% ID/g) was observed on day 1, and the uptake was maintained for a long time (0.0086% ID/g on day 12). The uptake in both SK melanoma and LS174T colonic carcinoma was very low (<0.0006% ID/g on day 1 and <0.00009% ID/g on day 3 after injection). For the Malme melanoma, the uptake was moderate on day 1 (0.004% ID/g) and low from day 3 after injection. Fast clearance of the radioactivity from normal tissues was observed except in the uveal tract (0.063% ID/g on day 1 and 0.027% ID/g on day 12). There was no radioactivity in the thyroid.

The kinetic uptake of [^{125}I]BZ18 in three sheep bearing only B16 melanoma was assessed from 1 h to 48 h after injection. The uptake in B16 melanoma reached a plateau at 1 h after injection. Respective concentrations in blood were low. The tumor/blood ratios were in the range of 14.8–558 from 1 h to 48 h after injection.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

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