N-[2-[*N*-Ethyl-*N*-[2-(2-[^{18}F]fluoropyridin-3-yloxy)ethyl]amino]ethyl]-6-iodoquinoxaline-2-carboxamide

[^{18}F]44

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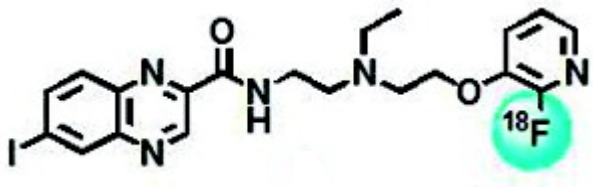
Chemical name:	*N*-[2-[*N*-Ethyl-*N*-[2-(2-[^{18}F]fluoropyridin-3-yloxy)ethyl]amino]ethyl]-6-iodoquinoxaline-2-carboxamide
Abbreviated name:	[^{18}F]44
Synonym:	
Agent Category:	Compounds
Target:	Melanin
Target Category:	Others
Method of detection:	Positron emission tomography
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Chemical structure of [^{18}F]44 (1).

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Background

[PubMed]

N-[2-[*N*-Ethyl-*N*-[2-(2-[^{18}F]fluoropyridin-3-yloxy)ethyl]amino]ethyl]-6-iodoquinoxaline-2-carboxamide, abbreviated as [^{18}F]44, is a quinoxaline benzamide (BZA) derivative that was synthesized for melanin-targeted radionuclide imaging and therapy of melanoma (1).

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 melanocytes (2-4). 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 (5-8).

The promising results with [^{123}I]BZA have prompted great efforts from several groups in screening BZA analogs (2, 9, 10). Among them is a group of investigators in France who synthesized a series of BZA derivatives *via* structure-activity studies (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 combined imaging and therapy. At the same time, the investigators also identified a group of quinoxaline analogs; radioiodinated derivative 3 (ICF01012) is one of these compounds, which show the most favorable pharmacokinetic properties for radionuclide therapy (15, 16). 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. 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 agents [^{125}I]56 and [^{18}F]44 (compound 56 is the dihydrochloride salt of 44) (1). 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]5I; 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 [^{18}F]44 (1).

Related Resource Links:

Melanin-targeted imaging agents in MICAD

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

Synthesis

[PubMed]

Maisonial et al. prepared [^{18}F]44 *via* a three-step, two-pot, radiosynthetic procedure that was automated with a Zymate laboratory automation system. ^{18}F was incorporated into precursor 75 (*tert*-butyl *N*-[2-[*N*-ethyl-*N*-[2-(2-nitropyridin-3-yloxy)ethyl]amino]ethyl]carbamate) to give [^{18}F]74 in yields ranging from 20% to 40%; acidic *N*-boc deprotection of [^{18}F]74 generated the radioactive intermediate [^{18}F]29, and acylation of [^{18}F]29 to provide [^{18}F]44 (1). Acylation yields of the conversion of [^{18}F]29 to [^{18}F]44 ranged between 20% and 40% (nonisolated decay-corrected yields). The chemical purity was >95%. [^{18}F]44 could be produced in 6% to 10% nonisolated decay-corrected yields with a specific radioactivity of 0.25–0.34 TBq/μmol (6.76–9.19 Ci/μmol) (calculated from three consecutive high-performance liquid chromatography analyses) in 110–130 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* data of the lead compound 3 were summarized in the literature regarding [^{125}I]ICF01012 (or [^{125}I]3) (15, 16). *In vitro* studies with cells were not performed for the compound 56 or the agent [^{18}F]44.

Animal Studies

Rodents

[PubMed]

Positron emission tomography (PET) imaging with [^{18}F]44 (7.4 MBq (0.2 mCi)) was performed in C57Bl6 mice bearing B16F0 and B16F10 tumors (n = 4). B16F0 tumors show a very high concentration of melanin, whereas B16F10 tumors exhibit a lower

melanin content. Animals were imaged for up to 4 h. The peak uptake in tumors was reached ~2 h after injection, with a value of 8.3 ± 1.7% of the injected dose per volume of tissue (% ID/cc) for the B16F0 tumors and 2.1 ± 0.4% ID/cc for the B16F10 tumors. At 4 h, the values remained similar, whereas the muscle uptake dropped from 0.6 ± 0.2% ID/cc at 2 h to 0.2 ± 0.1% ID/cc at 4 h, providing a good contrast with surrounding tissues. *In vitro* assays to determine the tumor melanin content produced a B16F0/B16F10 ratio of ~5 (data not shown), and PET quantification of the uptake gave a ratio of 4.0 ± 0.6. The difference of melanin content is clearly reflected in the difference of uptake between the two tumors. The biodistribution and kinetics profile were consistent with those observed with [^{125}I]56 (the dihydrochloride salt of 44). Blocking studies were not performed.

In summary, Maisonial et al. synthesized 14 new iodinated and fluorinated analogs of the lead compound 3 ([^{131}I]3) (1). All of these tracers contain a 2- or 6-fluoropyridine moiety incorporated in the *N*,*N*-diethylethylenediamine scaffold. Most of these novel radioiodinated compounds showed significant tumor retention, especially the derivative [$^{125/131}$I]56, which presented high, specific, and long-lasting tumor uptake combined with a rapid clearance from nontarget organs, offering both diagnostic (^{125}I and ^{18}F) and therapeutic (^{131}I) potentialities (1).

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

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