Radioiodinated *N*-(2-diethylaminoethyl)-6-iodoquinoxaline-2-carboxamide dihydrochloride salt

[^{125}I]ICF01012

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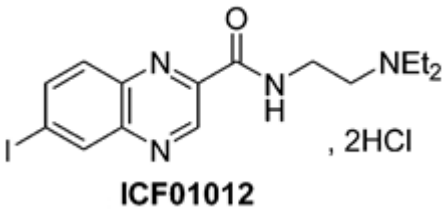
Chemical name:	Radioiodinated *N*-(2-diethylaminoethyl)-6-iodoquinoxaline-2-carboxamide dihydrochloride salt
Abbreviated name:	[^{125}I]ICF01012, [^{125}I]3
Synonym:	[^{131}I]ICF01012, [^{131}I]3
Agent Category:	Compounds
Target:	Melanin
Target Category:	Others
Method of detection:	Single-photon emission computed tomography (SPECT), planar imaging
Source of signal / contrast:	^{125}I
Activation:	No
Studies:	• *In vitro* • Rodents



Chemical structure of ICF01012 (1).

Background

[PubMed]

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Radioiodinated *N*-(2-diethylaminoethyl)-6-iodoquinoxaline-2-carboxamide dihydrochloride salt, abbreviated as [$^{125/131}$I]ICF01012 or [$^{125/131}$I]3, is a quinoxaline 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$(CH_2)_m NR_2$ (m = 1, 2) and exhibit comparable properties, including high and specific binding with melanin in melanoma cells and 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 (3, 10, 11). Among them is a group of investigators in France who synthesized a series of BZA derivatives *via* structure-activity studies (12, 13). 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 (14). 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 (15). 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 (1, 2). 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 the agent [^{18}F]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]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 [^{125}I]ICF01012 (1, 2).

Related Resource Links:

Melanin-targeted imaging agents in MICAD

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

Synthesis

[PubMed]

The procedure to synthesize ICF01012 has been reported previously in several papers (1, 2). Radioiodinated [^{125}I]ICF01012 and [^{131}I]ICF01012 were prepared using an iododestannylation reaction with [^{125}I]NaI and [^{131}I]NaI, respectively. Bonnet-Duquennoy et al. reported a 68% radiochemical yield with a radiochemical purity >98% and a specific activity of 114 GBq/μmol (3.08 Ci/μmol) for [^{131}I]ICF01012, and a 52% radiochemical yield with a radiochemical purity >99% and a specific activity of 95 GBq/μmol (2.57 Ci/μmol) for [^{125}I]ICF01012 (1).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Bonnet et al. analyzed the uptake of [^{125}I]ICF01012 in four melanoma cell lines after incubation with the cells for 24 h (2). The cell uptake (% of total labels) was 0.4 ± 0.1 and 0.8 ± 0.1 for the amelanotic lines A375 and M3Dau, respectively, and 3.0 ± 0.2 and 14.2 ± 2.3 for the pigmented lines M4Beu and SKMel3, respectively. The difference was significant between amelanotic and pigmented lines as well as between the highly pigmented line M4Beu and the less pigmented line SKMel3. The cell uptake level correlated with the melanin content in cells (Pearson correlation factor 0.981; $P < 0.0001$).

Bonnet-Duquennoy et al. imaged the localization of ICF01012 with secondary ion mass spectrometry after incubation with the culture colony of B16F0 melanoma cells (1). Images showed that ICF01012 was colocalized with the melanin polymers in the B16F0 cells (1).

Animal Studies

Rodents

[PubMed]

Bonnet et al. first investigated the accumulation of [^{125}I]ICF01012 in tumor-bearing Swiss *nu/nu* mice (n = 5–6 per tumor type) with scintigraphic imaging after intravenous injection of 3.7 MBq (0.1 Ci) [^{125}I]ICF01012 (2). In pigmented tumor models,

[^{125}I]ICF01012 showed rapid systemic elimination with a whole-body uptake of <20% in mice bearing M4Beu tumors and <15% in mice bearing SKMel3 tumors 24 h after injection. The uptake levels at 3, 6, and 24 h after injection were 6.5 ± 2.9, 6.4 ± 2.8, and 2.9 ± 1.4% injected dose per gram tissue (ID/g) in M4Beu tumors and 24.2 ± 4.8, 26.8 ± 4.5, and 11.7 ± 1.6% ID/g in SKMel3 tumors, respectively. In parallel to higher melanin content in SKMel3 tumors than in M4Beu tumors, the uptake was greater in SKMel3 tumors than in M4Beu tumors ($P = 0.02$ at 24 h after injection). The signal of [^{125}I]ICF01012 from non-pigmented A375 and M3Dau tumors was not detectable at 3 h, and the respective uptake levels were only 1.9 ± 0.5 and 1.8 ± 0.7% ID/g at 6 h after injection, indicating the background radioactivity level in amelanotic A375 and M3Dau tumors. The tumor uptake of [^{125}I]ICF01012 positively correlated with the tumor melanin content (correlation Pearson factor: 0.89; $P < 0.0001$).

Maisonial et al. investigated the accumulation of [^{125}I]ICF01012 in C57B16 mice bearing B16F0 melanoma ($n = 3$ mice) (16). Significant tumor accumulation was observed at 1 h, and the accumulation increased gradually to a maximum at 3–6 h and continued to be measurable for at least 5 days after injection. The tumor uptake levels were 21.8 ± 6.6, 26.3 ± 6.6, 29.6 ± 8.4, 28.0 ± 8.2, 12.3 ± 3.7, 7.3 ± 3.6, 3.4 ± 0.3, and 1.9 ± 0.4% ID/g 1, 3, and 6 h and 1, 3, 5, 7, and 10 days after injection.

Bonnet et al. examined the radiotherapy efficacy of [^{131}I]ICF01012 on M3Dau, M4Beu, and SKMel3 xenografts from the day that tumors became palpable (2). For all models, untreated groups ($n = 10$ mice) were studied in the same conditions. Lugol's iodine solution was added to the feed for all groups of mice to block the thyroid. For the M4Beu radiotherapy experiment ($n = 6$ mice), [^{131}I]ICF01012 was administered intravenously on days 14 and 18 (2 × 18.5 MBq (2 × 0.5 mCi)). A significant growth inhibition phase (GIP) of the M4Beu tumors was observed for up to 25 days. The GIP doubling times were 11.8 ± 2.0 and 8.4 ± 1.7 days for treated and untreated tumors, respectively ($P = 0.02$). Because SKMel3 tumors had higher melanin content and also higher [^{125}I]ICF01012 uptake, only one injection of 18.5 MBq (0.5 mCi) [^{131}I]ICF01012 was given to mice on day 35 after cell inoculation when tumors were measurable. SKMel3 tumors treated with [^{131}I]ICF01012 exhibited a significant GIP from day 4 to day 25. For 50% of the treated animals, GIP extended to 47 days after treatment and correlated with smaller tumors on the day of injection. These results indicate that [^{131}I]ICF01012 significantly decreased SKMel3 growth with GIP doubling times of 10.8 ± 2.4 and 18.1 ± 3.3 days for untreated and treated animals ($P = 0.003$), respectively. Using the same protocol with one injection, no significant difference was observed in M3Dau tumor growth. The doubling time was 6.7 ± 0.2 days for both treated and untreated M3Dau tumors ($P = 0.39$). After therapy, no gross changes of the organs, including liver, lung, and kidneys, were observed in any experiment (data not shown).

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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