3'-(*E*)-(2-[$^{123/131}$I]Iodovinyl)uridine

[$^{123/131}$I]IV-14

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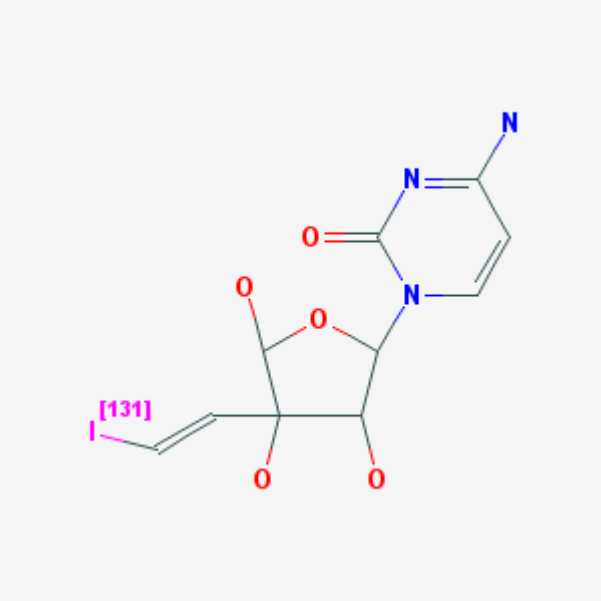
Chemical name:	3'-(*E*)-(2-[$^{123/131}$I]Iodovinyl)uridine
Abbreviated name:	[$^{123/131}$I]IV-14
Synonym:	
Agent category:	Compound
Target:	Uridine-cytidine kinase 2 (UCK2), human equilibrating nucleoside transporter 1 ($hENT_1$)
Target category:	Enzyme, transporter
Method of detection:	Single-photon emission computed tomography (SPECT)
Source of signal:	^{131}I
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

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One of the characteristics of tumor cells is their unchecked proliferation. It is important to measure the proliferation rate of cancer lesions to help differentiate benign tumors from malignant tumors and to characterize malignant tumors among normal tissues. 2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) has been approved for cancer imaging by the United States Food and Drug Administration. However, enhanced uptake of FDG also occurs in inflammatory cells and lesions as well as in necrotic cells (1, 2). Thymidine (TdR) and TdR analogs are the standard markers for DNA synthesis, and [^{11}C]TdR has been used in positron emission tomography (PET) imaging to measure tumor growth rate *in situ*. Because of the short half-life of ^{11}C and the extensive metabolism of [^{11}C]TdR in the blood (3), 3'-deoxy-3'-[^{18}F]fluorothymidine (FLT) was developed for PET imaging. FLT is an analog of TdR and is phosphorylated by TdR kinase-1 (TK-1), an enzyme expressed during the DNA synthesis phase (S-phase) of the cell cycle (4). On the other hand, RNA synthesis occurs in all phases of the cell cycle except the M phase, even in slow growing solid tumors. Tracers targeted to RNA synthesis could be used to visualize tumors with low TK-1 expression.

Phosphorylation of pyrimidine ribonucleosides is carried out with uridine-cytidine kinase (UCK) 1 and UCK2 (5). UCK2 is normally present only in human placenta (5) and testis (6) but is highly overexpressed in many blood and solid tumor cells (7). UCK1 is ubiquitously expressed in normal tissues. Phosphorylation of uridine and cytosine is 15–20 times faster with UCK2 than with UCK1. 3'-(Ethynyl)uridine is phosphorylated rapidly with UCK2 to its triphosphate, which blocks RNA synthesis by inhibition of RNA polymerase (8, 9). Zlatopolskiy et al. (10) reported the development of 3'-(*E*)-(2-[$^{123/131}$I]iodovinyl)uridine ([$^{123/131}$I]IV-14) for single-photon emission computed tomography (SPECT) imaging of UCK2 activity in tumors.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (UCK2,human equilibrating nucleoside transporter 1).
- Articles in OMIM

Synthesis

[PubMed]

Zlatopolskiy et al. (10) reported the synthesis of [$^{123/131}$I]IV-14 by the standard chloramine-T radioiodination of 3'-(2-*E*)-tributylstannylvinyl-uridine (4.4 ng) in the presence of $^{123/131}$I-NaI (159 MBq (4.3 mCi)). [$^{123/131}$I]IV-14 was purified with high-performance liquid chromatography with a radiochemical purity of >99% and a radiochemical yield of 71–82% (n = 12). The specific activity of [$^{123/131}$I]IV-14 was not reported. [^{131}I]IV-14 was stable in human serum for 24 h at 37°C, whereas [^{131}I]iododeoxyuridine was only 30% intact.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro enzyme assays of uridine phosphorylase with murine liver, mucosa, or intestine homogenates revealed that [^{131}I]IV-14 was resistant to hydrolysis of the uridine-to-glycosidic bond (10). *In vitro* cellular uptake assays with various cell lines showed that MIA PaCa-2, Panc-1, and CX-1 had high to moderate UCK2 and human equilibrating nucleoside transporter 1 ($hENT_1$) expression with high uptake of [^{131}I]IV-14 (2.24–4.27% incubation dose at 24 h after incubation). On the other hand, uptake of [^{131}I]IV-14 was marginal with BX-PC-3 and SK-PC-1cell lines (<0.5%), which had low expression of UCK2 and $hENT_1$. Interestingly, high accumulation (2.69%) of radioactivity was observed in HL60 cells with low UCK2 but high $hENT_1$ expression. The uptake was inhibited by a highly selective inhibitor of $hENT_1$ in HL60 and MIA PaCa-2 cells by 83% and 40% at 24 h of incubation, respectively. More than 90% of radioactivity was detected in the cytosolic fraction of HL60 cells with <5% in the RNA fraction. Mono-, di-, and tri-phosphate metabolites of [^{131}I]IV-14 were found at various time points in HL60 cells pretreated with 5-fluorouridine.

Animal Studies

Rodents

[PubMed]

Zlatopolskiy et al. (10) performed *ex vivo* biodistribution studies after injection of 10 MBq (270 μCi) [^{123}I]IV-14 in nude mice (n = 5/group) bearing HL60 tumors. There was high tumor radioactivity uptake, low normal organ radioactivity uptake, and rapid body clearance. The tumor radioactivity levels after injection were 1.4% injected dose per gram (% ID/g) at 0.5 h, 1.5% ID/g at 1 h, 0.5% ID/g at 4 h, and 0.1% ID/g at 24 h. At 0.5 h, the radioactivity levels in other major organs (spleen, intestine, liver, stomach, and kidneys) were slightly higher than in the tumor but decreased progressively with time except in the tumor and spleen. At 0.5 h, the tumor/tissue ratios were 0.37, 0.68, 0.68, 0.72, and 1.05 for the kidneys, small intestine, liver, spleen, and blood, respectively. At 4 h, the tumor/tissue ratios were 10, 7, 16, 3, and 30 for the kidneys, small intestine, liver, spleen, and blood, respectively. Gamma planar imaging was performed in nude mice bearing HL60 tumors. Good visualization was observed only in the tumor, stomach, and spleen at 4 h after injection. No blocking experiment was performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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