$^{67/68}$Ga-Tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-1,2-diaminoethane-γ-folate

$^{67/68}$Ga-P3026

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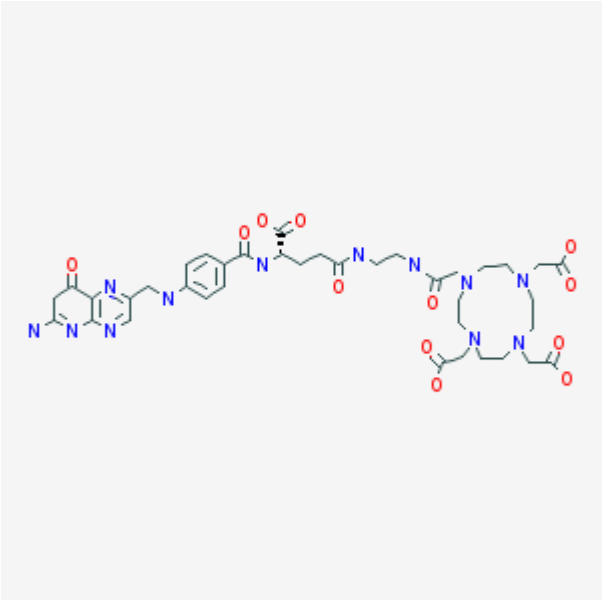
Chemical name:	$^{67/68}$Ga-Tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-1,2-diaminoethane-γ-folate
Abbreviated name:	$^{67/68}$Ga-P3026
Synonym:	
Agent category:	Compound
Target:	Folate receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET); single-photon emission computed tomography (SPECT)
Source of signal:	$^{67/68}$Ga
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

Folic acid (folate) is a water-soluble B vitamin (1) that is essential for methylation and DNA synthesis. The primary pathway for entry of folate into cells is through the facilitated transporter, which has a low affinity for folate (Michaelis constant (K_m) = 1–5 μM). Some cells in the choroid plexus, kidney, lung, thyroid, spleen, placenta, and thymus also possess a higher-affinity (dissociation constant (K_d) = 0.5 nM) receptor that allows folate uptake *via* receptor-mediated endocytosis. Some human epithelial tumor cells have been found to overexpress folate-binding protein (2). More than 90% of human ovarian and endometrial cancers express the high-affinity receptor, which is absent in the corresponding normal tissues. Breast, colorectal, renal, and lung carcinomas also overexpress the folate receptor but at lower frequencies (20%–50%). Activated macrophages, but not resting macrophages, have been also found to have the folate receptor (3).

Several folate-based conjugates (^{111}In-DTPA-folate, ^{99m}Tc-EC-folate, and [^{18}F]FBA-folate) have been studied in tumor imaging (4-8). Deferoxamine (DF), a chelating agent, was conjugated to folic acid forming a mixture of two isomers, DF-α-folate and DF-γ-folate. Only the DF-γ-folate isomer was able to displace [^{3}H]folic acid from its receptors with a 50% inhibition concentration similar to that of folic acid (2.5 nM *versus* 2.4 nM) (9). $^{68/67/66}$Ga-γ-DF-folate is being developed as an imaging agent for the detection of folate receptors *in vivo* with either positron emission tomography (PET) or single-photon emission computed tomography (SPECT). In this chapter, Fani et al. (10) prepared a γ-folate conjugate with tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid (DOTA) and 1,2-diaminoethane as a spacer to form P3026, which was labeled with $^{67/68}$Ga for detection of folate receptors.

Related Resource Links:

- Chapters in MICAD (folate receptor)
- Gene information in NCBI (folate receptor)
- Articles in OMIM (folate receptor)
- Clinical trials (folate receptors)
- Drug information in FDA (folate receptor)

Synthesis

[PubMed]

Fani et al. (10) coupled P3026 (10 nmol) with 74 MBq (2 mCi) $^{67}GaCl_3$ in acetate buffer (pH 5) for 30 min at 95°C to yield ^{67}Ga-P3026 with >92% radiochemical purity. Radiochemical yields exceeded 95% with a specific activity of 7 MBq/nmol (0.19 mCi/nmol). ^{68}Ga-P3026 was similarly radiolabeled for 10 min at 95°C with a specific activity of 9 MBq/nmol (0.24 mCi/nmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The human nasopharyngeal carcinoma KB cell line has putative folate receptors as determined with ^{67}Ga-P3026 saturation binding studies at 4°C (10). ^{67}Ga-P3026 showed a K_d (affinity constant) of 4.65 ± 0.82 nM and a B_{max} (receptor density) of 10.65 ± 0.45 nM. There were ~6.4 × 10^6 folate binding sites per KB cell. ^{67}Ga-P3026 (2.5 nM) was rapidly associated with KB cells at 37°C with 60% of incubation dose (ID) at 30 min and 80% ID at 4 h. Approximately 16% ID of ^{67}Ga-P3026 was internalized at 4 h. Excess folate blocked the cell-associated radioactivity to <0.5% ID. Approximately 80% of radioactivity was retained in the cells after 4 h incubation in fresh medium.

Animal Studies

Rodents

[PubMed]

Fani et al. (10) performed *ex vivo* biodistribution studies of 1.5 MBq (0.041 mCi, 0.4 nmol) ^{67}Ga-P3026 in nude mice (n = 4–7/group) bearing KB and HT1080 (low folate receptor expression) tumor xenografts. Accumulation of ^{67}Ga-P3026 in the KB tumors was 11.8 ± 2.8, 10.6 ± 2.1, and 14.3 ± 4.1% ID/g at 1, 2, and 4 h after injection, respectively. The accumulation in the HT1080 tumors was 1.0%–1.5% ID/g at these time points. The organ with the highest accumulation at 4 h after injection was the kidney (103.0% ID/g), followed by the pancreas (3.3% ID/g), adrenal (3.2% ID/g), heart (2.5% ID/g), pituitary (2.3% ID/g), and liver (2.1% ID/g). The accumulation in the blood was low (<0.5% ID/g). The tumor/blood ratios were 36, 50, and 70 at 1, 2, and 4 h, respectively. Pretreatment with excess folate (40 nmol, 5 min before injection) reduced the radioactivity accumulation by >90% in the tumors and kidney at 4 h after injection.

The whole-body distribution was also assessed with PET imaging at 1 h after injection of 4 MBq (0.11 mCi) ^{68}Ga-P3026 (0.4 nmol). The highest activity concentrations were visualized in the KB tumors and kidneys, whereas the HT1080 tumors were barely visible. The accumulation of ^{68}Ga-P3026 in the KB tumors and kidneys was blocked by pre-injection of excess folic acid (40 nmol, 5 min).

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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