^{68}Ga-Labeled (1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid)-1-NaI3-octreotide

[^{68}Ga]-DOTA-NOC

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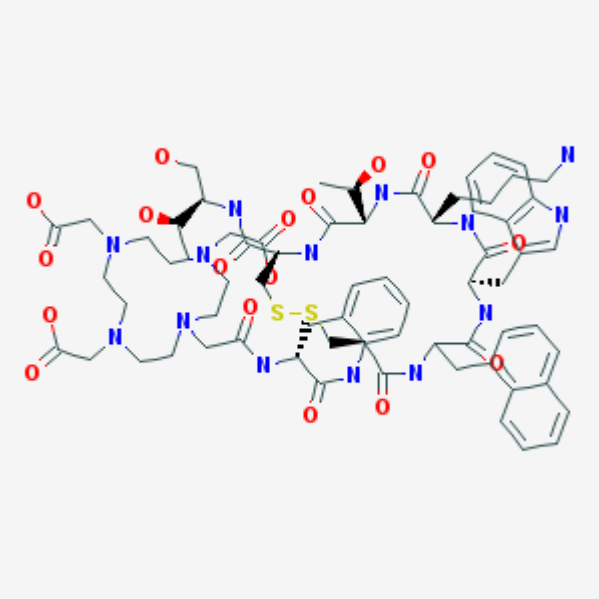
Chemical name:	^{68}Ga-Labeled (1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid)-1-NaI3-octreotide
Abbreviated name:	[^{68}Ga]-DOTA-NOC
Synonym:	
Agent Category:	Ligand
Target:	Somatostatin receptors 2, 3 and 5 (sstr2, sstr3 and sstr5)
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{68}Ga
Activation:	No
Studies:	• *In vitro* • Humans



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

Neuroendocrine tumors (NTs) are slow growing, can develop in almost any organ of the body (1), and are characterized by the overexpression of somatostatin receptors (sstr; designated 1–5) (2). Because the different sstrs may be expressed individually or simultaneously by the NT, these receptors are targeted with radiolabeled compounds for the imaging detection or the treatment of this ailment (3). Due to a very short plasma half-life (~3 min), somatostatin itself is not the preferred sstr ligand for radiolabeling, and several of its analogs, such as octreotide (OC), vapreotide, etc., have been developed for the imaging and therapy of NTs (4). OCs show a high affinity for sstr2 and sstr5, but they bind varyingly to the sstr3 and sstr4 receptors. The OCs are coupled with chelators like diethylenetriamine-pentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclododecane-*N*,*N*',*N*'',*N*'''-tetraacetic acid (DOTA) to facilitate nuclide binding before use with scintigraphic imaging (with ^{111}In or ^{99m}Tc (5, 6)) or positron emission tomography (PET; with ^{18}F, ^{64}Cu, or ^{68}Ga (7-9)) of NTs. The main advantage of using PET over planar scintigraphy is that the PET ligands do not have to be internalized by the cells to obtain good quality images of the NTs (10, 11).

Although (^{18}F)fluoro-deoxyglucose has been used to detect tumors of neuroendocrine origin, it has been shown to have little success because it cannot detect well-differentiated NTs (12). As an alternative, (^{111}In)DOTA-(tyrosine)^3-octreotide ((^{111}In)DOTA-TOC) was developed to detect NTs, but it too has limited application because it binds only to the sstr2 receptors and cannot detect NETs that express the other sstr subtypes (3). To circumvent this limitation, investigators developed (13) and evaluated (14) a ^{68}Ga-labeled sstr ligand, DOTA-1-NaI3-octreotide ((^{68}Ga)-DOTA-NOC), that binds sstr2, sstr3, and sstr5 (13). This was generated by substituting the third Phe moiety in OC (D-Phe-C[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol) with napthyl-L-Ala (15). The biodistribution of (^{68}Ga)-DOTA-NOC in humans has also been reported (16).

Synthesis

[PubMed]

DOTA-NOC used for the various studies was either synthesized as described by Wild et al. (13) or obtained from a commercial source (9). The ^{68}Ga labeling of DOTA-NOC was performed as described by Meyer et al. (17). In another publication describing the radiolabeling of DOTA-NOC with ^{68}Ga, the radiochemical yield and purity of the radiochemical were reported to be 81.6 ± 6.5% and >99%, respectively (15). The specific activity and stability of (^{68}Ga)-DOTA-NOC were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The receptor binding characteristics of ^{111}In-labeled DOTA-NOC were studied by Wild et al. (13) under *in vitro* conditions using cell lines respectively transfected with the various human sstr (hsstr) receptors as detailed by Reubi et al. (18). The 50% inhibition concentrations (in nM) of (^{111}In)-DOTA-NOC for hsstr1, hsstr2, hsstr3, hsstr4, and hsstr5 were reported to be >1,000, 3.3 ± 0.2, 26 ± 1.9, >1,000, and 10.4 ± 1.6, respectively.

Animal Studies

Rodents

[PubMed]

No references are currently available.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

In a preliminary study, the uptake of (^{111}In)-DOTA-TOC (using planar imaging) and (^{68}Ga)-DOTA-NOC (using PET imaging) in a 52-year-old patient with advanced neuroendocrine tumors was compared by Wild et al. (14). The investigators reported that bone metastasis in the patient was more clearly visible with (^{68}Ga)-DOTA-NOC than with (^{111}In)-DOTA-TOC. In addition, compared with (^{111}In)-DOTA-TOC, superior images of organs that are known to express the different sstr rather than just sstr2 (such as spleen, pituitary, and thyroid), were obtained with (^{68}Ga)-DOTA-NOC. From this preliminary study the investigators concluded that (^{68}Ga)-DOTA-NOC could be an excellent radiodiagnostic and investigational chemical for sstr-positive tumors.

Pettinato et al. investigated the biodistribution of (^{68}Ga)-DOTA-NOC in patients with neuroendocrine tumors (16). Nine patients were treated with (^{68}Ga)-DOTA-NOC, and whole-body PET scans were performed at 5, 20, 60, and 120 min after administration of the radiochemical. Urine samples were also collected from the patients at approximately the same time as the scans, and blood samples were obtained every 40 to 50 min after treatment with (^{68}Ga)-DOTA-NOC. In all patients an accumulation of the radiochemical was observed in the pituitary gland, spleen, liver, kidneys, and urinary bladder. The

kidneys had the highest absorbed dose, probably because the radioactivity was excreted primarily through the urinary route.

Ambrosini et al. compared the use of (^{18}F)3,4-dihydroxy-L-phenylalanine ((^{18}F)-DOPA) with the use of (^{68}Ga)-DOTA-NOC for the detection of gastro-entero-pancreatic and lung neuroendocrine tumors in 13 patients (19). PET imaging with (^{68}Ga)-DOTA-NOC was reported to show at least one lesion in each of the 13 patients, but (^{18}F)-DOPA visualized positive lesions in only 9 of the 13 patients. In addition, (^{68}Ga)-DOTA-NOC identified more lesions than did (^{18}F)-DOPA (71 *versus* 45), particularly in the liver, lungs, and lymph nodes. In addition, (^{68}Ga)-DOTA-NOC correctly identified the primary site of the tumors in six of the eight non-operated cases, whereas (^{18}F)-DOPA identified the primary tumors only in two of the eight non-operated cases. The investigators concluded that (^{68}Ga)-DOTA-NOC appeared to be a superior imaging agent for the detection of neuroendocrine tumors compared with (^{18}F)-DOPA.

Fanti et al. evaluated the use of (^{68}Ga)-DOTA-NOC for the detection of unusual neuroendocrine tumors in 14 patients (13 patients had lesions that were either uterine or located in the prostate, ovary, kidney, breast, ear, neck, abdomen, or mediastinum, and one patient had a lymphoma) (10). Results obtained with PET imaging were compared with those obtained with computed tomography (CT), ultrasonography, magnetic resonance, and SSR scintigraphy. PET imaging identified at least one lesion in 6 of 14 patients; five scans were negative and two were inconclusive. At the clinical level, (^{68}Ga)-DOTA-NOC, in comparison to the conventional imaging procedures, provided additional information in 7 of 14 patients and was considered helpful for 12 of 14 patients. With results from this study, the investigators concluded that (^{68}Ga)-DOTA-NOC could be used to detect unusual neuroendocrine tumors particularly in the neck, abdomen, and mediastinum, but cautioned that care was required to investigate lesions in an organ having a high accumulation of the radioactivity or if inflammation was evident at the lesion site.

Ambrosini et al. evaluated the use of (^{68}Ga)-DOTA-NOC with PET/CT for the identification of well-differentiated and proven bronchial carcinoids in 11 patients (9). The PET results were compared with pathology, clinical investigations, and contrast-enhanced CT data. At least one lesion was detected in 9 of 11 patients, and two scans were negative according to (^{68}Ga)-DOTA-NOC PET/CT. The PET/CT results did not agree with contrast-enhanced CT in 8 of 11 patients, and in 3 patients both techniques provided similar results. During the clinical investigation, PET/CT provided additional data for 9 of 11 patients and resulted in changes in the clinical management of 3 of 9 patients. The investigators concluded that using (^{68}Ga)-DOTA-NOC with PET/CT was better than using contrast-enhanced CT alone for the evaluation and determination of the extent of the disease in patients with bronchial carcinoids.

Supplemental Information

[Disclaimers]

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