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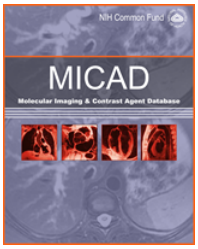

3-Cyano-4-[^{18}F]fluoro-benzoyl-Ala(SO_3H)-Ava-Gln-Trp-Ala-Val-NMeGly-His-Sta-Leu-NH_2

[^{18}F]7b

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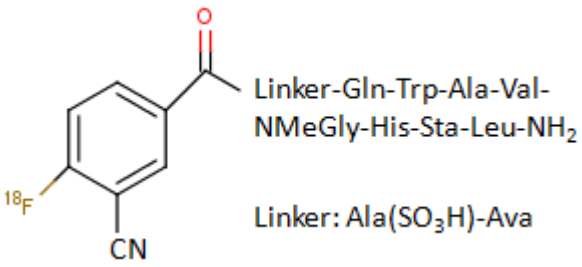
Chemical name:	3-Cyano-4-[^{18}F]fluoro-benzoyl-Ala(SO_3H)-Ava-Gln-Trp-Ala-Val-NMeGly-His-Sta-Leu-NH_2
Abbreviated name:	[^{18}F]7b
Synonym:	
Agent Category:	Peptides
Target:	Gastrin-releasing peptide receptor (GRPR)
Target Category:	Receptors
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of [^{18}F]7b

Background

[PubMed]

3-Cyano-4-[^{18}F]fluoro-benzoyl-Ala(SO_3H)-Ava-Gln-Trp-Ala-Val-NMeGly-His-Sta-Leu-NH_2, abbreviated as [^{18}F]7b, is a bombesin (BN)-based ^{18}F-labeled peptide synthesized by Mu et al. for positron emission tomography (PET) of tumors expressing gastrin-releasing peptide receptor (GRPR) (1).

BN is an amphibian neuropeptide consisting of 14 amino acids (pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2) (2). The C-terminal region of BN is responsible for its receptor binding and signal transduction (3). BN and its mammalian counterpart, gastrin-releasing peptide (GRP), produce a wide range of biological responses in diverse tissues (3). They also act as growth factors for cancer cells. Of the BN receptors, GRPR (also known as BB_2 or BRS2) is best characterized (2). GRPR is a glycosylated G-protein–coupled receptor and is normally expressed in non-neuroendocrine tissues of the breast and pancreas and in neuroendocrine cells of the brain, gastrointestinal tract, lung, and prostate (1). Because GRPR is overexpressed

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in various tumors, a large number of BN analogs have been tested for GRPR-targeted imaging and therapy (4, 5). These analogs have been synthesized on the basis of either truncated BN (6–14 or 7–14) or full-length BN (1–14), and most analogs exhibit a high affinity to GRPR (6, 7). The truncated BN analogs appear more stable *in vivo* than the full-length tetradecapeptides, but the full-length peptides offer more labeling options by attachment of functional groups to the amino acids on positions 1 to 6 (8-10). For most analogs, the amino acids on positions 13 (Leu) and 14 (Met) have been replaced with non-natural amino acids for increasing stability, and Lys has been placed on position 3 for attaching radiolabels. Spacers, chelators, or radiometals have also been widely used for conjugation and for favorable kinetics (1, 4, 9). Functionally, most BN analogs act as agonists, and only a few to date are antagonists (8, 11). Agonists are internalized into and accumulate within cells, and they have been assumed to exhibit higher uptake by cancer cells than antagonists. However, some studies have shown that tumor uptake of antagonists is higher than that of agonists because antagonists may have stronger binding for GRPR than agonists (11).

Mu et al. synthesized a series of BN-based peptides by using different linkers, peptide sequences, and non-natural amino acids (1, 12). These peptides have been labeled with ^{18}F with a one-step approach *via* ^{18}F-for-$^{+}$N(CH$_3$)$_3$ substitution using a less lipophilic benzonitrile labeling moiety. Amino acids such as His, Trp, Arg, and non-natural amino acids such as statine (Sta) and cysteine sulfonic acid (Ala(SO$_3$H)) in the peptide sequence did not require any protection group during radiosynthesis. Two analogs, one named as [^{18}F]6b and another [^{18}F]7b, exhibited specific uptake in GRPR-expressing PC-3 tumors and the pancreas in nude mice (1). [^{18}F]6b is positively charged, while [^{18}F]7b is negatively charged. Compared to [^{18}F]6b, [^{18}F]7b exhibits superior tumor uptake, is higher in specificity, and has more favorable tumor/nontarget ratios (1). The data suggest that [^{18}F]7b is a promising PET tracer candidate for the diagnosis of GRPR-positive tumors in humans. This chapter describes the data obtained with [^{18}F]7b. The data obtained with [^{18}F]6b are described in the MICAD chapter on [^{18}F]6b.

Related Resource Links:

- Protein, nucleotide (RefSeq), and gene information for GRPR
- Structure information of BN and analogs in PubChem
- GRPR-targeted imaging agents in MICAD

Synthesis

[PubMed]

Mu et al. synthesized [^{18}F]7b on the basis of the amino acid sequence 7–14 of the natural BN (1). Met^{14} was replaced with Leu for stabilization against aminopeptidases, and Leu^{13} was replaced with Sta for prevention of neutral endopeptidase cleavage. Gly^{11} was changed to its methylated version (NMeGly). A polar spacer, Ala(SO$_3$H)-Ava, was inserted between the labeling moiety and the binding sequence to improve the peptide pharmacokinetics and to avoid the interference of radiolabels with the binding region. For ^{18}F labeling, the peptide in anhydrous dimethyl sulfoxide was mixed with dry Cs[^{18}F]F/K$_{2.2.2}$ complex and then heated for 15 min at 90°C. The ^{18}F-incorporation was 76%. The decay-corrected radiochemical yield of [^{18}F]7b was ~14%, and its radiochemical purity and specific activity were >99% and 77 GBq/μmol (2.08 Ci/μmol), respectively, at the end of synthesis. The lipophilicity, expressed as distribution coefficient *D* (log $D_{7.4}$), was −1.1. The fluorinated peptide had calculated and found molecular weights of 1,376.6 and 1,378.0, respectively.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The receptor binding affinity of [^{18}F]7b was determined with the use of cell membranes transfected with human GRPR (1). Nonspecific binding was determined with an excess of 10 μM Tyr^4-BN. The binding affinity (K_i) of the non-labeled peptide (Ala(SO_3H)-Ava-Gln-Trp-Ala-Val-NMeGly-His-Sta-Leu-NH_2) was 0.1 nM, and its half maximal inhibitory concentration (IC_{50}) was 0.4 nM. The corresponding K_i and IC_{50} values of the [^{18}F]7b were 1.43 nM and 0.94 nM, respectively.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]7b was studied in nude mice bearing subcutaneous PC-3 human prostate tumors (n = 3 mice/group) (1). [^{18}F]7b showed clear tumor targeting. The tumor uptake was 4.67 ± 0.04% injected dose per gram of tissue (ID/g) at 30 min after injection, which increased to 4.88 ± 0.36, 5.40 ± 0.58, and 5.16 ± 1.32% ID/g at 1, 2, and 4 h after injection, respectively. Uptake in the GRPR-rich pancreas was almost 50% ID/g at 1 h after injection. Uptake in the tumor and pancreas was effectively blocked by co-administration of unlabeled BN (83% and 97% specificity, respectively). [^{18}F]7b also showed fast blood clearance, leading to favorable tumor/blood ratios of 30.59, 51.77, and 55.03 at 1, 2, and 4 h after injection, respectively. [^{18}F]7b was mainly excreted *via* the hepatobiliary system, resulting in bile/tumor ratios of >20. *In vivo* defluorination of [^{18}F]7b was not evident on the basis of its accumulation in the bone. The % ID/g values in bone were 0.84 ± 0.08, 1.52 ± 0.22, 1.60 ± 0.12, and 1.75 ± 0.23 at 0.5, 1, 2, and 4 h after injection, respectively.

PET imaging with [^{18}F]7b was performed in four nude mice bearing subcutaneous PC-3 tumor xenografts (1). The tumors (n = 2 mice) were clearly imaged with [^{18}F]7b, which was blocked with unlabeled BN (n = 2 mice). As expected from the biodistribution study, the highest radioactivity was observed in the gallbladder and intestine. The pancreas could not be visualized with PET due to the proximity to the bowel. Postmortem tissue sampling of these mice after PET scanning (107 min after injection) confirmed the data obtained in the biodistribution study. The absolute radioactivity uptake values in the GRPR-rich tissues were 5% ID/g for the tumor and 30% ID/g for the pancreas. The specificity of uptake amounted to 85% and 95% for the tumor and pancreas, respectively. Bone imaging data were not described.

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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