^{11}C-BMS-5p and ^{18}F-FBzBMS: radiolabeled analogs of BMS-207940, a potent and selective antagonist of endothelin receptor subtype A

[^{11}C]-BMS-5p and [^{18}F]FBzBMS

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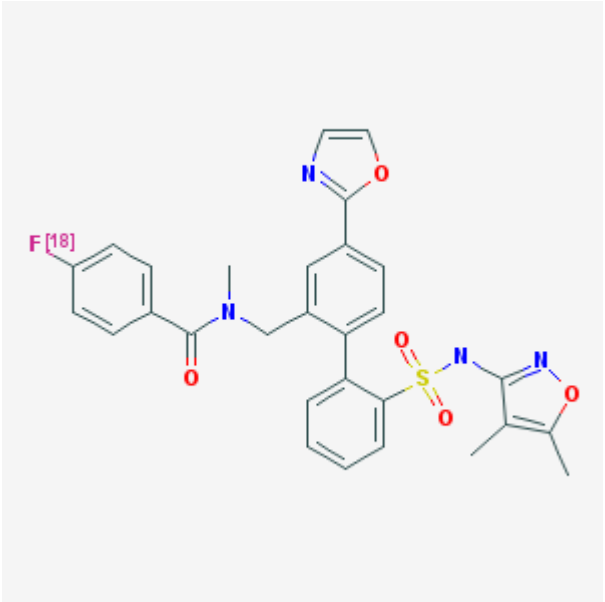
Chemical name:	^{11}C-BMS-5p and ^{18}F-FBzBMS: radiolabeled analogs of BMS-207940, a potent and selective antagonist of endothelin receptor subtype A
Abbreviated name:	[^{11}C]-BMS-5p and [^{18}F]FBzBMS
Synonym:	
Agent Category:	Compound
Target:	Endothelin receptor subtype A (ET_A)
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No



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Studies:	• *In vitro* • Rodents • Non-human primates	Click on the structure of [^{18}F]FBzBMS above for more information in PubChem.

Background

[PubMed]

The endothelin (ET) family consists of three isoform peptides, ET-1 (22 amino acids (aa)), ET-2 (23 aa), and ET-3 (27 aa), that mediate their activity through two G-protein–coupled ET receptors (ETR) designated as A (ET_A) and B (ET_B) (1). Each isoform of ET has a distinct receptor affinity and physiological activity. ET_A is located primarily on the smooth muscle cells and has a high affinity for the ET-1 and ET-2 peptides. ET_B has an affinity for all of the ET peptides and is expressed in several cells types such as epithelial cells, endothelial cells, endocrine cells, and nerve cells (1). Binding of ETs to ET_A results in vasoconstriction and the development of hypertension; however, binding of ETs to ET_B results in the production of nitric oxide and prostaglandins, which promote vasodilation (1). There is much evidence that ET-1 plays a prominent role in the development of pulmonary hypertension and even heart failure (2). In addition, it is well known that ETs, particularly ET-1, are involved in the growth of cancerous tumors because they promote cell transformation and angiogenesis; an elevated level of ET-1 in the blood indicates a poor prognosis for the patient (3). Because of their involvement in the development of cardiovascular disorders, the United States Food and Drug Administration (FDA) approved the use of small molecule ETR antagonists for the treatment of these conditions.

It has been shown that radioiodinated ($^{123/125}$I) or ^{18}F-labeled ET-1 is suitable for the noninvasive imaging of ETRs in rodents and non-human primates (4). Although radiolabeled small molecule antagonists of ET_A have been developed and evaluated *in vitro* and for the *in vivo* imaging of ETRs in animals, none of these radiolabeled compounds has been used for the imaging of this receptor in humans (4). In a continuing effort to develop ET_A antagonists, Murugesan et al. showed that BMS-207904, a biphenyl sulfonamide, is a highly potent (K_i = 10 pM) antagonist that is 80,000-fold more selective

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of ET_A than of ET_B (5). Mathews et al. synthesized ^{11}C-labeled and ^{18}F-labeled analogs of BMS-207904, designated as [^{11}C]-BMS-5p and [^{18}F]FBzBMS, and studied the biodistribution of these radiolabeled antagonists in normal mice (4). The tracers were also evaluated for the imaging of ET_A with positron emission tomography (PET) in a baboon (4). In another study, [^{18}F]FBzBMS was used with PET to assess the *in vivo* expression of ET_A in healthy and infarcted rat hearts (6).

Related Resource Links

Related chapters in MICAD

Clinical trials related to endothelin receptors

Endothelin receptors in Online Mendelian Inheritance in Man Database (OMIM)

Protein sequence of a precursor of human endothelin-1 receptor isoform

Human endothelin receptor subtype A, transcript variant 2, mRNA sequence

Synthesis

[PubMed]

The synthesis of [^{11}C]-BMS-5p and [^{18}F]FBzBMS has been described by Mathews et al. (4).

[^{11}C]-BMS-5p was synthesized in 36 min and had an average radiochemical yield (RCY) of 1.5 ± 0.4% as determined with high-performance liquid chromatography (HPLC). The radiochemical purity (RCP) of [^{11}C]-BMS-5p was >99%, with a specific activity (SA) of 1.051 TBq/μmol (28.4 Ci/μmol; $n = 5$ reactions) at the end of synthesis (4).

The synthesis of [^{18}F]FBzBMS was completed in 130 min, and [^{18}F]FBzBMS had RCY, RCP, and SA values of 0.54 ± 0.44%, 99%, and 12.9 GBq/μmol (349 mCi/μmol; $n = 7$ reactions), respectively, at the end of synthesis (4).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The 50% inhibitory concentrations (IC_{50}) of BMS-207940, nonradioactive BMS-5p, and nonradiactive FBzBMS for ET_A were determined with a mixture of human kidney cortex and medulla cell membranes (4). [^{125}I]-ET was used as the receptor ligand for this assay. The IC_{50} values of BMS-207940, BMS-5p, and FBzBMS were reported to be 4.73 nM, 14.26 nM, and 3.09 nM, respectively.

The *in vivo* stability of the two tracers was determined in healthy mice ($n = 4$ animals) (4). The rodents were given an intraperitoneal injection of either 37 MBq (1 mCi) [^{11}C]-BMS-5p or 7.4 MBq (0.2 mCi) [^{18}F]FBzBMS, and blood was collected from the animals at various time points (4). HPLC analysis of plasma isolated from the various blood samples

showed that only 14% of [^{11}C]-BMS-5p was metabolized at 25 min p.i. compared with 8.5% of [^{18}F]FBzBMS at 40 min p.i. A similar study with a baboon showed that ~36% of both [^{11}C]-BMS-5p and [^{18}F]-FBzBMS were metabolized in the plasma by 90 min p.i.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{11}C]-BMS-5p and [^{18}F]FBzBMS was studied in healthy mice (4). The animals (n = 3 mice/tracer) were injected with either 11.3 MBq (306 μCi, 0.2 μg/kg body weight (BW)) [^{11}C]-BMS-5p or 2.7 MBq (72 μCi, 2.55 μg/kg BW) [^{18}F]FBzBMS through the tail vein, and the rodents were euthanized at preselected time points to retrieve the organs of interest. The amount of radioactivity accumulated in the different tissues was determined and presented as percent of injected dose per gram tissue (% ID/g; Table 1). With both radiochemicals, maximum uptake of radioactivity was observed in the liver, followed by lungs and heart at all of the time points. The liver showed a higher accumulation of label with [^{18}F]FBzBMS than with [^{11}C]-BMS-5p during the entire course of the study. All other organs showed a constant level of radioactivity at all of the time points.

To determine the ET_A binding specificity of [^{11}C]-BMS-5p and [^{18}F]FBzBMS, the mice (n = 3 animals/labeled compound) were given an intravenous injection of BMS-207940 (1 mg/kg BW) 5 min before administration of the labeled compounds (4). At 60 min p.i., the animals were euthanized and treated as described above to determine the amount of radioactivity accumulated in the various tissues. The lungs and the kidneys showed >64% specific binding of label with both radiotracers. The heart showed 63% and 81% specific uptake of radioactivity with [^{11}C]-BMS-5p and [^{18}F]FBzBMS, respectively.

In another study, [^{18}F]FBzBMS was evaluated with PET imaging to determine the level of ET_A expression in healthy and injured rat hearts (injury induced by myocardial infarction) (6). *In vivo* blocking studies with BMS-207940 and bosentan (an oral ETR antagonist approved by the FDA for the treatment of pulmonary hypertension) confirmed that the tracer can be used with PET to visualize the expression of ETR in these rodents. In addition, it has been shown that [^{18}F]FBzBMS can be used with PET to compare the expression of ETR in the hearts of healthy rats (n = 5 animals) and the infarcted hearts of the animals (n = 32 rats).

Table 1: Biodistribution of radioactivity from [^{11}C]-BMS-5p and [^{18}F]FBzBMS in healthy mice (4).

Organ	[^{11}C]-BMS-5p	[^{18}F]FBzBMS
	Time p.i. (min)	

NA, not available; p.i., postinjection. Data are presented as % injected dose per gram (ID/g). For complete data, see Mathews et al. (4).

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	5	30	90	120	5	30	90	120
Liver	43.46 ± 4.99	20.72 ± 0.37	13.43 ± 0.74	NA	62.70 ± 1.26	44.66 ± 8.14	23.37 ± 2.67	12.95 ± 2.36
Lungs	9.22 ± 1.40	7.50 ± 0.54	7.16 ± 0.82	NA	3.76 ± 0.29	5.80 ± 1.01	5.89 ± 0.98	5.09 ± 2.16
Heart	5.07 ± 0.27	2.82 ± 0.29	3.42 ± 0.51	NA	2.37 ± 0.11	3.07 ± 0.08	3.05 ± 0.02	3.08 ± 0.68
Kidney	9.15 ± 1.55	3.93 ± 0.18	2.59 ± 0.37	NA	8.42 ± 1.39	4.67 ± 1.00	3.02 ± 0.12	1.83 ± 0.62
Blood	12.91 ± 0.38	5.17 ± 3.41	1.12 ± 0.20	NA	3.44 ± 0.27	1.85 ± 0.34	0.61 ± 0.05	0.40 ± 0.12

NA, not available; p.i., postinjection. Data are presented as % injected dose per gram (ID/g). For complete data, see Mathews et al. (4).

Other Non-Primate Mammals

[PubMed]

No reference is currently available.

Non-Human Primates

[PubMed]

[^{11}C]-BMS-5p and [^{18}F]FBzBMS were evaluated for the noninvasive imaging of ET_A in a non-human primate (4). For this, a baboon (*Papio anubis*; under anesthesia) was injected intravenously with either 292 ± 25 MBq (7.88 ± 0.68 mCi, 0.22 ± 0.01 μg) [^{11}C]-BMS-5p or 158 ± 12 MBq (4.28 ± 0.33 mCi, 9.82 ± 3.15 μg) [^{18}F]FBzBMS, and PET images of the animal's heart were acquired for up to 90 min p.i (4). Subsequently regions of interest were drawn around the myocardium and the lungs on the PET images, and time-activity curves for the organs were generated. At all of the time points, a high uptake of radioactivity was observed in the myocardium compared with the lungs with both tracers. With both radioligands, the heart/blood label uptake ratio was reported to be 4.7 between 35 min p.i. and 85 min p.i. For blocking studies, the animal was pretreated with 1 mg/kg BW BMS-207940, and both tracers exhibited specific binding of 85% in the heart at 85 min p.i. From this study, the investigators concluded that both [^{11}C]-BMS-5p and [^{18}F]FBzBMS are suitable for the detection and characterization of ET_A in the non-human primates (4).

Human Studies

[PubMed]

No information is currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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