*N*2-{6-[(4-Amino-6,7-dimethoxy-2-quinazolinyl)(methyl)amino]hexyl}-*N*2-[^{11}C]methyl-2-furamide

[^{11}C]GB67

Kam Leung, PhD[1]

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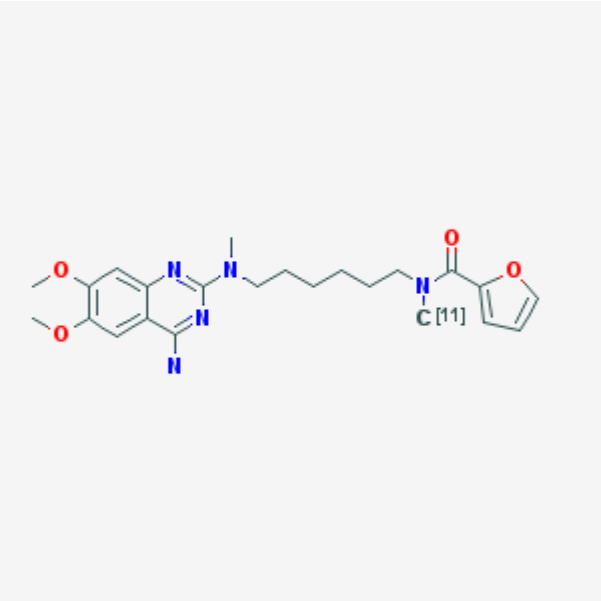
Chemical name:	*N*2-{6-[(4-Amino-6,7-dimethoxy-2-quinazolinyl)(methyl)amino]hexyl}-*N*2-[^{11}C]methyl-2-furamide
Abbreviated name:	[^{11}C]GB67
Synonym:	
Agent category:	Compound
Target:	α_1-Adrenoceptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Humans



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[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: micad@ncbi.nlm.nih.gov.

Corresponding author.

Background

[PubMed]

Malfunction of the sympathetic nervous system may play a primary role in the pathogenesis of heart diseases. There are two subtypes of α-adrenoceptors: α_1 and α_2 in the heart. α-Adrenoceptors play a backup role for β_1-adrenoceptors (1). The cardiac adrenoceptors are responsible for the regulation of heart rate and myocardial contractility (2). About 15% of cardiac adrenoceptors are made up of α_1-adrenoceptors. Presynaptic α_1-adrenoceptors modulate noradrenalin release. α_1-Adrenoceptors are present predominately in larger blood vessels, whereas α_2-adrenoceptors are more prominent in smaller blood vessels. Increases in α_1-adrenoceptor sites are usually observed when the number of β-adrenoceptors decreases in heart diseases (3). Imaging of the pathologic changes of adrenergic receptors offers a non-invasive assessment of myocardial diseases.

*N*2-{6-[(4-Amino-6,7-dimethoxy-2-quinazolinyl)(methyl)amino]hexyl}-*N*2-methyl-2-furamide (GB67) was reported to be a structural and pharmacologic analog of the α_1-adrenoceptor antagonist prazosin (an antihypertensive agent) (4). GB67 exhibited high potency and selectivity for α_1-adrenoceptors. [^{11}C]GB67 is being developed as a positron emission tomography (PET) agent for use in non-invasive study of α_1-adrenoceptors in the heart.

Related Resource Links:

- Chapters in MICAD (Adrenoceptors)
- Gene information in NCBI (α_1-adrenoceptors, α_2-adrenoceptors)
- Articles in OMIM (α_1-adrenoceptors, α_2-adrenoceptors)

Synthesis

[PubMed]

[^{11}C]GB67 was synthesized remotely via a one-pot reaction of [^{11}C]methyl iodine with desmethyl precursor (*N*2-{6-[(4-amino-6,7-dimethoxy-2-quinazolinyl)(methyl)amino]hexyl}-2-furamide or *N*-desmethylamido-GB67) in the presence of NaH. [^{11}C]GB67 was purified by high-performance liquid chromatography (HPLC) with a radiochemical yield of 18% (end of bombardment) (5). The radiochemical purity was >99%, and the specific activity was 20-60 GBq/μmol (0.54-1.62 Ci/μmol) at end of synthesis. Time of synthesis was not reported.

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In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro competition binding studies of [^{3}H]prazosin with human heart membranes produced a K_d of 0.9 ± 0.08 nM and a B_{max} of 58 ± 5 fmol/mg protein (6). In the rat heart membranes, the K_d and B_{max} were reported to be 0.23 ± 0.04 nM and 63 ± 0.04 fmol/mg protein, respectively.

Animal Studies

Rodents

[PubMed]

Law et al. (5) performed biodistribution studies in normal rats and found high accumulation of radioactivity in the kidney (tissue/plasma ratio of 42), followed by the liver (37), lung (25), heart (29), and muscle (2) at 60 min after injection of 0.4-0.8 nmol/kg [^{11}C]GB67. Radioactivity in the brain was very low (tissue/plasma ratio of 0.5). Pretreatment of rats with unlabeled GB67 (0.1 or 5 μmol/kg) significantly decreased the accumulation of [^{11}C]GB67 in the heart but not in the other tissues. Co-injection of 1-100 nmol/kg GB67 decreased the accumulation in the myocardium in a dose-dependent manner. Injection of unlabeled prazosin (100 nmol/kg) 5 min after injection of [^{11}C]GB67 produced significant displacement of radioactivity from the myocardium at 20 min after injection of the tracer. Rx 821002 (α_2-adrenoceptors) and CGP 12177 (β-adrenoceptors) at 5 μmol/kg had no effect on blocking [^{11}C]GB67 accumulation in the heart, indicating α_1-adrenoceptor selectivity for [^{11}C]GB67. In a competitive binding model, the B_{max} and K_d for the myocardium were estimated to be 13 pmol/g tissue and 1.5 nmol/kg of body weight, respectively. Almost all of the radioactivity in the heart was intact [^{11}C]GB67 at 60 min post injection. The fraction of unchanged [^{11}C]GB67 in blood, as determined by HPLC, was 82% at 5 min and 54% at 25 min.

Other Non-Primate Mammals

[PubMed]

PET studies (n = 7) were performed in pigs. [^{11}C]GB67 volume of distribution (V_T) values (in ml cm^{-3}) were estimated to be 24.2 ± 5.5 (range, 17.3-31.3), 10.1 (predose) and 11.6 (displacement). MBF did not differ within each pig, including between baseline and predose conditions. Predose and displacement studies showed that specific binding of [^{11}C]GB67 to myocardial α_1-adrenoceptors accounts for ~50% of V_T.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

Law et al. (5) reported a human PET study in which [^{11}C]GB67 (153.2-384.5 MBq (4.1-10.4 mCi)) was administered to 2 healthy male volunteers. The myocardium was clearly visualized early, and the retention of radioactivity remained unchanged up to 60 min. On the other hand, radioactivity in the lung decreased rapidly. The fraction of unchanged [^{11}C]GB67 in blood, as determined by HPLC, was 96% at 5 min and 82% at 25 min.

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