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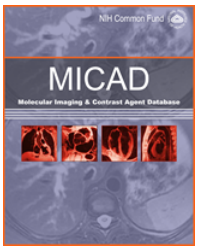

2-Butyl-5-[^{11}C]methoxymethyl-6-(1-oxopyridin-2-yl)-3-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[4,5-b]pyridine

[^{11}C]KR31173

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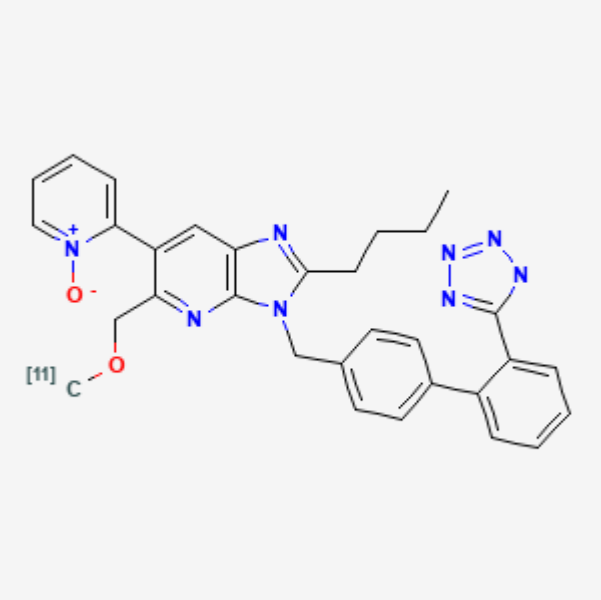
Chemical name:	2-Butyl-5-[^{11}C]methoxymethyl-6-(1-oxopyridin-2-yl)-3-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[4,5-b]pyridine
Abbreviated name:	
Synonym:	[^{11}C]KR31173
Agent category:	Compound
Target:	Angiotensin type 1 (AT_1) receptor
Target category:	Receptor
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-Human Primates



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Background

[PubMed]

Angiotensin II (Ang II), an octapeptide, plays an important role in the regulation of cardiovascular, renal and endocrine function (1, 2). Ang II induces a variety of physiological changes such as constricting of vascular smooth muscle cells, modulation of glomerular filtration rate, and sodium retention, resulting in an increase in

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blood pressure. Two subtypes of Ang II receptors, AT_1 and AT_2, have been well characterized pharmacologically and biochemically (3, 4). AT_1 is indicated in all known pressor effects of Ang II, whereas no known biological functions have been found for AT_2. The AT_1 receptor subtype is found mainly in all vascular tissues, the pituitary gland and is the only subtype in the liver. The AT_2 receptor subtype is found mainly in the rat adrenal medulla, human uterus, rat ovarian granulosa cells, and rat striatum. In other tissues, such as the adrenal cortex, kidneys, heart and brain, there is a mixture of both subtypes.

The AT_1 nonpeptide antagonist, losartan (MK-954 or DuP753), was shown to be effective anti-hypertensive agent (5). MK-996 (L-159,282) was found to be a potent and selective AT_1 antagonist with high affinity (IC_{50} = 0.15 nM for AT_1 and >300 nM for AT_2) (6). L159,884, the methoxyl analog of MK-996 (IC_{50}, 0.08 nM), has been radiolabeled as [^{11}C]L-159,884 for in vivo investigation of AT_1 expression by PET in the kidneys, adrenal gland and heart (7). Another nonpeptide AT_1 antagonist (IC_{50}, 3.27 nM), 2-Butyl-5-methoxymethyl-6-(1-oxopyridin-2-yl)-3-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[4,5-b]pyridine (KR31173), is a methoxyl analog of SK-1080, which has been shown to be a selective AT_1 antagonist (IC_{50}, 11.6 nM) (8). [^{11}C]KR31173 (2-Butyl-5-[^{11}C]methoxymethyl-6-(1-oxopyridin-2-yl)-3-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[4,5-b]pyridine) is being studied as a radioligand for PET imaging of AT_1 receptors.

Related Resource Links

- Chapters in MICAD (AT_1)
- Gene information in NCBI (AT_1).
- Articles in Online Mendelian Inheritance in Man (OMIM) (AT_1)
- Clinical trials (AT_1)
- Drug information in FDA (AT_1)

Synthesis

[PubMed]

Mathews et al. (9) reported synthesis of [^{11}C]KR31173 by O-methylation of the corresponding desmethyl phenolic precursor with [^{11}C]methyl chloride in the presence of NaH in DMF or terahydrofuran, followed by acid hydrolysis to remove the protecting group from the tetrazole moiety. An average radiochemical yield was 5% (based on [^{11}C]methyl chloride, not corrected for decay) with a total synthesis time of 25 min. An average specific activity was 258.3 GBq/μmol (6979 mCi/μmol at end of synthesis) with a radiochemical purities of >99%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

KR31173 was shown to have an IC_{50} of 3.27 nM determined using rat liver homogenates (AT_1) (9).

Animal Studies

Rodents

[PubMed]

Biodistribution studies in mice were performed by Mathews et al. (9) showing high accumulation of radioactivity in the liver (30.32% injected dose (ID)/g), followed by the kidney (22.70% ID/g), adrenal (19.71% ID/g), lung (3.23% ID/g), and heart (2.16% ID/g) at 5 min after injection of [^{11}C]KR31173. There was marked accumulation of the tracer in the liver within the first 5 min, followed by a rapid decrease of radioactivity to

4.56% ID/g at 90 min. After 30 min, the highest accumulation was in the adrenal gland and kidney with tissue/blood ratios >10. Pretreatment (1-2 mg/kg) with MK-996, KR31173 or SK-1080 effectively inhibited specific binding of [^{11}C]KR31173 to the adrenal glands (91-98% inhibition), kidneys (82-90%), lungs (88-96%) and heart (92-96%) (9, 10). Only 33-50% inhibition was seen in the liver. PET imaging of mice showed that renal accumulation of radioactivity was inhibited by 49 ± 6% at 10-60 min with SK-1080 pretreatment (10).

Higuchi et al. (11) performed [^{11}C]KR31173 PET imaging studies in a myocardial ischemia reperfusion injury rat model. The left coronary artery was ligated for 20-25 min with subsequent perfusion for 16–18 h. A 30-min static scan was obtained at 20 min after the intravenous injection of 55.5 MBq (1.5 mCi) of [^{11}C]KR31173 at 7 d after the induction of ischemia (n = 3). The infarct/normal ratio was 2.2 ± 0.9. The ratio decreased to 1.26 ± 0.10 (P < 0.01) with SK-1080 pretreatment.

Other Non-Primate Mammals

[PubMed]

Zober et al. (10) performed PET imaging quantitative measurements of [^{11}C]KR31173 binding in the kidneys of three dogs with kinetic and graphical analyses (Logan), using arterial input function. The dogs were injected intravenously with 275 ± 58 MBq (7.43 ± 1.57 mCi) of [^{11}C]KR31173. PET scans showed distinct accumulation of [^{11}C]KR31173 in the adrenal and renal cortex. Renal accumulation and kinetics of [^{11}C]KR31173 were imaged at baseline and after pretreatment with 1 mg/kg AT_1 antagonist SK-1080. Within the time interval between 75 and 95 min after injection, the radioactivity retained in the kidneys was 63 nCi/ml/mCi of the injected dose for the control and was reduced by 92% with SK-1080 pretreatment, The distribution volume of [^{11}C]KR31173 decreased by 84% from a baseline of 5.71 ± 0.56 to a post-SK-1080 value of 0.90 ± 0.13.These results demonstrate distinct binding of [^{11}C]KR31173 in the renal cortex with a specific binding component suitable for quantitative PET imaging of AT_1 receptors. The fraction of unchanged [^{11}C]KR31173 in plasma samples determined by HPLC was 15% at 90 min after injection.

Non-Human Primates

[PubMed]

Zober et al. (10) studied one male baboon with [^{11}C]KR31173 and [^{11}C]L-159884 PET imaging under baseline conditions and after pretreatment with SK-1080. There was a higher accumulation of [^{11}C]KR31173 (345 nCi/ml/mCi injected dose) than [^{11}C]L-159884 (96 nCi/ml/mCi injected dose) in the renal cortex. Pretreatment with SK-1080 revealed that the specific binding of [^{11}C]KR31173 was higher (81%) than the specific binding of [^{11}C]L-159,884 (34%). The distribution volume (Logan analysis) of [^{11}C]KR31173 decreased by 92% from a baseline of 13 to a post-SK-1080 value of 1. On the other hand, The distribution volume of [^{11}C]L-159,884 decreased only by 12% from a baseline of 1.5 with SK-1080 pretreatment. The fraction of unchanged [^{11}C]KR31173 in plasma samples determined by HPLC was 21% at 90 min after injection.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

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