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NLM Citation: Lutanie E, Leung K. *N,N*-Diethyl-2-2(2-(4-[^{11}C]methoxyphenyl)-5,7-dimethyl-pyrazolo(1,5-*a*)pyrimidin-3-yl)-acetamide. 2006 Apr 19 [Updated 2010 Mar 11]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
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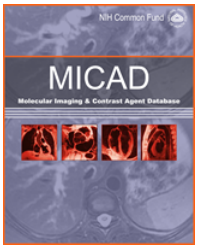

N,N-Diethyl-2-2(2-(4-[^{11}C]methoxyphenyl)-5,7-dimethyl-pyrazolo(1,5-*a*)pyrimidin-3-yl)-acetamide

[^{11}C]DPA-713

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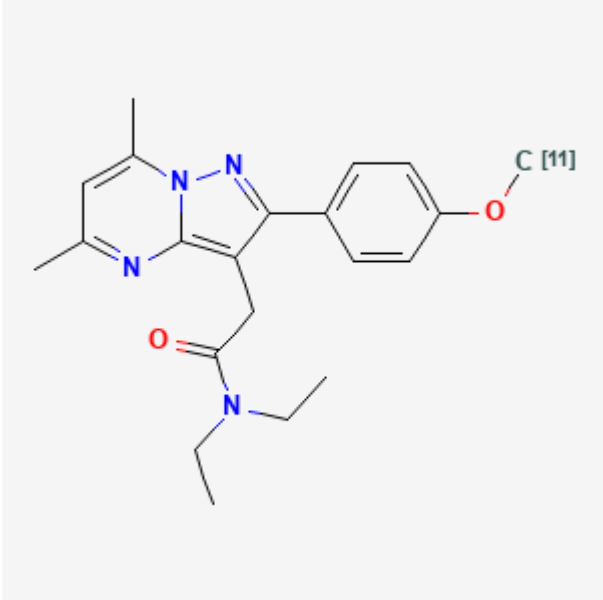
Created: April 19, 2006; Updated: March 11, 2010.

Chemical name:	*N,N*-Diethyl-2-2(2-(4-[^{11}C]methoxyphenyl)-5,7-dimethyl-pyrazolo(1,5-*a*)pyrimidin-3-yl)-acetamide
Abbreviated name:	[^{11}C]DPA-713
Synonym:	
Agent Category:	Compound
Target:	Peripheral benzodiazepine receptor (PBR), also known as translocator protein (TSPO)
Target Category:	Receptor
Method of detection:	PET
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

Benzodiazepines are used for their sedative, anxiolytic, and muscle-relaxant properties (1). Their mechanism of action involves the binding of a ligand to a specific benzodiazepine receptor. Two types of benzodiazepine receptors have been identified: a central receptor and a peripheral one. The central benzodiazepine receptor

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(CBR) is found exclusively in the central nervous system on the membranes of neurons and is coupled to the γ-aminobutyric acid receptor/chloride channel (2). The peripheral benzodiazepine receptor (PBR), first thought to be a subtype of the CBR, was later identified as a separate class of receptor with its own structure, physiologic functions, and location on the outer membrane of the mitochondria (3).

The PBR structure consists of a trimeric complex with an adenine nucleotide carrier and a voltage-dependent anion that form the mitochondrial permeability transition pore (3). Although it has been shown to be involved in numerous biological processes, the physiologic role of the PBR is still unclear (4). PBR is abundant in peripheral organs such as the kidneys, lungs, and heart, whereas lower levels are found in the brain (5). A significant increase in PBR expression after neural injury or inflammation (e.g., Alzheimer's disease, Wernicke's encephalopathy, multiple sclerosis, and epilepsy) has been observed and has been associated with microglial activation (6, 7).

The development of PBR radioligands for positron emission tomography (PET) has enabled the study of microglial activation in the brain (8). One of these radioligands, 1-(2-chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide ([^{11}C]PK11195), was developed as a probe for studying the function and expression of PBR (9). Unfortunately, [^{11}C]PK11195 displays a poor signal-to-noise ratio and low brain permeability, which decreases its sensitivity for detecting areas of microglia activation.

Other ligands displaying better brain kinetics have recently been synthesized and studied. Among them, *N,N*-diethyl-2-2(2-(4-[^{11}C]methoxyphenyl)-5,7-dimethyl-pyrazolo(1,5-*a*)pyrimidin-3-yl)-acetamide ([^{11}C]DPA-713), a compound from the family of pyrazolopyrimidines (10), has shown a slightly higher affinity (K_i = 4.7 nM) for PBR than does [^{11}C]PK11195 (K_i = 9.3 nM). [^{11}C]DPA-713 is substantially more selective for the PBR than for the CBR (K_i > 10,000 nM for the CBR).

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (PBR)
- Articles in OMIM
- Clinical trials (PBR)

Synthesis

[PubMed]

[^{11}C]DPA-713 can be prepared by O-alkylation of the phenolic derivative *N,N*-diethyl-2-[2-(4-hydroxyphenyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidin-3-yl]-acetamide with [^{11}C]methyl iodide ([^{11}C]MeI), as described by James et al. (11). The radiochemical yield of [^{11}C]DPA-713 was 9% (non-decay-corrected) with a radiochemical purity >98%. The specific activity of the radioligand measured at the end of the synthesis was 36 GBq/μmol (973 mCi/μmol), and the total time of synthesis was about 13 min.

In 2006, Thominiaux et al. (12) reported another radiosynthesis method using [^{11}C]methyl triflate ([^{11}C]MeOTf) instead of [^{11}C]MeI. Their method gave an improved yield (30-38%) compared with [^{11}C]MeI, and used a simpler purification method (with HPLC)). Briefly, [^{11}C]MeOTf was bubbled through 0.3-0.5 mg of DPA-713 dissolved in acetone (300 μl) and aqueous NaOH (12 μmol, 3 N), at –10 °C (in an ethanol-ice bath). After trapping of [^{11}C]MeOTf for about 3 min, the reaction mixture was concentrated to dryness at 110 °C, cooled, diluted with 0.6 ml of the HPLC mobile phase, and injected onto the HPLC column. This last step enabled separation of the radioligand from its unlabeled precursor.

Log P (P = octanol-water partition coefficient) for [^{11}C]DPA-713 was found to be 2.4 (11), which is within the optimum range (2 to 3) for achieving high brain uptake with weak nonspecific binding (13).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

PBR binding affinities of DPA-713, DPA-714 and PK1195 were assessed with competitive binding with [3H]PK11195 in rat kidney membranes with K_i values of 7.0 ± 0.4, 4.7 ± 0.2, and 9.3 ± 0.5 nm, respectively (10, 11, 14). The three compounds exhibited K_i values of > 10, 000 nM for CBR. DPA-713 did not stimulate pregnenolone synthesis in a standard steroidogenic assay, whereas DPA-714 and PK1195 increase pregnenolone synthesis by 80% and 60%, respectively.

Animal Studies

Rodents

[PubMed]

Boutin et al. (15) performed PET imaging in rats (n = 4-5/group) with neuroinflammation induced with alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate in the brain. Binding potential values for [11C]DPA-713 was significantly higher than that of [11C]PK11195 (1.57 ± 0.36 versus 0.66 ± 0.15; $P < 0.05$). Displacement studies were performed by injection of 1 mg/kg of DPA-713 or PK11195 at 20 min after injection of [11C]DPA-713. Rapid displacement of radioactivity in the brain lesion site was observed with both unlabeled compounds with complete displacement within 15 min after injection of unlabeled compounds. No change in radioactivity was observed in the contralateral side.

Doorduin et al. (16) performed PET imaging in rats (n = 4-5/group) with Herpes encephalitis. Accumulation of [11C]DPA-713 in the infected brain areas was comparable to that of [11C]PK11195, but [11C]PA-713 showed lower non-specific binding. The radioactivity levels in the infected brain areas were about 1-fold higher than the control brain areas. Pretreatment with 5 mg/kg PK11195 significantly reduced the accumulation in the infected brain areas to background levels ($P < 0.05$). *Ex vivo* biodistribution studies showed that the infected brain areas with specific accumulation were the bulbus olfactorius, hippocampus, medulla, and pons. The lung exhibited a high specific binding for [11C]PA-713 in the infected animals.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

James et al. (11) evaluated the uptake of [11C]DPA-713, using dynamic PET brain scans of 13-year-old *Papio hamadryas* baboons (~26.5 kg each) injected with 200 MBq (5.4 mCi) of the radiotracer. Data were acquired every 2 min for a total time period of 60 min post injection. Maximal accumulation of ~0.006% of injected dose (ID)/ml was reached at 20 min post injection and stayed approximately constant for the remaining 40 min of the imaging procedure. To assess the *in vivo* specificity and selectivity of [11C]DPA-713, two blocking studies were performed 3 weeks apart, in which either flumazenil (a CBR-specific ligand) or PK11195 (a PBR-specific ligand) was injected intravenously into the baboons 5 min before they received the radiotracer. It was observed that the pretreatment with PK11195 (5 mg/kg) significantly decreased the accumulation of [11C]DPA-713 compared with the baseline study described above. The measured values for brain activity (in % ID/ml) were as follows: 0.007 at ~2 min post injection, 0.0035 at 10 min, 0.0035 at 20 min, and 0.002 at 60 min. In contrast, pretreatment

with flumazenil (1 mg/kg) showed no inhibitory effect on the uptake of [^{11}C]DPA-713. In that case, the brain activity pattern was not significantly different from the pattern obtained with no-carrier-added [^{11}C]DPA-713. A maximum uptake of almost 0.006% ID/ml was reached at 20 min post injection.

Human Studies

[PubMed]

Endres et al. (17) reported on PET studies in 7 healthy volunteers after injection of 689 MBq (18.6 mCi) of [^{11}C]DPA-713 or 681 MBq (18.4 mCi) of [^{11}C]PK11195. Tracer uptake was evaluated for the cerebellum, frontal cortex, white matter, and pons with a preference for the 2-tissue model over the 1-tissue model. The radioactivity of [^{11}C]DPA-713 in the brain regions was 2-3 folds greater that of [^{11}C]PK11195. The volume of distribution values for [^{11}C]DPA-713 (3.08-5.06) were >10-folds than those for [^{11}C]PK11195 (0.25-0.42). Accumulation in the lung was high up to 10 min post injection. The radioactivity in the myocardium became detectable at 2 min. The radioactivity in the heart decreased for 20 min and remained constant at 75 min. Injection of excess unlabeled PK11195 (650 nmol/kg) 30 min after [^{11}C]PK11195 (0.94 nmol/kg) led to a rapid decrease (48%) in the radioactivity in the myocardium.

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