6-Chloro-2-(4'-[^{123}I]iodophenyl)-3-(*N*,*N*-diethyl)imidazo[1,2-*a*]pyridine-3-acetamide

[^{123}I]CLINDE

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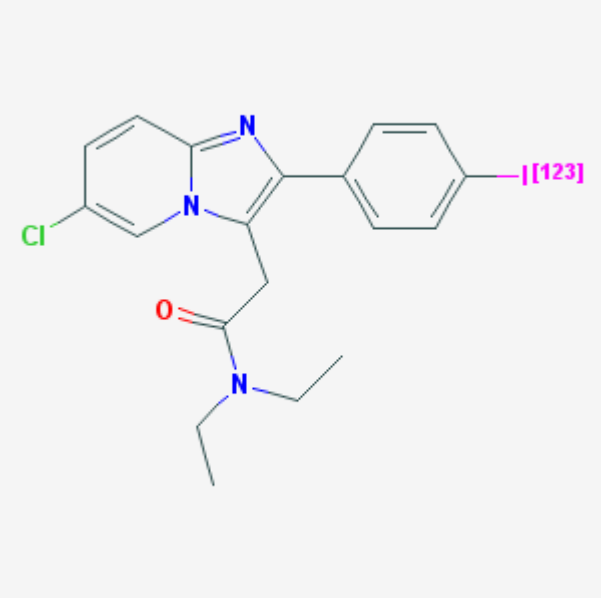
Chemical name:	6-Chloro-2-(4'-[^{123}I]iodophenyl)-3-(*N*,*N*-diethyl)imidazo[1,2-*a*]pyridine-3-acetamide
Abbreviated name:	[^{123}I]CLINDE
Synonym:	
Agent Category:	Compound
Target:	Peripheral benzodiazepine receptor, PBR
Target Category:	Receptor binding
Method of detection:	Single-photon emission computed tomography (SPECT), planar gamma imaging
Source of signal:	^{123}I
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

Benzodiazepines are potent psychoactive drugs used for their sedative and anxiolytic properties (1, 2). There are two types of benzodiazepine receptors, which have been designated as central benzodiazepine receptors (CBR) and peripheral benzodiazepine receptors (PBR). The CBR is found exclusively in the central nervous system (CNS) on the membranes of neurons and is coupled to the γ-aminobutyric acid receptor/chloride channel (3). In contrast, the PBR is a mitochondrial protein found in brain and peripheral tissues (adrenal gland, heart, lung, kidney, and testis) (4). The brain has lower levels of PBR than do the peripheral tissues. Both glial cells and macrophages contain high levels of PBR (5-7). Increased PBR expression after brain injury or neuroinflammation is associated with microglial activation, such as occurs with the neuronal damage that accompanies several neurodegenerative diseases, including Alzheimer's disease, Wernicke's encephalopathy, multiple sclerosis, and epilepsy.

PBRs have been studied *in vivo* by positron emission tomography (PET) with 1-(2-chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide ([^{11}C]PK11195), an isoquinoline carboxamide with specific PBR antagonistic activity. [^{11}C]PK11195 has been developed as a PET agent for non-invasive studies of microglia and macrophage activation in the brain, lung, and heart. However, accumulation of this tracer in the brain is limited. *N*-(2,5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106) was found to be a selective agonist for studying PBRs in the CNS (8, 9). DAA1106 was reported to have a higher affinity for PBRs in mitochondrial fractions of rat and monkey brains compared with PK11195 (8, 9). Therefore, both tracers are able to cross the normal cell membrane to reach the mitochondrial receptor sites. *N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{18}F]fluoroethyl-5-methoxybenzyl)acetamide ([^{18}F]FEDAA1106) and [^{11}C]DAA1106 have been developed as potential PET ligands with highly selective and specific binding to PBRs. 6-Chloro-2-(4'-iodophenyl)-3-(*N,N*-diethyl)imidazo[1,2-*a*]pyridine-3-acetamide (CLINDE), which has an imidazopyridine-3-acetamide structure, has also been shown to have high affinity for PBRs (10, 11). 6-Chloro-2-(4'-[^{123}I]iodophenyl)-3-(*N,N*-diethyl)imidazo[1,2-*a*]pyridine-3-acetamide ([^{123}I]CLINDE) has been developed for single-photon emission computed tomography imaging of PBRs in the brain.

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Synthesis

[PubMed]

Mattner et al. (11) reported the synthesis of [^{123}I]CLINDE by ^{123}I-iodination of the tributyltin precursor with Na^{123}I. [^{123}I]CLINDE was purified with high-performance liquid chromatography and exhibited a specific activity of >185 GBq/μmol (5 Ci/μmol), a radiochemical yield of 75–85%, and a radiochemical purity of >95%. [^{123}I]CLINDE has a log $P_{7.4}$ of 3.1.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{3}H]PK11195 PBR-binding studies have shown that CLINDE has 50% inhibition concentration values of 1.7 ± 0.05 and 360 ± 29 nM for PBRs and CBRs, respectively (11). Binding of [^{123}I]CLINDE to the adrenal, kidney, and brain cortex mitochondrial membranes was saturable with K_d values of 12.6, 0.20, and 3.84 nM and B_{max} values of 163, 5.3, and 0.34 pmol/mg protein, respectively. *In vitro* autoradiography images of the brain showed a heterogeneous distribution of radioactivity. The ependyma and choroid plexus exhibited high levels of radioactivity accumulation, which was blocked by 10 μM PK11195.

Animal Studies

Rodents

[PubMed]

Mattner et al. (11) performed biodistribution studies in rats (n = 3/group) at set time points from 5 min to 48 h. Each rat received 0.5–0.7 MBq (0.014–0.019 mCi) of [^{123}I]CLINDE by i.v. injection. High accumulation (% injected dose/gram (ID/g)) was observed in the adrenal gland (5.4% ID/g), thyroid gland (4.0% ID/g), heart (1.5% ID/g), lungs (1.5% ID/g), and kidney (1.5% ID/g) at 6 h after injection. In the brain, the olfactory bulbs displayed the highest accumulation (0.20% ID/g at 60 min) with approximately three times the activity in the blood. Pre-administration of CLINDE (1 mg/kg) 5 min before tracer injection reduced the accumulation of [^{123}I]CLINDE by 37% in the adrenal gland, by 73% in olfactory bulbs, and by 85–90% in the kidney and heart at 3 h. Flumazenil and haloperidol had no effect on uptake in peripheral organs and the brain. Thin-layer chromatography analysis indicated that >90% of the extractable radioactivity in the above tissues was intact [^{123}I]CLINDE at 3 h, whereas the plasma contained only 2% intact [^{123}I]CLINDE.

Mattner et al. (10) showed that [^{123}I]CLINDE accumulation was enhanced in the CNS of all rats exhibiting with experimental autoimmune encephalomyelitis (EAE) when compared to controls. Binding reflected the ascending nature of EAE inflammation, with

the lumbar/sacral cord (0.53% ID/g) > thoracic cord (0.34% ID/g) > cervical cord (0.24% ID/g) > medulla (0.21% ID/g) > cerebellum (0.10% ID/g) > brain (<0.10% ID/g). The amount of [^{123}I]CLINDE binding reflected the clinical severity of EAE. Pre-administration of CLINDE (1 mg/kg) 5 min before tracer injection reduced the uptake of [^{123}I]CLINDE by 80–90% in all CNS regions. *Ex vivo* autoradiography and immunohistochemistry revealed a good spatial correspondence between radioactivity and foci of inflammation with ED-1–positive cells (macrophages and microglia).

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[Pub Med]

No publications are currently available.

References

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