2-{[4-(4-[^{125}I]Iodobenzyl)piperidin-1-yl]methyl}benzimidazol-5-ol

[^{125}I]**8**

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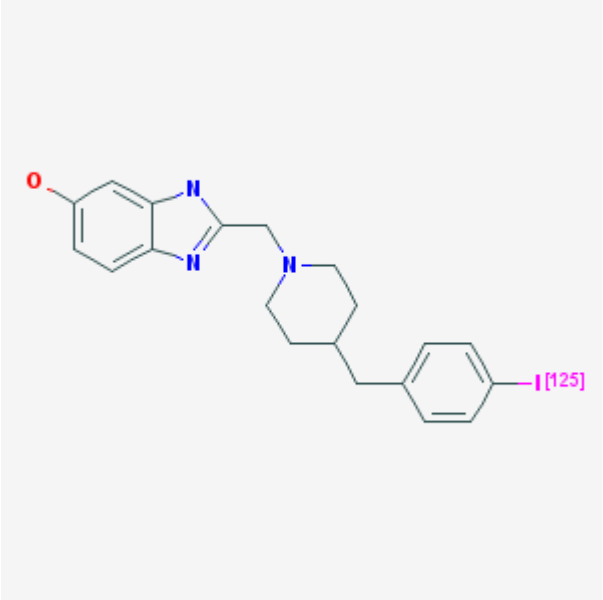
Chemical name:	2-{[4-(4-[^{125}I]Iodobenzyl)piperidin-1-yl]methyl}benzimidazol-5-ol
Abbreviated name:	[^{125}I]**8**
Synonym:	
Agent Category:	Compound
Target:	*N*-methyl-D-aspartate (NMDA) receptor
Target Category:	Receptor
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging
Source of signal / contrast:	^{125}I
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information on [^{125}I]**8** in PubChem.

Background

[PubMed]

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The *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) belongs to a sub-group of the glutamate receptor family and has a heteromeric structure that is made up of three subunits (NR1, NR2, and NR3) as dimeric combinations (NR1/NR2 or NR1/NR3). There are four subtypes of NR2 (NR2A–NR2D), and NR3 has two subtypes, NR3A and NR3B. The NMDAR can bind several different types of ligands and has important functions in the process of learning and in the performance of memory tasks in a variety of animal species (invertebrate and vertebrate) (1, 2). These receptors are involved in the development of neurological conditions such as Parkinson's disease, Alzheimer's disease, bipolar disorder, etc (2, 3). The structure, distribution, and function of the NMDAR in the rodent brain has been reviewed elsewhere (1, 4). The NR1 subunit of the NMDAR is known to be distributed in all parts of the brain; of the different NR2 subtypes, NR2A is found throughout the brain, whereas NR2B, NR2C, and NR2D are present mainly in the forebrain (including the cerebral cortex, hippocampus, and the olfactory lobes), cerebellum, and the lower brain stem, respectively. High levels of the NR3A subtype are detected in many brain regions of only prenatal and newborn mice, whereas NR3B levels are low during these developmental stages. However, the NR3 subtype is expressed predominantly in the adult brain (4).

Among the different NR2 and NR3 subunits, primarily the NR2B subunit is believed to modulate the various physiological and pharmacological activities of the NMDAR as mentioned above. Attempts to study the distribution of the NMDAR that contains the NR2B subunit in the brain through the use of positron emission tomography with radiolabeled compounds have been unsuccessful because the tracers lack binding specificity for the receptor (3). However, among these tracers, the uptake of 6-{3-[4-(4-fluorobenzyl)piperidino]propionyl}-3*H*-benzoxazol-2-[^{11}C]-one ([^{11}C]EMD-95885; a benzimidazole derivative) in the rodent brain was reduced by pretreatment of the animals with ifenprodil, a selective antagonist of the NR2B subunit, suggesting that [^{11}C]EMD-95885 could be a suitable platform for the development of new imaging probes to study the location and distribution of NMDARs that contain the NR2B subunit in the rodent brain (3). Results from *in vitro* assays demonstrated that novel compounds with a structure resembling EMD-95885 maintained their affinity for the NR2B subunit (5). On the basis of this information, Fuchigami et al. synthesized a series of ^{125}I-labeled benzimidazole derivatives and investigated their *in vitro* receptor binding and *in vivo* brain uptake characteristics in normal mice (3). Among these radioiodinated compounds, only two, 2-{[4-(4-[^{125}I]iodobenzyl) piperidin-1-yl]methyl}benzimidazol-5-ol ([^{125}I]**8**) and *N*-{2-[4-(4-[^{125}I]iodobenzyl)-piperidin-1-ylmethyl]benzoimidazol-5-yl}-methanesulfonamide ([^{125}I]**9**), were shown to have a high affinity for the NR2B subunit under *in vitro* conditions. This chapter discusses the *in vitro* and *in vivo* results obtained with [^{125}I]**8**; the characteristics of [^{125}I]**9** are described in a separate chapter of MICAD (www.micad.nih.gov) (6).

Other Sources of Information

Other chapters on NMDAR in MICAD

Protein and mRNA sequence of NMDA1 receptor (zeta 1) (Grin1), transcript variant 2

Information regarding NMDAR on FDA site

Clinical trials on NMDAR

NR2A subunit in OMIM (Online Mendelian Inheritance in Man)

NR2B subunit in OMIM (Online Mendelian Inheritance in Man)

Synthesis

[PubMed]

The synthesis of [^{125}I]**8** has been detailed by Fuchigami et al. (3). The radiochemical yield of [^{125}I]**8** was reported to be 85%–90% based on the amount of [^{125}I]sodium iodide used in the synthesis. The radiochemical purity of the final product was >98% as determined with high-performance liquid chromatography. The specific activity and *in vitro* stability of [^{125}I]**8** were not reported.

Using the shake-flask method, the partition coefficient of **8** between octanol and phosphate-buffered saline (pH 7.4) was determined to be 3.95 (3).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Using an *in vitro* [^{3}H]ifenprodil displacement assay with rat cortical membrane homogenates, the K_i of **8** was determined to be 7.28 ± 2.93 nM (3).

In another study, the distribution of [^{125}I]**8** in rat brain sections was investigated with an autoradiographic technique as described elsewhere (3). Radioiodinated **8** accumulated primarily in the forebrain (cerebral cortex and hippocampus; these regions are rich in NR2B), but a low level of the tracer was detected in the cerebellum, which exhibits low expression of NR2B. In general, the tracer showed a high non-specific binding in the brain sections. Pretreatment of the brain sections with Ro-25,6981, an NR2B-selective anatagonist, was shown to inhibit the binding of [^{125}I]**8** in the different parts of the forebrain, indicating that the tracer probably had some specificity for the NR2B subunit of the NMDAR.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{125}I]**8** was investigated in normal ddY mice (n = 5–6 animals per time point) as described by Fuchigami et al. (3). The animals were injected with the tracer through the tail vein and euthanized at predetermined time points to measure the amount

of radioactivity that accumulated in the major organs. Data were presented as percent injected dose per gram tissue (% ID/g). Maximum uptake of the radioiodinated compound was observed in the liver. Accumulation in the liver was 25.03 ± 4.20% ID/g at 5 min postinjection (p.i.), increased to 32.22 ± 6.56% ID/g at 180 min p.i., and remained relatively constant up to 360 min p.i. In the kidneys, the accumulation was 12.20 ± 3.18% ID/g at 5 min p.i. and decreased to 5.46 ± 0.67% ID/g at 360 min p.i. The lungs showed an uptake of 14.48 ± 2.52% ID/g at 5 min p.i., which decreased to 3.44 ± 0.80% ID/g at 360 p.i. Accumulation in the brain was 0.42 ± 0.06% ID/g at 5 min p.i. and increased to 0.55 ± 0.14% ID/g at 360 min p.i. The brain/blood (B/B) ratio for [^{125}I]**8** increased from 0.36 ± 0.03 at 5 min p.i. to 0.67 ± 0.12 at 30 min p.i. and to 2.23 ± 0.99 at 360 min p.i.

To confirm the binding specificity of [^{125}I]**8** in different regions of the brain, blocking studies were performed by the administration of unlabeled **8** or Ro-25,6981 (3 mg/kg body weight) to the animals (n = 5 mice/blocking drug) 30 min before injecting the labeled compound (3). The animals were euthanized at 180 min p.i., and the brains were removed to determine the amount of radioactivity accumulated in the cerebral cortex, hippocampus, and cerebellum. Animals pretreated with the blocking drugs were reported to have markedly lower ($P < 0.01$) cerebral cortex/blood (~0.4 and ~0.6 for **8** and Ro-25,6981, respectively), hippocampus/blood (~0.4 and ~0.6 for **8** and Ro-25,6981, respectively), and the cerebellum/blood (~0.4 and ~0.6 for **8** and Ro-25,6981, respectively) ratios compared to controls (~1.0 for each brain area). This indicated that [^{125}I]**8** probably had a binding specificity for the NMDAR that contains the NR2B subtype subunit On the basis of observations that there was a low, uniform uptake of [^{125}I]**8** in almost all regions of the rodent brain and little evidence that it bound specifically to the NMDAR that contains the NR2B subunit the investigators concluded that this radioiodinated compound was probably not suitable for single-photon emission computed tomography imaging of the cerebral NMDAR.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No publications are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

References

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