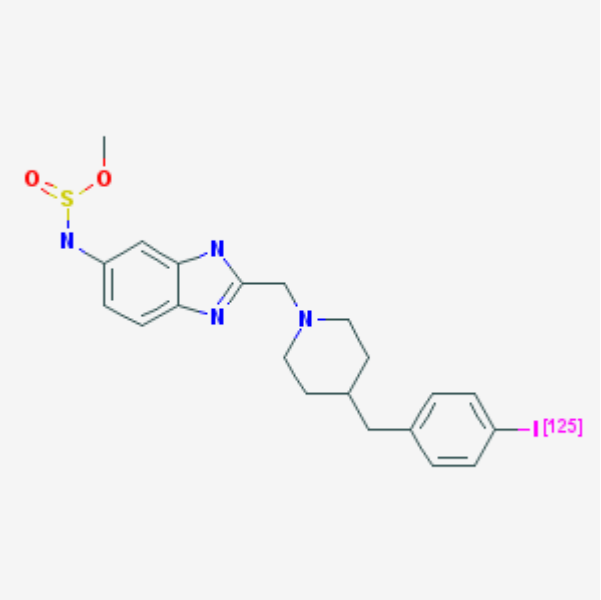
N-{2-[4-(4-[^{125}I]Iodobenzyl)-piperidin-1-ylmethyl]benzoimidazol-5-yl}-methanesulfonamide

[^{125}I]**9**

Arvind Chopra, PhD[1]

Created: January 31, 2011; Updated: March 31, 2011.

Chemical name:	*N*-{2-[4-(4-[^{125}I]Iodobenzyl)-piperidin-1-ylmethyl]benzoimidazol-5-yl}-methanesulfonamide
Abbreviated name:	[^{125}I]**9**
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.

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

Background

[PubMed]

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, inspite of a high non-specific 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 the amount of radioactivity in the organ 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 the NMDAR that contains 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

NLM Citation: Chopra A. *N*-{2-[4-(4-[^{125}I]Iodobenzyl)-piperidin-1-ylmethyl]benzoimidazol-5-yl}-methanesulfonamide. 2011 Jan 31 [Updated 2011 Mar 31]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

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]**9**; the characteristics of [^{125}I]**8** 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 database)

NR2B subunit in OMIM (Online Mendelian Inheritance in Man database)

Synthesis

[PubMed]

The synthesis of [^{125}I]**9** and [^{125}I]**8** has been detailed by Fuchigami et al. (3). The radiochemical yields of [^{125}I]**9** and [^{125}I]**8** were reported to be 78%–81% and 85%–90%, respectively, based on the amount of [^{125}I]sodium iodide used in the synthesis. The radiochemical purity values of the final product for both labeled compounds were >98% as determined with high-performance liquid chromatography. The specific activity and *in vitro* stability of [^{125}I]**9** and [^{125}I]**8** were not reported.

Using the shake-flask method, the partition coefficients of **9** and **8** between octanol and phosphate-buffered saline (pH 7.4) were determined to be 3.54 and 3.95, respectively (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 values of **9** and **8** were determined to be 5.75 ± 1.19 nM and 7.28 ± 2.93 nM, respectively (3).

In another study, the distribution of [^{125}I]**9** and [^{125}I]**8** on rat brain sections was investigated with an autoradiographic technique as described elsewhere (3). Radioiodinated **9** and **8** accumulated primarily in the forebrain (cerebral cortex and hippocampus; these regions are rich in NR2B), and a low level of the tracer was detected in the cerebellum, which exhibits low expression of NR2B. However, in general, both

tracers showed a high non-specific binding in the brain sections. Pretreatment of the brain sections with Ro-25,6981, a NR2B-selective anatagonist, was shown to inhibit the binding of [^{125}I]**9** and [^{125}I]**8** in the different parts of the forebrain, indicating that the tracers probably had some specificity for the NR2B subunit of the NMDAR.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{125}I]**9** and [^{125}I]**8** was investigated in normal ddY mice (n = 5–6 animals/time point per tracer) as described by Fuchigami et al. (3). The animals were injected with the respective tracers 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 [^{125}I]**9** and [^{125}I]**8** was observed in the liver, with an accumulation of 19.35 ± 9.22% ID/g and 25.03 ± 4.20% ID/g of the two compounds, respectively, at 5 min postinjection (p.i.), which increased to 17.81 ± 4.07% ID/g and 32.22 ± 6.56% ID/g, respectively, at 180 min p.i. Although the accumulation remained relatively constant for [^{125}I]**8** at 360 min p.i., accumulation decreased to 10.93 ± 2.51% ID/g for [^{125}I]**9** at this time point. In the kidneys, the accumulation was 10.99 ± 4.46% ID/g and 12.20 ± 3.18% ID/g for [^{125}I]**9** and [^{125}I]**8**, respectively, at 5 min p.i. and increased to 10.51 ± 1.97% ID/g for [^{125}I]**9** at 360 min p.i., but decreased to 5.46 ± 0.67% ID/g for [^{125}I]**8** at this time point. The lungs showed an uptake of 9.07 ± 5.18% ID/g and 14.48 ± 2.52% ID/g for [^{125}I]**9** and [^{125}I]**8**, respectively, at 5 min p.i. and decreased to 3.62 ± 0.21% ID/g and 3.44 ± 0.80% ID/g, respectively, at 360 p.i. In the brain, the accumulation was 0.32 ± 0.12 and 0.42 ± 0.06% ID/g for [^{125}I]**9** and [^{125}I]**8**, respectively, at 5 min p.i., which increased to 0.47 ± 0.09% ID/g and 0.55 ± 0.14% ID/g, respectively, at 360 min p.i. The brain/blood (B/B) ratios for [^{125}I]**9** and [^{125}I]**8** increased from 0.46 ± 0.09 and 0.36 ± 0.03, respectively, at 5 min p.i. to 1.34 ± 0.28 and 2.23 ± 0.99, respectively, at 360 min p.i.

Because the brain uptake profile of [^{125}I]**8** appeared to be superior to that of [^{125}I]**9**, the binding specificity of [^{125}I]**9** in the different regions of the brain was not investigated with blocking studies. Blocking studies performed with [^{125}I]**8** are discussed elsewhere (6).

On the basis of observations that there is a low, uniform uptake of both [^{125}I]**9** and [^{125}I]**8**, respectively, in almost all regions of the rodent forebrain and little evidence that the two tracers bound specifically to the NMDAR that contains the NR2B subunit the investigators concluded that these radioiodinated compounds were 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

1. Magnusson K.R., Brim B.L., Das S.R. *Selective Vulnerabilities of N-methyl-D-aspartate (NMDA) Receptors During Brain Aging.* Front Aging Neurosci. 2010;2:11. PubMed PMID: 20552049.
2. Teng H., Cai W., Zhou L., Zhang J., Liu Q., Wang Y., Dai W., Zhao M., Sun Z. *Evolutionary mode and functional divergence of vertebrate NMDA receptor subunit 2 genes.* PLoS One. 2010;5(10):e13342. PubMed PMID: 20976280.
3. Fuchigami T., Yamaguchi H., Ogawa M., Biao L., Nakayama M., Haratake M., Magata Y. *Synthesis and biological evaluation of radio-iodinated benzimidazoles as SPECT imaging agents for NR2B subtype of NMDA receptor.* Bioorg Med Chem. 2010;18(21): 7497–506. PubMed PMID: 20875744.
4. Low C.M., Wee K.S. *New insights into the not-so-new NR3 subunits of N-methyl-D-aspartate receptor: localization, structure, and function.* Mol Pharmacol. 2010;78(1):1–11. PubMed PMID: 20363861.
5. Borza I., Kolok S., Gere A., Nagy J., Fodor L., Galgoczy K., Fetter J., Bertha F., Agai B., Horvath C., Farkas S., Domany G. *Benzimidazole-2-carboxamides as novel NR2B selective NMDA receptor antagonists.* Bioorg Med Chem Lett. 2006;16(17):4638–40. PubMed PMID: 16782335.
6. Chopra, A., *2-{[4-(4-[125I]iodobenzyl)piperidin-1-yl]methyl}benzimidazol-5-ol.* Molecular Imaging and Contrast agent Database (MICAD) [database online]. National Library of Medicine, NCBI, Bethesda, MD, USA. Available from www.micad.nih.gov, 2004 -to current.