5-[^{76}Br]-*N*-(4-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)butyl)-2,3-dimethoxybenzamide

[^{76}Br]RHM-4

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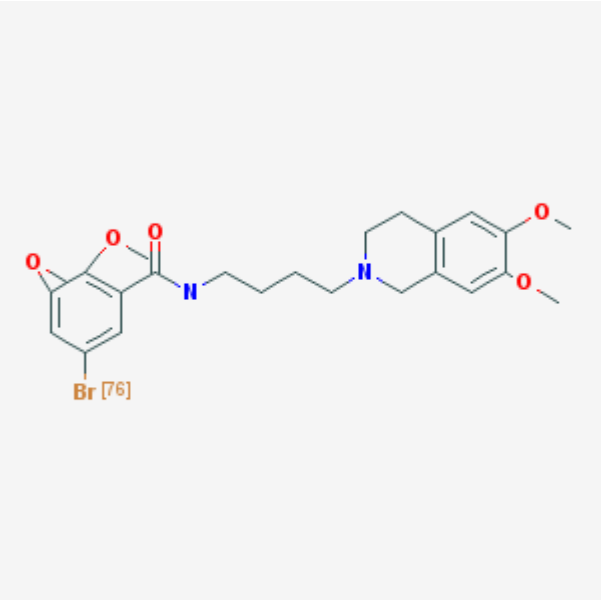
Created: October 5, 2006; Updated: April 3, 2012.

Chemical name:	5-[^{76}Br]-*N*-(4-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)butyl)-2,3-dimethoxybenzamide
Abbreviated name:	[^{76}Br]RHM-4, [^{76}Br]1
Synonym:	
Agent category:	Compound
Target:	σ_2 sigma receptor
Target category:	Receptor
Method of detection:	positron emission tomography (PET)
Source of signal:	^{76}Br
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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NLM Citation: Leung K. 5-[^{76}Br]-*N*-(4-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)butyl)-2,3-dimethoxybenzamide. 2006 Oct 5 [Updated 2012 Apr 3]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

Sigma receptors are functional, membrane-bound proteins distributed in the central nervous system (CNS) and peripheral organs such as the liver, kidneys, and endocrine glands (1, 2). The CNS sigma receptors are unique binding sites related to higher brain function. There are at least two subtypes of sigma receptors, σ_1 and σ_2 receptors. These receptors appear to be involved in numerous pharmacological and physiological functions, and they also modulate a number of central neurotransmitter systems. Studies have shown that these receptors may play a role in the pathogenesis of psychiatric disorders (3, 4). The σ_1 receptors appear to play in a role in motor function and CNS disorders. The σ_2 receptors, linked to potassium channels and calcium release, are also implicated in malignant cancers (5-7). The density of σ_2 receptors in tumor cells was found to be greater than that of σ_1 receptors in tumor cells. The density of σ_2 receptors was found to be 10-fold higher in proliferating *versus* quiescent mouse mammary adenocarcinoma cells. Furthermore, σ_2 receptor ligands were observed to induce apoptosis in tumor cells. Because of these effects, sigma receptor ligands may be useful for detection and treatment in neurology and oncology.

5-[^{76}Br]-*N*-(4-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)butyl)-2,3-dimethoxybenzamide ([^{76}Br]RHM-4), a conformationally flexible benzamide analog, has been shown to have a high affinity (K_i = 8.2 nM) and selectivity (σ_2/σ_1 ratio > 1573) for σ_2 receptors on rat liver membranes (8). [^{76}Br]RHM-4 (^{76}Br $t_{1/2}$ = 16.2 h) has been evaluated as a positron emission tomography (PET) agent for imaging breast tumor in mice (9).

Related Resource Links:

- Chapters in MICAD (Sigma receptors, RHM-1/4)
- Gene information in NCBI (Sigma receptors)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Sigma receptors)

Synthesis

[PubMed]

Rowland et al. (9) reported the synthesis of [^{76}Br]RHM-4 by a standard electrophilic destannylation reaction of *N*-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-butyl]-2-methoxy-5-(tributylstannyl)benzamide with ^{76}Br in NH_4OH, followed by addition of peracetic acid in dilute acetic acid. High-pressure liquid chromatographic separation gave radiochemical yields of 47–76% (n = 7), with a radiochemical purity >99%. The average specific activity was 40.33 GBq/μmol (1.09 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Rowland et al. (9) reported that [^{76}Br]RHM-4 had an affinity constant (K_d) of 1.43 ± 0.09 nM and a σ_2 receptor density (B_{max}) of 1,800 ± 83 fmol/mg protein for EMT-6 mouse breast tumors.

Animal Studies

Rodents

[PubMed]

Rowland et al. (9) performed biodistribution studies in EMT-6 tumor–bearing mice showing high accumulation of radioactivity in the kidney [31.2% injected dose per gram (ID/g)], followed by the lung (24.64% ID/g), spleen (12.50% ID/g), liver (10.99% ID/g), and heart (7.31% ID/g) at 5 min after injection of [^{76}Br]RHM-4. Tumor accumulation of [^{76}Br]RHM-4 was 4.78% ID/g at 5 min, 5.31% ID/g at 30 min, 3.98% ID/g at 60 min, and 1.71% ID/g at 120 min after injection. The liver and kidney showed higher initial uptake than the tumors, with rapid clearances to 1.67% and 1.85% ID/g at 120 min, respectively. Coinjection of [^{76}Br]RHM-4 with YUN 143 (a high-affinity σ_2 and σ_1 ligand, 1 mg/kg) decreased the tumor, liver, and kidney accumulation significantly ($P < 0.005$) to 0.98%, 1.38%, and 1.28% ID/g at 120 min, respectively. Another study comparing the tumor uptake and tumor/tissue ratios of [^{76}Br]RHM-4 with those of 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT), a radiolabeled nucleoside analog for measuring tumor proliferation, was also conducted. It was found that [^{18}F]FLT had a higher tumor uptake (3.05 ± 0.49% ID/g) than [^{76}Br]RHM-4 (1.71 ± 0.17% ID/g) at 120 min. However, [^{76}Br]RHM-4 had better tumor/tissue ratios than [^{18}F]FLT in the tissues of brain, muscle, fat, heart, bone, blood, and lung. PET imaging studies also showed a higher contrast of the tumor/background tissues with [^{76}Br]RHM-4 than with [^{18}F]FLT, and YUN 143 decreased accumulation of [^{76}Br]RHM-4 in the tumor.

Other Non-Primate Mammals

[PubMed

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

Human Studies

F32 CA88487, P30 CA91842, R24 CA86307, R33 CA102869-01

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