(2-*methoxy*-^{11}C)-*N*-(4-(3,4-Dihydro-6,7-dimethoxy-isoquinolin-2(1*H*)-yl)butyl)-5-methylbenzamide

[^{11}C]RHM-1

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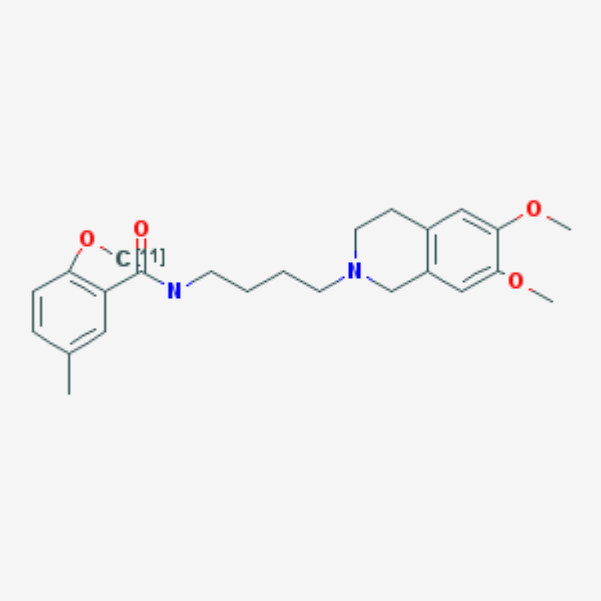
Chemical name:	(2-*methoxy*-^{11}C)-*N*-(4-(3,4-Dihydro-6,7-dimethoxy-isoquinolin-2(1*H*)-yl)butyl)-5-methylbenzamide
Abbreviated name:	
Synonym:	[^{11}C]RHM-1, [^{11}C]2
Agent Category:	Compound
Target:	σ_2 sigma receptors
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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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. These receptors appear to be involved in numerous pharmacologic and physiologic functions, and they also modulate a number of central neurotransmitter systems. Studies suggest that these receptors may play a role in the pathogenesis of psychiatric disorders (3, 4). The σ_1 receptors appear to play a role in CNS disorders and motor functions. The σ_2 receptors (linked to potassium channels and calcium release) are also implicated in malignant neoplastic diseases (5-7). The density of σ_2 receptors was found to be greater than that of σ_1 receptors in tumor cells. For example, the density of σ_2 receptors was found to be 10-fold higher in proliferating *versus* quiescent mouse mammary adenocarcinoma cells. Furthermore, it has been observed that σ_2 receptor ligands can induce apoptosis in tumor cells. Because of these effects, sigma receptor ligands may be useful for detection and treatment in neurology and oncology.

N-[4-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-*yl*)butyl]-2-methoxy-5-methyl-benzamide (RHM-1) and *N*-[2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-*yl*)ethyl]-2-methoxy-5-methylbenzamide (RHM-2), two conformationally flexible benzamide analogs, have been shown to have a high affinity (K_i < 15 nM) and selectivity (σ_2/σ_1 ratio > 300) for σ_2 receptors (8). The 2-methoxy group of RHM-1 and RHM-2 was used to introduce the ^{11}C-labeled methyl group *via* O-alkylation of the corresponding phenol precursor. [^{11}C]RHM-1 has been evaluated as a PET agent for imaging breast tumors in mice (9).

Synthesis

[PubMed]

[^{11}C]RHM-1 was synthesized by O-alkylation of the desmethyl compound, *N*-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-butyl]-2-hydroxy-5-methyl-benzamide, with [^{11}C]methyl iodide (9). Reaction in NaOH/DMF with subsequent chromatographic separation gave radiochemical yields of 60–75%, with a total synthesis time of 50–60 min and a radiochemical purity >95%. The average specific activity was 148 GBq/μmol (4 Ci/μmol) at the end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

RHM-1 has been reported to have selective binding affinity to σ_2 receptor sites in homogenates of rat liver membranes (8). The K_i values for σ_2 and σ_1 were 10.3 ± 1.5 and

3,078 ± 87 nM, respectively. The affinity of RHM-1 for the σ_2 receptors is about 300-fold lower than that for the σ_1 receptors. Xu et al. (10) reported that [^{3}H]RHM-1 had a higher affinity [dissociation constant (K_d) = 0.66 nM] for σ_2 receptors than [^{3}H]RHM-2 (K_d = 19.48 nM). The [^{3}H]RHM-1 σ_2 receptor densities (B_{max}) for rat liver, MDA-MB human breast tumors, and EMT mouse breast tumors were found to be 1,099 ± 67, 1,820 ± 70, and 2,290 ± 30 fmol/mg protein, respectively.

Animal Studies

Rodents

[PubMed]

Tu et al. (9) performed biodistribution studies in EMT-6 tumor-bearing mice. Their studies showed the highest accumulation of radioactivity in the tumors with [^{11}C]RHM-1 compared with three other ^{11}C-labeled RHM-1 analogs. Tumor accumulation of [^{11}C]RHM-1 was 4.22% injected dose (% ID)/g at 5 min, 2.35% ID/g at 30 min, and 1.32% ID/g at 60 min after injection. The liver and kidneys showed higher uptake than the tumors with a rapid clearance. Coinjection of [^{11}C]RHM-1 with 1 mg/kg YUN 143 (a σ_2 and σ_1 high-affinity ligand) decreased the tumor/blood, tumor/lung, tumor/muscle, and tumor/fat ratios by 18–46% at 30 min. A study was also conducted comparing the tumor uptake and tumor/tissue ratios of [^{11}C]RHM-1 against 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT), a radiolabeled nucleoside analog for measuring tumor proliferation. It was found that [^{18}F]FLT had a higher tumor uptake (approximately 5.75% ID/g) than [^{11}C]RHM-1 (approximately 2.25% ID/g) at 30 min. However, [^{11}C]RHM-1 had either similar (lung, fat) or better (blood, muscle) tumor/tissue ratios than [^{18}F]FLT in the tissues that are important for breast tumor imaging.

Other Non-Primate Mammals

[PubMed]

No relevant publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

CA 102869

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