[7-*methyl*-^{11}C]-(*E*)-8-(3,4,5-Trimethoxystyryl)-1,3,7-trimethylxanthine

[^{11}C]TMSX

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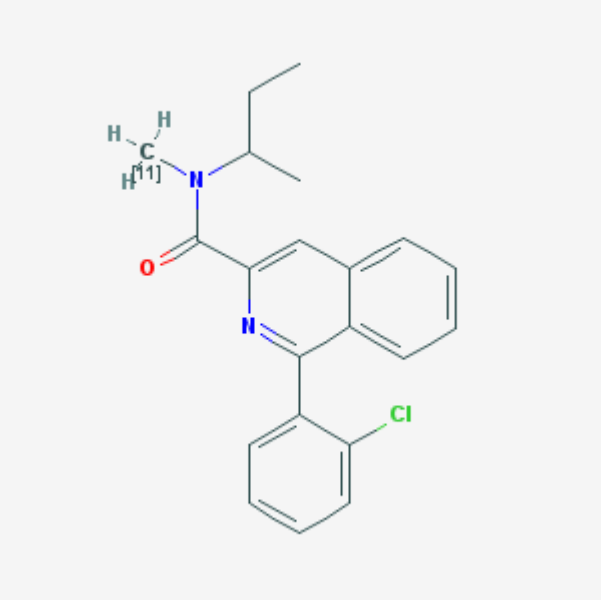
Chemical name:	[7-*methyl*-^{11}C]-(*E*)-8-(3,4,5-Trimethoxystyryl)-1,3,7-trimethylxanthine
Abbreviated name:	[^{11}C]TMSX
Synonym:	[^{11}C]KF18446
Agent category:	Compound
Target:	Adenosine A_{2A} receptor
Target category:	Receptor
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

Adenosine is an endogenous nucleoside that modulates a number of physiologic functions in the central nervous system (CNS) and in peripheral organs such as the heart, kidney, and muscle (1, 2). The effect is mediated by two major subtypes of receptors (A_1 and A_{2A} receptors) and two minor subtypes (A_{2B} and A_3). In the CNS, A_1 receptors are present both pre- and postsynaptically in the hippocampus, cerebral cortex, thalamus, striatum, and cerebellum. A_{2A} receptors are highly concentrated and co-localized with dopamine D_1 and D_2 receptors in the striatum, nucleus accumbens, and olfactory tubercle. A_{2A} receptors are also present in low amounts in the hippocampus and cortex. A_{2B} receptors are widely distributed, but the density is higher in the gastrointestinal tract. A_3 receptors are also widely distributed but with higher density in the testis. A_1 and A_3 receptors mediate inhibition of adenylyl cyclase, whereas A_{2A} and A_{2B} receptors mediate stimulation. Changes in the adenosine receptor functions are implicated in epilepsy, ischemic cerebral stroke, movement disorders, sleep disorders, and psychiatric disorders (3-5).

A_{2A} receptors have been studied *in vivo* by positron emission tomography (PET) using [7-*methyl*-^{11}C]-(*E*)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine ([^{11}C]TMSX), a methylxanthine analog of KF17387 with selective A_{2A} antagonistic activity (6). TMSX showed better selectivity for A_{2A} over A_1 receptors than KF17387 and had little affinity in various neuroreceptor-binding assays (7). [^{11}C]TMSX is being developed as a PET agent for the non-invasive study of A_{2A} receptors in the human brain and heart.

Synthesis

[PubMed]

In the report by Ishiwata et al. (8), [^{11}C]TMSX was synthesized by alkylation of the 7-desmethyl precursor ((*E*)-8-(3,4,5-trimethoxystyryl)-1,3-dimethylxanthine) with [^{11}C]methyl iodide. Purification by high-performance liquid chromatography (HPLC) provided a decay-corrected radiochemical yield of 25-46%, radiochemical purity >99%, and specific activity of 10-72 GBq/μmol (0.27-1.95 Ci/μmol) in 20-25 min.

Kawamura et al. (9) described the synthesis of [^{11}C]TMSX from the desmethyl precursor with [^{11}C]methyl triflate in the presence of Cs_2CO_3. This procedure provided improved radiochemical yield (decay-corrected) of 55.3 ± 5.2% based on [^{11}C]methyl triflate. No time of synthesis or specific activity was reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In the study by Ishiwata et al. (8), the K_i values of TMSX and KF17837 were 5.9 and 1.0 nM, respectively, for the A_{2A} receptors and 1,600 and 62 nM for the A_1 receptors. Hence, TMSX showed better selectivity for A_{2A} over A_1 receptors than KF17387. *In vitro* autoradiography (ARG) studies of brain sections with [^{11}C]TMSX showed high binding in the caudate putamen, nucleus accumbens, and olfactory tubercle with a striatum/cortex ratio of 8.4 ± 2.2. TMSX (20 μM) blocked 91% of [^{11}C]TMSX binding in the striatum but only 54% in the cortex. Saturation binding experiments of [^{11}C]TMSX in the rat striatum and cortex gave estimated K_d values of 9.8 and 16.4 nM, with B_{max} values of 170 and 33 fmol/mm^3 tissue, respectively (7).

Animal Studies

Rodents

[PubMed]

Biodistribution studies in normal mice showed high initial accumulation of radioactivity in the liver, followed by the kidney (12.08% injected dose (ID)/g), heart (10.94% ID/g), liver (4.42% ID/g), pancreas (4.23%ID/g), and lung (3.92% ID/g) at 1 min after injection of [^{11}C]TMSX (10). The levels of radioactivity were low in the brain (2.49% ID/g) and blood (1.58% ID/g). Radioactivity levels decreased gradually in all studied organs, with the exception of the liver, which showed an increase for the first 15 min followed by a gradual decrease. E*x vivo* ARG indicated that uptake of [^{11}C]TMSX was higher in the striatum than the cortex and cerebellum with a striatum/cortex ratio of 3.16 ±0.24 (8). This high, selective binding of [^{11}C]TMSX in the striatum was also confirmed by *in vitro* ARG and *iv vivo* regional brain distribution studies. Coadiministration of the A_{2A} antagonist KF17837, but not the A_1 antagonist KF15372, decreased the accumulation in the brain in a dose-dependent manner at 15 min post injection. Pretreatment with 10 and 100 mg/kg theophylline (a low-affinity adenosine antagonist) 15 min before [^{11}C]TMSX injection in mice significantly reduced striatal accumulation. About 80% and >98% of radioactivity in the plasma and striatum, respectively, was intact [^{11}C]TMSX at 30 min post injection.

Ishiwata et al. (11) reported *ex vivo* ARG studies in the rat globus pallidus. The highest uptake by the globus pallidus was for [^{11}C]SCH 23390 (dopamine D_1 receptor) followed by [^{18}F]fluorodeoxyglucose (FDG), [^{11}C]TMSX, and [^{11}C]raclopride (dopamine D_2 receptor). Receptor-specific uptake by the globus pallidus was observed for [^{11}C]TMSX and [^{11}C]SCH 23390, but not for [^{11}C]raclopride. The globus pallidus/striatum uptake ratios for FDG and [^{11}C]TMSX were ~0.6, which was twice as large as that for [^{11}C]SCH 23390. In a rat model of degeneration of gamma-aminobutyric acid-ergic-enkephalin neurons induced by intrastriatal injection of quinolinic acid, the accumulation and binding potentials of [^{11}C]TMSX and [^{11}C]raclopride in the lesioned striatum were remarkably reduced but were higher than the values for [^{11}C]SCH 23390 (11, 12).

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

Using PET, Ishiwata et al. (8) obtained serial brain scans in 1 monkey after injection of 102 MBq (2.8 mCi) of [^{11}C]TMSX. The accumulation of radioactivity in the striatum peaked at 5-10 min and then decreased for the final 60 min of study. The uptake was the highest in the striatum, followed by the thalamus, cerebellum, and cortex. The striatum/cortex and striatum/cerebellum ratios gradually increased from 1.3 and 1.2, respectively, at 5 min to 1.56 and 1.46 at 60 min.

Human Studies

[PubMed]

Ishiwata et al. (13) reported on PET myocardial imaging in 1 healthy volunteer after injection of 590 MBq (16 mCi) of [^{11}C]TMSX. The levels in the left ventricular wall, left ventricular anterior wall, and interventricular septum increased during the first 3 min after injection and then decreased gradually. In contrast, the radioactivity in the lung decreased rapidly. The fraction of unchanged [^{11}C]TMSX in blood samples, as determined by HPLC, was 97, 94, and 95% at 10, 30, and 60 min, respectively. In other studies of 2 subjects, infusion of theophylline (3.3 mg/kg) reduced the distribution volumes (DVs; baseline values, 3.62-3.73) of the three heart regions by 18-22% as determined by Logan analysis (14). The DV (1.57) of the brachii muscle was reduced by 10%. The A_{2A} receptors have also been preliminarily visualized in human brain with relatively high DVs in the caudate (1.72) and putamen (1.72), followed by the thalamus (1.64), cerebellum (1.52), brainstem (1.42), and cerebral cortex (1.26) (15). Mishina et al. (16) was used a two-tissue, three-compartment model to estimate the distribution of A_{2A} receptors in the brain (n = 5) using metabolite-correction arterial input function. The binding potential (BP) was the largest in the anterior (1.25) and posterior putamen (1.20), followed by la the head of caudate nucleus (1.05), thalamus (1.03), and frontal cortex lobe (0.46). On the other hand, Naganawa et al. (17) showed that Logan plot estimated BPs matching those derived from compartment analysis (n = 5) with or without arterial blood sampling. Without the metabolite correction, the estimate of BP underestimated the true value by only 5%. Internal dosimetry data for [^{11}C]TMSX in humans are not available in the literature.

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