1(*trans*-[^{123}I]Iodopropen-2-yl)-4-[(4-cyanophenoxy)methyl]piperidine

[^{123}I]TPCNE

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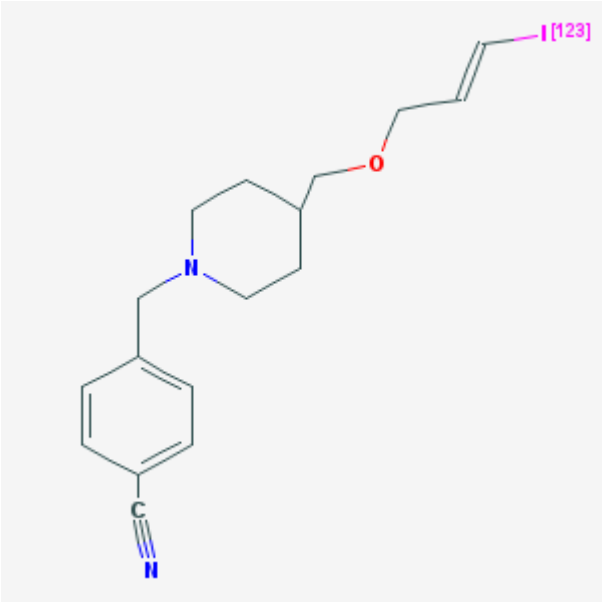
Chemical name:	1(*trans*-[^{123}I]Iodopropen-2-yl)-4-[(4-cyanophenoxy)methyl]piperidine
Abbreviated name:	[^{123}I]TPCNE
Synonym:	[^{123}I]1-(4-Cyanobenzyl)-4-[[(*trans*-iodopropen-2-yl)oxy]methyl]piperidine
Agent Category:	Compound
Target:	Sigma (σ) receptors
Target Category:	Receptor binding
Method of detection:	Single photon emission computed tomography (SPECT)
Source of signal/ contrast:	^{123}I
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



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Background

[PubMed]

1(*trans*-[^{123}I]Iodopropen-2-yl)-4-[(4-cyanophenoxy)methyl]piperidine ([^{123}I]TPCNE) is a radioligand developed for single photon emission computed tomography (SPECT) imaging of the sigma (σ) receptors (1, 2). [^{123}I]TPCNE is a highly selective σ_1 receptor radioligand labeled with ^{123}I, a gamma emitter with a physical half-life ($t_{½}$) of 13.2 h.

The σ receptors are functional, membrane-bound, G-protein–coupled receptors that are distributed in the central nervous system (CNS) and peripheral organs (3). The CNS σ receptors are unique binding sites related to higher brain functions (4). They are distinct from opiate and phencyclidine binding sites. There are at least two subtypes of σ receptors: σ_1 and σ_2 receptors. The precise mechanism of the functional response of these receptors is not entirely known. These receptors appear to be involved in numerous pharmacological and physiological functions, and they also modulate a number of central neurotransmitter systems, including noradrenergic, glutamatergic, and dopaminergic systems. Phencyclidine and derivatives, cocaine and derivatives, some neuroleptics, atypical antipsychotic agents, and other chemically unrelated compounds are able to bind to the σ receptor sites. Studies have shown that these receptors may play a role in the pathogenesis of psychiatric disorders (5, 6). These receptors are also expressed on a number of human and murine tumors (7).

The σ_1 receptor subtypes have a molecular mass of ≈25 kDa, and through the process of cloning they have shown a 30% sequence homology with the yeast C89-C7 sterol isomerase (3, 8, 9). The σ_2 receptor subtypes have a molecular weight of ≈21.5 kDa, and they have not been cloned. The σ_1 receptors are thought to be involved in certain neuropsychiatric disorders, and the σ_2 receptors are implicated in malignant neoplastic diseases. Because of these effects, σ receptor ligands may be useful for detection and treatment in neurology and oncology. A number of ligands for these receptors have been labeled with radionuclides for SPECT and positron emission tomography (PET) imaging to map their *in vivo* brain distribution and expression on tumors (10). Watanabe et al. (11) showed that a tritiated compound, [^{3}H]DuP 734, had high affinity and selectivity for σ receptors and good brain uptake in mice. However, this compound also had high affinity for serotonin ($5HT_2$) receptors *in vitro*. Gilligan et al. (12) studied the structure-activity relationships of a series of more selective analogs that included 1-benzyl-4-[[(cyclopropylmethyl)oxy]methyl]piperidine. The study showed that a wide variety of lipophilic groups could be attached to the ether linkage without a significant effect on the σ receptor affinity. On the basis of this finding, Waterhouse et al. (2) proposed that the cyclopropylmethyl group could be replaced by a radioiodinated iodopropenyl group to provide a radioligand for σ receptor imaging. [^{123}I]TPCNE was designed and synthesized from this concept with an additional cyano group added to the aromatic ring to help offset the increased lipophilicity induced by the radioactive iodine atom.

Synthesis

[PubMed]

Waterhouse et al. (2) described the synthesis of a vinyl organostannane precursor for [^{123}I]TPCNE radiolabeling from 4-hydroxymethylpiperidine. The radioligand was then synthesized by electrophilic radioiododestannylation of the tributyltin precursor at acidic pH using chloramine-T dehydrate as the oxidant. Briefly, 4-hydroxymethylpiperidine was alkylated by reacting with 4-cyanobenzyl bromide in dichloromethane and potassium carbonate to give 1-(4-cyanobenzyl)-4-hydroxymethylpiperidine (58% yield). This sodium alkoxide salt was reacted with propargyl bromide in tetrahydrofuran and sodium hydride to produce a propargyl ether, 1-(4-cyanobenzyl)-4-[[(propargyl)oxy]methyl]piperidine (78% yield). This was then reacted with tri-*n*-butyltin hydride in the presence of a radical initiator to form the trans-vinyl stannane precursor 1-(4-cyanobenzyl)-4-[[(*trans*-tri-*n*-butyltinpropen-2-yl)-oxy]methyl]piperidine (71% yield). In the radiolabeling procedure, chloramine-T dissolved in methanol and water was added to sodium [^{123}I]iodide ([^{123}I]NaI) in sodium hydroxide solution acidified by acetic acid. The precursor was added immediately, and the radiolabeling was allowed to proceed for 1 min before quenching with sodium metasulfite. The radiolabeled ligand was purified by high-performance liquid chromatography (HPLC). The radiochemical yield was 68.4 ± 5.1% (n = 5) at the end of synthesis, and the radiochemical purity was >99%. The specific activity was determined to be >77,000 MBq/μmol (2,100 mCi/μmol).

Stone et al. (1) reported that the use of hydrogen peroxide (H_2O_2) as the oxidant to reduce the amount of precursor from 1 mg to 50 μg improved radiolabeling in human studies. In this method, [^{123}I]NaI was first acidified by hydrochloric acid. The tributyltin precursor dissolved in ethanol and H_2O_2 were added to the [^{123}I]NaI solution. The resulting radiolabeled ligand was purified by HPLC. To use this radioligand in humans, [^{123}I]TPCNE was reformulated by extraction with a C18 cartridge and sterilization by filtration. The product was analyzed before injection into humans. The final radiochemical yield was 50–55%. The specific activity was >58 GBq/μmol (1.57 Ci/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Waterhouse et al. (2) determined the lipophilicity of TPCNE by the HPLC method using standards of known log *P* values. The log $P_{7.5}$ value of TPCNE was 3.24. *In vitro* receptor competitive binding assays were performed by the NIMH/NovaScreen Discovery & Development Program to determine the affinity and specificity of [^{123}I]TPCNE. The inhibition constant (K_i) values of TPCNE were 0.38 nM and 21.3 nM for σ_1 and σ_2, respectively. The K_i σ_1/σ_2 ratio was 0.02. The affinity of TPCNE to $5HT_2$ receptors was negligible (K_i >10,000 nM).

Animal Studies

Rodents

[PubMed]

Waterhouse et al. (2) examined the biodistribution of [^{123}I]TPCNE from 10 min to 240 min in rats (n = 3). There was a prolonged retention of radioactivity in the brain, heart, lungs, and other organs known to contain σ receptors. The radioactivity levels in the thyroid (unblocked) were relatively low, from 0.03 ± 0.00% injected dose/g (% ID/g) at 10 min after injection to 0.26 ± 0.02% ID/g at 240 min after injection. This indicated a slow *in vivo* deiodination of [^{123}I]TPCNE. The radioactivity levels (% ID/g) in major organs at 20 min were 14.11 ± 1.98 (lungs), 1.57 ± 0.20 (heart), 1.40 ± 0.21 (kidney), 0.06 ± 0.01 (blood), and 0.10 ± 0.01 (liver). The radioactivity levels (% ID/g) in the brain at 20 min were 1.11 ± 0.14 (whole brain), 0.09 ± 0.02 (posterior cortex), 0.85 ± 0.16 (frontal cortex), 0.56 ± 0.12 (striatum), and 0.57 ± 0.10 (cerebellum). These levels increased to 1.49 ± 0.14 (whole brain), 1.14 ± 0.05 (posterior cortex), 1.02 ± 0.11 (frontal cortex), 0.74 ± 0.10 (striatum), and 0.75 ± 0.11 (cerebellum) at 240 min.

Specific binding studies were performed by giving unlabeled TPCNE, DuP 734 (σ, $5HT_2$), and haloperidol (dopamine D_2, σ) at a dose of 1 mg/kg at 5 min before the radioligand injection (10 μCi/rat) (2). The study reported that a significant reduction of radioactivity ($P < 0.01$) at 30 min after injection was observed in all brain regions and peripheral organs known to contain σ receptors. In the brain regions, the radioactivity levels were reduced by 50–80% ($P < 0.001$, extrapolation from Figure 4), with the biggest blocking effect by TPCNE, and the effect of DuP 734 was greater than that of haloperidol.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Human studies of [^{123}I]TPCNE were performed in 7 healthy volunteers (1). Each subject received a single bolus i.v. dose of ≈180 MBq (5 mCi) of [^{123}I]TPCNE and scanned from the time of injection until 3–3.5 h after injection. Whole-body imaging revealed that the radioactivity distribution pattern was different from rats. In humans, the liver and brain

showed the greatest radioactivity level. Radioactivity uptake was rapid in the brain with a widespread distribution. The brain uptake kinetics appeared to be best described by an irreversible model. The total brain radioactivity reached ≈8.7% ID in 30 min and remained almost constant for 3–3.5 h. The posterior cingulate had the highest radioactivity level with an irreversible model effective uptake rate constant (*K*) of ≈0.33 (estimated from Figure 7), which was proportional to regional binding. The cerebellum and thalamus had a similar *K* value of ≈0.30. The striatum and white matter had *K* values of ≈0.26 and ≈0.13, respectively. When subjects received an oral dose of 2.5 mg of haloperidol ≈1 h before the study, there was a clear washout in all brain regions. Displaceable [^{123}I]TPCNE binding was estimated to be 73% in the thalamus, 58% in the posterior cingulate, 42% in the cerebellum, and 20% in the white matter. The authors suggested that the binding distribution and kinetics of [^{123}I]TPCNE were similar to those of two other σ PET ligands, [^{18}F]FPS and [^{11}C]SA4503.

Arterial sampling was performed during the scans and the in vivo metabolism of [^{123}I]TPCNE was determined by HPLC analysis of the plasma samples (1). The radioactivity in the blood peaked at ≈45 s, and then a rapid clearance was observed. At 30 min, <1% of the peak radioactivity level was found. The metabolism study showed that ≈80% of [^{123}I]TPCNE remained unchanged at 67 min after injection. Only one labeled highly polar metabolite appeared at 45 min.

NIH Support

NIMH-2003.

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