^{131}I-Labeled [*Z*]-2-[4-(1,2-diphenyl-1-di-butenyl)-phenoxy]-*N*,*N*-dimethylethanamine

^{131}I-TAM

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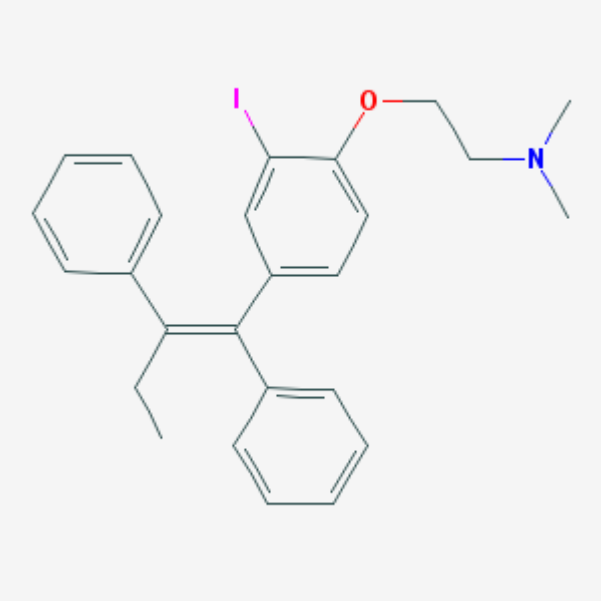
Created: July 6, 2009; Updated: August 18, 2009.

Chemical name:	^{131}I-Labeled [*Z*]-2-[4-(1,2-diphenyl-1-di-butenyl)-phenoxy]-*N*,*N*-dimethylethanamine
Abbreviated name:	^{131}I-TAM
Synonym:	Tamoxifen
Agent Category:	Compound
Target:	Estrogen receptor (ER)
Target Category:	Receptor
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging
Source of signal / contrast:	^{131}I
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Tamoxifen ([*Z*]-2-[4-(1,2-diphenyl-1-di-butenyl)-phenoxy]-*N*,*N*-dimethylethanamine (TAM)) is the first selective estrogen receptor (ER) modulator with extensive investigation for its anticancer properties (1, 2). The ^{131}I-labeled form of TAM (^{131}I-TAM) was developed to study the tumor response to antiestrogenic treatment and the ER expression in tumors and critical normal tissues (3).

TAM as first approved by the United States Food and Drug Administration in the 1970s for use in breast cancer treatment. Currently, it is widely used for the treatment of both early and advanced ER-positive breast cancer, as well as for the prevention of breast cancer in high-risk women (1, 4, 5). TAM itself is a prodrug, having relatively little affinity to ER. It is metabolized in the liver, mainly by the CYP2D6 and CYP3A4 enzymes (5, 6). Active metabolites such as 4-hydroxytamoxifen and N-desmethyl-4-hydroxytamoxifen have 30–100 times more affinity with the ER than TAM itself. These metabolites compete with estrogen for binding to ER and form a nuclear complex that inhibits DNA synthesis and blocks estrogen effects (5, 6). As a result, tumor cells stop proliferating and remain in the G_0 and G_1 phases of the cell cycle. In combination with other therapeutic agents or alone, TAM has also been shown to be antiangiogenic, which is, at least in part, independent of its ER-antagonist properties (7). TAM also has a number of other beneficial properties. For example, TAM lowers low-density lipoprotein cholesterol levels, increases bone density in postmenopausal women, and is effective against infertility in women with anovulatory disorders. In men, TAM is used to treat breast cancer, and it is also used to treat gynecomastia that arises from anti-androgen treatment in patients with prostate cancer.

TAM has some side effects. It blocks the estrogen effects on mammary epithelial cells, but it mimics the estrogen actions in other tissues (2). The result of such selective effects on the uterus is stimulated proliferation of the endometrium (8). Each year, the risk of developing endometrial cancer is ~2‰ in women taking TAM compared with ~1‰ in women taking placebo (9). TAM also slightly increases the risk of developing uterine sarcoma. The other side effects include blood clots, strokes, cataracts, and symptoms of menopause. To maintain the beneficial properties without sharing the potentially harmful effects of TAM, a number of derivatives have been developed (2). However, these derivatives demonstrate differing amounts of success. Their ability to inhibit cancer ranges widely.

NLM Citation: Shan L. ^{131}I-Labeled [*Z*]-2-[4-(1,2-diphenyl-1-di-butenyl)-phenoxy]-*N*,*N*-dimethylethanamine. 2009 Jul 6 [Updated 2009 Aug 18]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Studies of tissue-based pharmacokinetics of TAM and its derivatives provide direct concentration-effect relationships in tumors and critical normal tissues, thus providing a more rational basis for the evaluation of new compounds and tumor response to treatment (10, 11). Generally speaking, the study results are controversial. Imaging studies have shown that [^{18}F]fluorotamoxifen is useful in predicting the effect of TAM therapy in patients with ER-positive breast cancer (12, 13). The ^{123}I-trans-Z-iodomethyl-*N*,*N*-diethyltamoxifen has also been shown to be preferentially taken up by ER-positive tumors in patients with untreated primary breast cancer (14, 15). On the contrary, studies have failed to show the suitability for tumor localization of some derivatives, such as ^{131}I- and ^{99m}Tc-labeled geometrical isomers (*E* and *Z*) of the aminotamoxifen, ^{125}I-idoxifene and ^{11}C-toremifene (16-19). Recently, Muftuler et al. produced ^{131}I-TAM and investigated its biodistribution in rats. Their study demonstrated that the biodistribution of ^{131}I-TAM is ER-specific (3).

Synthesis

[PubMed]

The synthesis of ^{131}I-TAM was based on the oxidation of iodide by iodogen as described in detail by Muftuler et al. (3). Briefly, four reaction vials of iodogen in CH_2Cl_2 solution (100 µg (578.6 nmol/ml)) were prepared and evaporated separately to form a thin solid layer of iodogen on the wall of each reaction vial. TAM (1 ml, 0.54 µmol/ml) and Na^{131}I (0.4 ml, 185 MBq (5 mCi)) were added to the first reaction vial. The mixture (pH 8.0) was gently mixed and incubated for 5 min at room temperature. The reaction solution was then successively transferred to the other three vials with incubation in each vial for 5 min at room temperature. As the final step, 0.1 ml Na_2SO_3 solution (0.1 N) was added to the last vial to reduce the unincorporated iodine. Radioelectrophoresis revealed that ^{131}I-TAM had a neutral structure at room temperature. Structural analysis showed that stable ^{127}I was attached to TAM in the ortho position of the aromatic ring containing the ether group. The product yield and the specific activity of ^{131}I-TAM were 88.56 ± 3.10% and 0.53 GBq/µmol (14.32 mCi/µmol), respectively (n = 8 replicates). The purity of ^{131}I-TAM was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The stability of ^{131}I-TAM was analyzed *in vitro* by incubation with human serum at 37°C for different times. It was shown that ~45% of the ^{131}I-TAM existed as an intact complex in human serum within 24 h.

Animal Studies

Rodents

[PubMed]

Muftuler et al. investigated the biodistribution of ^{131}I-TAM in healthy female Albino Wistar rats weighing 130–180 g (3). A total of 7.4 MBq (200 μCi) ^{131}I-TAM was given to each rat *via* the tail vein. The animals were euthanized at 30, 60, and 180 min (n = 3 animals/time point), and the accumulated radioactivity in each organ was measured. To block the iodine uptake by the thyroid gland, potassium iodide was added to the animals' drinking water. To determine whether the uptake of ^{131}I-TAM in tissues was ER-specific, an ER-blocking experiment was performed by administration of 4.4 μg (11.84 nmol) of the non-labeled TAM to each rat through the tail vein 15 min before the injection of ^{131}I-TAM. The non-labeled TAM was prepared under the same conditions as the ^{131}I-TAM.

The detailed biodistribution data were reported by Muftuler et al. (Table 3) (3). In animals without ER blocking, uptake of ^{131}I-TAM in all ER-rich tissues was considerably high at the time points examined. Analysis of the blood samples suggested that the biological half-life of ^{131}I-TAM was ~11 h, which was shorter than the physical half-life of ^{131}I (8.02 days). In the uterus, the ^{131}I-TAM reached the maximum level of accumulation (15.66 ± 0.76% injected dose per gram (ID/g)) within 30 min after injection, and it remained in the uterus within 180 min. Uptake of the ^{131}I-TAM in this study was faster than that of estrogen derivatives in other reports (3). The uterus/blood and uterus/muscle uptake ratios at 30 min were ~1 and ~3, respectively. The ^{131}I-TAM level in the uterus was three times higher in animals without ER blocking than in animals with ER blocking (5.74 ± 0.48% ID/g). The kidney, as the primary organ of metabolism and excretion of estrogen, showed a high uptake of ^{131}I-TAM. The uptake level increased within 60 min (22.83 ± 4.86% ID/g at 60 min) after injection, followed by a rapid decrease. The lung is known to have a specific affinity for all kinds of amines. Consistent with that, a high level of ^{131}I-TAM uptake (15.81 ± 3.3% ID/g at 30 min) was observed in the lung without ER blocking. The ^{131}I-TAM level at 180 min was two times higher in the lung without ER blocking (11.06 ± 3.43% ID/g) than in the lung with blocking (4.04 ± 1.68% ID/g). Differences in tissue uptake levels between animals without and with ER blocking were also significant ($P < 0.05$) for heart, liver, kidneys, small intestine, large intestine, muscle, and fat tissue.

An imaging study was also performed with female rats weighing 150–200 g (n = 6) with the use of an e-Cam Single Camera equipped with a low-energy high-resolution collimator (3).. ^{131}I-TAM (~9.6 MBq (~260 μCi)/rat) was administered *via* the tail vein. To block the ER, 10 μg (26.92 nmol) of non-labeled TAM was given to each rat through the tail vein 15 min before injection with ^{131}I-TAM. Imaging showed that the stomach had the highest uptake among all organs. The uptake level increased over time. The ratio of radioactivity in the stomach without ER blocking to radioactivity in the stomach with ER blocking was ~1.5 at both 30 and 60 min. The uptake levels in the liver and gastrointestinal tract were low. Detailed imaging data were not shown for other organs, including uterus and breast.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

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