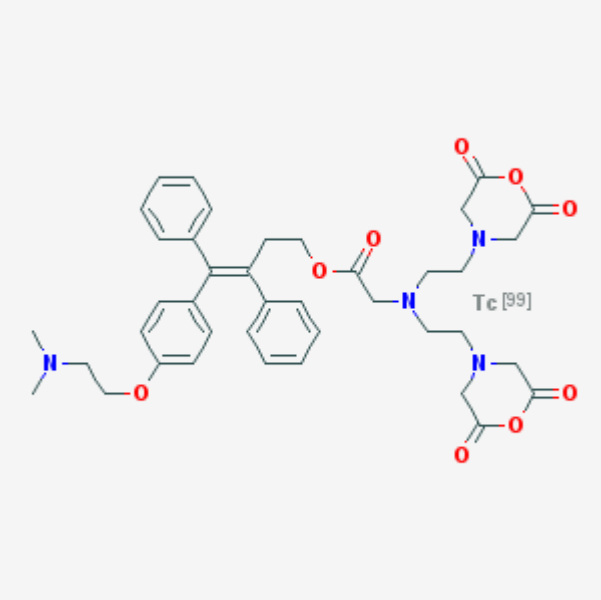
^{99m}Tc-(3Z)-4-{4-[2-(Dimethylamino)ethoxy]phenyl}-3,4-diphenylbut-3-en-1-yl*N*,*N*-bis[2-(2,6-dioxomorpholin-4-yl)ethyl]glycinate

^{99m}Tc-DTPA-TOR

Kam Leung, PhD[1]

Created: May 25, 2010; Updated: July 7, 2010.

Chemical name:	^{99m}Tc-(3Z)-4-{4-[2-(Dimethylamino)ethoxy]phenyl}-3,4-diphenylbut-3-en-1-yl*N*,*N*-bis[2-(2,6-dioxomorpholin-4-yl)ethyl]glycinate
Abbreviated name:	^{99m}Tc-DTPA-TOR, ^{99m}Tc-TOR-DTPA
Synonym:	
Agent category:	Compound
Target:	Estrogen receptor
Target category:	Receptor
Method of detection:	Single-photon emission computed tomography (SPECT), gamma planar imaging
Source of signal:	^{99m}Tc
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

Background

[PubMed]

Estrogens and progestins are endogenous hormones that produce many physiological effects (1). Estrogens act primarily by regulating gene expression. Estrogen receptors (ERs) are found in the cytoplasm and nucleus of cells of the female reproductive tract, breast, pituitary, hypothalamus, bone, liver, and other tissues, and also in various tissues in men. Estrogens are lipophilic in that they enter the cell passively by diffusion through the cellular membrane. Estrogens bind to ERs that are present in the cytoplasm and the complexes are transported into the nucleus.

Breast cancer is the most common malignancy in women. Approximately 33% of women who have this disease will die of disseminated breast cancer. The growth of breast epithelial cells is dependent on estrogen stimulation, which induces progestin receptor expression. Two thirds of breast carcinomas express ERs. It has also been established that the ER status of the tumor is an important prognostic indicator in breast cancer (2). Women with ER-positive breast tumors have a better prognosis than women with ER-negative tumors in terms of responsiveness to anti-estrogen treatment. ER content in breast cancer is assessed *in vitro* with receptor binding assays, which suffer from interassay variability, are limited by intrinsic receptor heterogeneity of the tumor, and do not yield information on the ER density in metastases. 16α-[^{18}F]Fluoro-17β-estradiol ([^{18}F]FES) has been proven to be a valuable tracer for studies of the ER status of primary and metastatic breast cancer (3). However, [^{18}F]FES was cleared from the blood and was metabolized in 20 min with only 20% of [^{18}F]FES intact in a study of 15 breast cancer patients (4). Toremifene (TOR) is a chlorinated analog of tamoxifen (5, 6), which was first approved by the United States Food and Drug Administration in the 1970s for use in breast cancer treatment. TOR is primarily used in the treatment of patients with metastatic breast cancer (7). Yurt et al. (8) coupled diethylenetriamine pentaacetic acid (DTPA) to TOR to form (3Z)-4-{4-[2-(dimethylamino)ethoxy]phenyl}-3,4-diphenylbut-3-en-1-yl*N*,*N*-bis[2-(2,6-dioxomorpholin-4-yl)ethyl]glycinate (DTPA-TOR) and radiolabeled the DTPA-TOR with ^{99m}Tc. ^{99m}Tc-DTPA-TOR exhibited high breast tissue/background ratio in female rats.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (Estrogen receptor)

NLM Citation: Leung K. ^{99m}Tc-(3Z)-4-{4-[2-(Dimethylamino)ethoxy]phenyl}-3,4-diphenylbut-3-en-1-yl*N*,*N*-bis[2-(2,6-dioxomorpholin-4-yl)ethyl]glycinate. 2010 May 25 [Updated 2010 Jul 7]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

- Articles in OMIM
- Clinical trials (Toremifene)
- Drug information in FDA

Synthesis

[PubMed]

Yurt et al. (8) reported the radiolabeling of DTPA-TOR with ^{99m}Tc. DTPA-anhydride (0.12 mmol) was added to a solution of TOR (0.05 mmol) in acetone to produce DTPA-TOR. Mass spectroscopy showed that the agents bound in a ratio of one DTPA per TOR. The mixture was incubated for 12 h at room temperature. DTPA-TOR (0.1 mg) was mixed with 740 MBq (20 mCi) $^{99m}TcO_4^-$ and $SnCl_2$ (0.1 mg). The mixture was incubated for 25 min at room temperature. The ^{99m}Tc-labeling efficiency was ~80%, and the specific activity was ~15 MBq/nmol (0.4 mCi/nmol) at the time of injection.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

^{99m}Tc-DTPA-TOR exhibited an experimental log *P* value of -2.04 at pH 7.0 (8). ^{99m}Tc-DTPA-TOR was intact in human serum for up to 60 min of incubation at 37°C and was ~45% intact after 24 h.

Animal Studies

Rodents

[PubMed]

It was demonstrated that ^{99m}Tc-DTPA-TOR accumulation by target tissue (breast) in young female rats (n = 3/group) is highly specific (8). Rats were injected with ~30 MBq (0.8 mCi (5.7 nmol)) ^{99m}Tc-DTPA-TOR. The tissue accumulations were expressed as tissue/muscle ratios. The breast/muscle ratios were 1.6, 8.5, and 13.2 at 30, 60, and 240 min after injection, respectively. The ovary/muscle and uterus/muscle ratios were 3.9 and 3.3 at 240 min, respectively. The stomach (130.4), kidney (16.7), intestines (21.7–29.8), and urinary bladder (32.2) exhibited high tissue/muscle ratios at 240 min after injection. Pretreatment with 10-fold excess DTPA-TOR (57 nmol) showed significant inhibition (P < 0.05) of the breast/muscle ratios (88% at 60 min and 68% at 240 min after injection). However, little inhibition was observed in the uterus and ovary.

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.

References

1. Beato M., Klug J. *Steroid hormone receptors: an update.* Hum Reprod Update. 2000;6(3):225–36. PubMed PMID: 10874567.
2. Vollenweider-Zerargui L., Barrelet L., Wong Y., Lemarchand-Beraud T., Gomez F. *The predictive value of estrogen and progesterone receptors' concentrations on the clinical behavior of breast cancer in women. Clinical correlation on 547 patients.* Cancer. 1986;57(6):1171–80. PubMed PMID: 3943040.
3. Flanagan F.L., Dehdashti F., Siegel B.A. *PET in breast cancer.* Semin Nucl Med. 1998;28(4):290–302. PubMed PMID: 9800236.
4. Mankoff D.A., Tewson T.J., Eary J.F. *Analysis of blood clearance and labeled metabolites for the estrogen receptor tracer [F-18]-16 alpha-fluoroestradiol (FES).* Nucl Med Biol. 1997;24(4):341–8. PubMed PMID: 9257333.
5. da Costa G.G., Pereira P.C., Churchwell M.I., Beland F.A., Marques M.M. *DNA adduct formation in the livers of female Sprague-Dawley rats treated with toremifene or alpha-hydroxytoremifene.* Chem Res Toxicol. 2007;20(2):300–10. PubMed PMID: 17261033.
6. Kim S.Y., Suzuki N., Santosh Laxmi Y.R., Rieger R., Shibutani S. *Alpha-hydroxylation of tamoxifen and toremifene by human and rat cytochrome P450 3A subfamily enzymes.* Chem Res Toxicol. 2003;16(9):1138–44. PubMed PMID: 12971802.
7. Saeki T., Okita A., Aogi K., Kakishita T., Okita R., Taira N., Ohama Y., Takashima S., Nishikawa K. *Pharmacokinetic analysis of a combined chemoendocrine treatment with paclitaxel and toremifene for metastatic breast cancer.* Breast Cancer. 2009;16(2):113–20. PubMed PMID: 18936884.
8. Yurt A., Muftuler F.Z., Unak P., Yolcular S., Acar C., Enginar H. *Synthesis of a novel antiestrogen radioligand (99mTc-TOR-DTPA).* Cancer Biother Radiopharm. 2009;24(6):707–16. PubMed PMID: 20025551.
9. Federici L., Blondet C., Imperiale A., Sibilia J., Pasquali J.L., Pflumio F., Goichot B., Blaison G., Weber J.C., Christmann D., Constantinesco A., Andres E. *Value of (18)F-FDG-PET/CT in patients with fever of unknown origin and unexplained prolonged inflammatory syndrome: a single centre analysis experience.* Int J Clin Pract.64(1):55–60. PubMed PMID: 18479364.