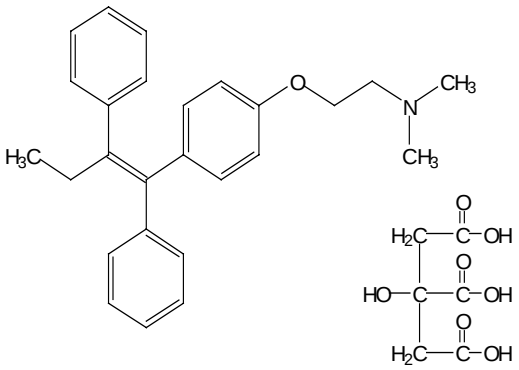
# ProductInformation

**TAMOXIFEN CITRATE**
**Sigma Prod. No. T9262**



**CAS NUMBER:** 54965-24-1
**SYNONYMS:** (Z)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine, 2-Hydroxy-1,2,3-Propanetricarboxylate (1:1);[1] trans-1-(p-ß-Dimethylaminoethoxyphenyl)-1,2-Diphenylbut-1-ene Citrate; Kessar; Tamofen; Terimon; ICI 46474; Z-Tamoxifen Citrate[2]

**PHYSICAL DESCRIPTION**

Appearance: a white powder.[3]
Melting Point: approx. 140-142°C[4]
Molecular formula: $C_{26}H_{29}NO.C_6H_8O_7$
Molecular weight: 563.6
E-isomer (cis-form) content: less than 0.5% (High Performance Liquid Chromatography, HPLC)[5]
$pK_a$: approx. 8.85[6]; approx. 6.9 (in Triton X-100)[7,8]

**METHOD OF PREPARATION:**

Tamoxifen citrate (TC) is synthetically prepared[5.] Synthetic methods for the preparation of Tamoxifen free base (Tam) have been reported.[4,9,10] Spectrophotometric methods for the determination of TC[11] including the use of Naphthalene Blue 12BR and Alizarine Red-S[12] have been reported. Methods for determination of the purity of TC or Tam by Gas Chromatography (GC), Mass Spectrometry (MS), HPLC, and Thin-Layer Chromatography (TLC) have been reported.[13-16] The GC-MS analysis of Tam and its metabolites in plasma[17] and the X-ray crystallographic structure of Tam have been reported.[18]

**STABILITY / STORAGE AS SUPPLIED:**

TC should be stable for at least two years when stored desiccated at 2-8°C in the dark.[3] TC is hygroscopic at high relative humidities and is sensitive to UV light.[4,5,9]

## SOLUBILITY / SOLUTION STABILITY:

The solubility in water is 0.3 mg/L at 20°C; the pH is approx. 3.0-3.5 at 20°C.[5] TC is soluble at 0.2 mg/ml in 0.02 N HCl, at 37°C.[6] TC is soluble in ethanol, methanol and slightly soluble in acetone and in chloroform;[4,19] solutions are sensitive to UV light[4,9] (photolysis products are the E isomer and the phenanthrenes formed by cyclization of both isomers[9]). TC has been solubilized in methanol at 50 mg/ml (some heat may be needed) and in ethanol at 10 mg/ml with sonication; it is insoluble in ethanol at 50 mg/ml.[3] Preparation and storage of a sterile 10 mg/ml solution of TC in absolute ethanol at 4°C was reported.[20] Injections of solutions of 20 mg/kg TC each in ethanol[21] and in ethanol:phosphate buffer (2:8, v/v)[22] were given to rats. A 4.0 mM solution in DMSO can be prepared[7]; DMSO solutions were stored at -20°C.[23] Store solutions in the dark.

## USAGE / APPLICATIONS (Tam/TC):

TC has been shown to protect bone from estrogen-deficiency bone loss and lower plasma cholesterol in the rat.[21] TC (10 μM) exhibited pH dependent fungicidal activity (optimal, pH 7.5) against yeast cells of C. albicans.[7] TC has been implicated in liver carcinogenesis in rats.[22] A possible mechanism for the DNA adduct formation leading to carcinogenesis was reported.[24] TC (100 nM) combined with vinblastine was cytotoxic to both rat prostate adenocarcinoma cell line and human prostate cancer cells.[20] Flow cytometric analysis of DNA content and BrdU (5-bromo-2'-deoxuridine) labeling in MCF-7 (estrogen-responsive human clonal breast cancer cell line) cells have shown that the effect of Tam on the growth of estrogen-dependent cells in culture may be due to accumulation of cells in $G_1$ phase (before onset of S-phase) and the exit of some cells from the cycling compartment in the cell cycle progress.[25] The mechanism of TC/Tam action may involve interactions in the signaling transduction pathway: Tam is a competitive inhibitor of calmodulin-stimulated phosphodiesterase activity; molecular interactions between Tam and calmodulin were reported.[26] Tam and TC inhibits protein kinase C (PKC) activity ($IC_{50}$=50-200 μM depending on assay conditions)[27] in MCF-7 cells[28] and in rat brain ($IC_{50}$=100 μM).[23] Both inhibitions were dependent on the concentration of phospholipids. Tam inhibits both calmodulin-dependent and calmodulin-independent $Ca^{2+}$-, $Mg^{2+}$-ATPase. Other actions of TC/Tam are: reduction of plasma levels of insulin-like growth factor; induction of cells surrounding cancer cells to secrete transforming growth factor ß; and inhibition of membrane lipid peroxidation probably by decreasing membrane fluidity.[29] TC is reported to be a carcinogen and teratogen in animals.[19]

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**GENERAL NOTES:**

TC is a nonsteroidal triphenylethylene derivative that inhibits the action of estrogens and has actions similar to those of clomiphene citrate. It is a mixed estrogen agonist and antagonist which suppresses tumor growth[21] (the pharmaceutical drug is widely used in the treatment of hormone-sensitive breast cancer). Mechanism of action studies indicate that TC binds to estrogen receptors forming a TC-17ß-estradiol receptor complex which binds to the nuclear binding sites on the genome. TC binds to cytoplasm estrogen receptors in breast, anterior pituitary and prostate tissues.[20] The binding prevents the receptors from recycling thereby reducing the number of receptor molecules available for subsequent 17-ß-estradiol activity.[30,31] In cytosols from human breast adrenocarcinomas, Tam competes with estradiol for estrogen receptor protein[6]. This may represent only the initial steps in the complex mechanism of action. Additional interactions include nuclear binding, effects on RNA polymerase, receptor transformation and location and effects on DNA synthesis, and others.[32] The biochemistry, including uptake into target tissues, receptor binding, effects on gene transcription; pharmacology of TC and Tam and its metabolites, 4'-hydroxytamoxifen, N-desmethyltamoxifen and others; effects in tumor models; metabolism, pharmacokinetics, mechanism of antitumor activity and drug resistance have been reported.[9,16,33-36] Studies of the conformation of Tam to help explain the molecular interactions with estrogen receptors were reported.[37] TC is a possible carcinogen and possible teratogen. See information on product label and on the Sigma Material Safety Data Sheet (MSDS) for handling information.

**REFERENCES:**


1. Chemical Abstracts Registry data, American Chemical Society.
2. Sigma Material Safety Data Sheet
3. Sigma Quality Control Data
4. *The Merck Index*, 12th, #9216, (1996).
5. Supplier Data
6. *Physicians' Desk Reference*, 47th ed., 1126, (1993).
7. Beggs, W.H.J., *Antimicrob. Chemother.* 37, 841, (1996).
8. Bottega, R. and Epand, R.M., *Biochem.* 31, 9025, (1992).
9. Furr, B.J.A. and Jordan, V.C., *Pharmacol. Ther.* 25, 127, (1984).
10. Al-Hassan, M.I., *Synth. Commun.* 17, 1247, (1987).
11. Sastry, C.S.P. et al., *Talanta* 42, 1479, (1995).
12. Sastry, C.S.P. and Lingeswara Rao, J.S.V.M., *Indian J. Pharm. Sci.* 57, 133, (1995).
13. Berthou, F. and Dreano, Y., *J. Chromatogr.* 616, 117, (1993).
14. Weir, P.J. et al., *J. Pharm. Biomed. Anal.* 7, 393, (1989).
15. Jalonen, H.G.J. *Pharm. Sci.* 77, 810, (1988).
16. Adam, H.K. Non-Steroidal Antioestrogens: *Mol. Pharmacol. Antitumor Act.*, eds. Sutherland, R.L. and Jordan, V.C., Academic, Sydney, Australia, 1981, 59 (review).
17. Murphy, C. et al., *J. Steroid Biochem.* 26, 547, (1987).
18. Precigoux, G. et al., *Acta Cryst.* B35:3070, (1979).
19. *Martindale, The Extra Pharmacopoeia*, 30th ed., 500, (1993).

**REFERENCES:** (continued)

20. Pienta, K.J. et al., *The Prostate* 26, 270, (1995).
21. Gold, E. et al., *Horm. Metab. Res.* 26, 100, (1994).
22. Han, X. and Liehr, J.G., *Cancer Res.* 52, 1360, (1992).
23. O'Brian, C.A. et al., *Cancer Res.* 45, 2462, (1985).
24. Kuramochi, H., *J. Med. Chem.* 39, 2877, (1996).
25. Danova, M. et al., *Annals N Y Acad. Sci.* 698, 174, (1993).
26. Edwards, K.J. et al., *J. Med. Chem.* 35, 2753, (1992).
27. Powis, G., *Trends Pharmacol. Sci*. 12, 188, (1991).
28. Issandou, M. et al., *Cancer Res.* 50, 5845, (1990).
29. Wiseman, H., *Methods Enzymol.* 234, 590, (1994).
30. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, Seventh ed., 1297, 1424, (1985).
31. Jordan, V.C. et al., *Mol. Cell. Endocrinol.* 7, 177, (1977).
32. Nicholson, R.I. and Griffiths, K., *Advances in Sex Hormone Res.* 4, 119, (1980).
33. Jordan, V.C., *Annu. Rev. Pharmacol. Toxicol.* 35, 195, (1995).
34. Lau, C.K. et al., *Proc. Natl. Acad. Sci.* USA, 88, 829, (1991).
35. Jordan, V.C. *Breast Cancer Res. Treat.* 2, 123, (1982) (review).
36. Buckley, M.M.T. and Goa, K.L., *Drugs* 37, 451, (1989) (review).
37. Duax, W.L. et al., *Environ. Health Perspect.* 61, 111, (1985).