ProductInformation

TAMOXIFEN FREE BASE
Sigma Prod. No. T5648

CAS NUMBER: 10540-29-1
SYNONYMS: (Z)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine[1]; ICI 47699; Trans-Tamoxifen; Z-Tamoxifen; (Z)-2-(p-(1,2-Diphenyl-1-Butenyl)-Phenoxy)-N,N-Dimethylethylamine[2]

PHYSICAL DESCRIPTION:

Appearance: a white to white with a yellow cast powder.[3]
Melting Point: approx. 96-98°C[4]
Molecular Formula: $C_{26}H_{29}NO$
Molecular Weight: 371.5
pK_a: approx. 8.85[5] and approx. 6.9 (in Triton X-100)[6,7]

METHOD OF PREPARATION:

Tamoxifen (Tam) is synthetically prepared.[8] Synthetic methods of preparation have been reported.[4,9,10] Spectrophotometric methods for the determination of Tamoxifen Citrate (TC)[11] including the use of naphthalene Blue 12BR and Alizarine Red-S[12] have been reported. Methods for determination of the purity by Gas Chromatography (GC), Mass Spectra (MS), High Performance Liquid Chromatography (HPLC), and Thin-Layer Chromatography (TLC) have been reported.[13-16] The GC-MS analysis of Tam and it metabolites in plasma[17] and the X-ray crystallographic structure of Tam have also been reported.[18]

STABILITY / STORAGE AS SUPPLIED:

Tam should be stable for at least two years when stored desiccated at 2-8°C in the dark.[3]

SOLUTION / SOLUTION STABILITY:

Tam is practically insoluble in water (solubility is <0.01%, 20°C). Tam is soluble in methanol, ethanol, 2-propanol[8] and in propylene glycol.[19] Tam solutions were prepared in DMSO (no stock concentration given)[20] and in chloroform at 50 mg/ml.[3] Solutions are sensitive to UV light. Photolysis products (reported for Tamoxifen Citrate, TC) are the E isomer and the phenanthrenes formed by cyclization of both isomers.[9] It is possible that solutions in DMSO may be stable when stored at -20°C in the dark (as with TC).[21]

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USAGE/APPLICATIONS (Tam,TC):

TC has been shown to protect bone from estrogen-deficiency bone loss and lower plasma cholesterol in the rat.[22] TC (10 μM) exhibited pH dependent fungicidal activity (optimal, pH 7.5) against yeast cells of C. albicans.[6] TC has been implicated in liver carcinogenesis in rats.[23] 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.[25] 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.[26] The mechanism of Tam or TC action may involve interactions in the signal transduction pathway: Tam is a competitive inhibitor of calmodulin-stimulated phosphodiesterase activity; molecular interactions between Tam and calmodulin were reported.[27] Tam and TC inhibit protein kinase C (PKC) activity (IC_{50}=50-200 μM depending on assay conditions)[28] in MCF-7 cells[20] and in rat brain (IC_{50}=100 μM).[21] 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 Tam/TC 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.[30]

GENERAL NOTES:

Tam 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[22] (the pharmaceutical drug is widely used in the treatment of hormone-sensitive breast cancer). Mechanism of action studies indicate that Tam binds to estrogen receptors forming a Tam-17ß-estradiol receptor complex which binds to the nuclear binding sites on the genome. Tam binds to cytoplasm estrogen receptors in tissues such as breast, anterior pituitary and prostate tissues.[25] The binding prevents the receptors from recycling thereby reducing the number of receptor molecules available for subsequent 17-ß-estradiol activity.[31,32] In cytosols from human breast adrenocarcinomas, Tam competes with estradiol for estrogen receptor protein[5]. 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.[33] 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.[9,16,19,34-36]

GENERAL NOTES: (continued)

Studies of the conformation of Tam to help explain the molecular interactions with estrogen receptors were reported.[37] Tam 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:

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2. Sigma Material Safety Data Sheet
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