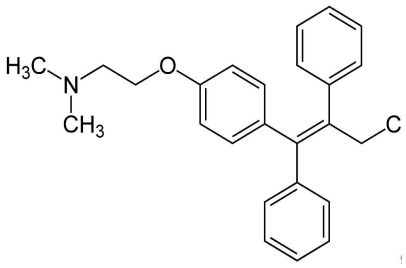
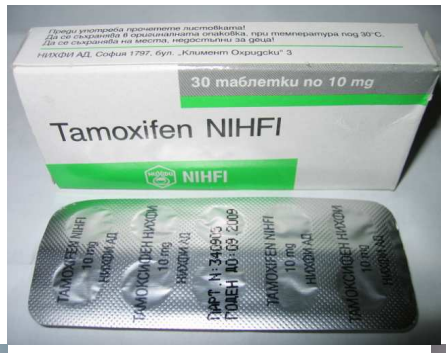
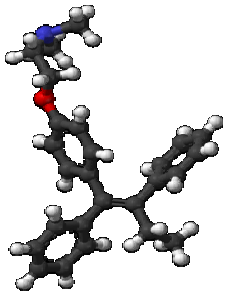
AL Chemistry Group Project (TAS)

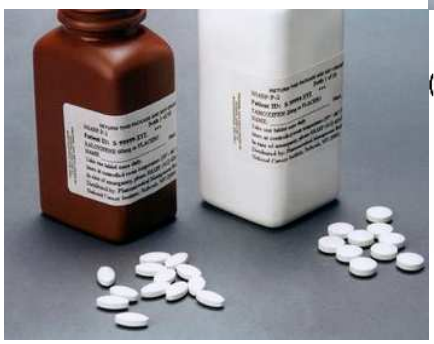
Drugs development:

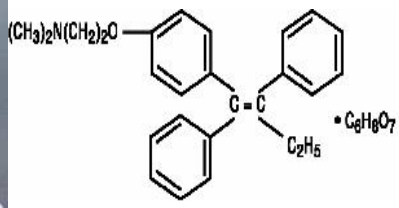
Tamoxifen

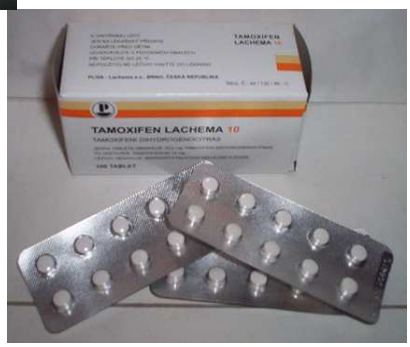






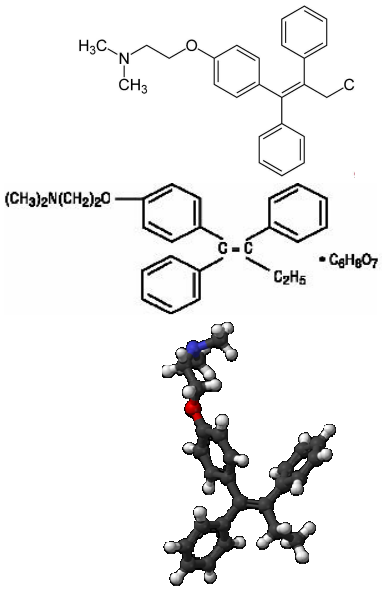






6S Cheng Hoi Wah (5)
6S Tang Chi Chung (21)
6S Wong Chung Ming (26)

Introduction to Tamoxifen



Tamoxifen citrate tablets USP, a **nonsteroidal antiestrogen**, are for oral administration. Each tablet contains 10 mg or 20 mg Tamoxifen (equivalent to 15.2 mg or 30.4 mg, respectively, of Tamoxifen citrate).

The inactive ingredients in each tablet are as follows: croscarmellose sodium, hypromellose, lactose (monohydrate), magnesium stearate, polyethylene glycol 400, povidone, corn starch, and titanium dioxide.

Chemically, Tamoxifen is the trans-isomer of a **triphenylethylene** derivative. The chemical name is (Z)2-[4-(1,2-diphenyl-1-butenyl)phenoxy]- N,N-dimethylethanamine 2-hydroxy-1,2,3- propanetricarboxylate (1:1).

The structural formula, empirical formula, and molecular weight are as shown on the right:

$C_{32}H_{37}NO_8$

Molecular Weight: 563.62

Tamoxifen citrate has a pKa' of 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/mL and in 0.02 N HCl at 37°C, it is 0.2 mg/mL.

Lead compound discovery of Tamoxifen

Tamoxifen is an anticancer drug that is discovered in a failed attempt to create another drug, a birth control pill. In the 1950s, when researchers failed to create a birth control pill from "onsteroidal antioestrogens."they tried to find a new class of anti-estrogen compounds.

In 1962, Research done by ICI Pharmaceuticals discovered the compound ICI46,474 and focused it on birth control. This created the foundation for the manufacture of a group of drugs known as triphenylethylenes later.

Harper & Walpole (1967) succeeded in identifying the trans isomer of a substituted triphenylethylene, Tamoxifen. The early research focused on birth control, but groups of cancer researchers quickly realized that these drugs might also be useful as estrogen antagonists to inhibit the growth of cancer cells, specifically breast cancer cells.

During laboratory testing at ICI Pharmaceuticals in the 1970s, the estrogen receptor alpha ligant (a protein) was found to bond to estrogen and estrogendiol to create new cells. Tamoxifen inhibited this bonding process and slowed the creation of cancer cells.

Molecular modification

To improve the efficacy and reduce its side effects, chemists work on the molecular structure of Tamoxifen .The modifications can be divided into three areas, organic modifications, inorganic and organometallic modifications .All of them have been explored as well. These include platinum complexes, carborane complexes, organorhenium, titanocene, ferrocene, and ruthenocene.

Among these, the most well-studied and potentially most successful metal-containing analogues of tamoxifen are those containing the ferrocene moiety, or ferrocifens. For example, hydroxyferrocifen was found to have a stronger anti-proliferative effect than hydroxytamoxifen, and this has been attributed to the cytotoxic activity of the ferrocenium ion, which results from the oxidation of the ferrocene moiety in vivo Hydroxyferrocifen was originally synthesized via a series of Grignard and dehydration reactions, but since then this has been superseded by a more efficient McMurry coupling route.

The same McMurry coupling route has been adopted for the incorporation of CpRe(CO)3 into the tamoxifen skeleton, illustrating the usefulness of the McMurry protocol. Since tamoxifen is capable of tolerating a considerable degree of structural variation while still retaining its affinity for the estrogen receptor, people were interested in investigating the effect of incorporating a metal carbonyl cluster.

It was hoped that the multiple low-valent metal centres in such derivatives may be oxidized to yield a multiply-charged cluster which would represent a potent cytotoxic species contained within a small volume, enabling tumour suppression to be more effective. No organometallic cluster-containing derivative of tamoxifen has ever been reported.

People were thus interested in exploring the possibilities for synthesizing such a class of modified tamoxifens.

Formulation development

While tamoxifen can be given to patients alone, it is often given in combination with other chemotherapeutic drugs such as 5-fluorouracil (5-FU, or fluorouracil). In French Adjuvant Study Group-02/07, giving FEC (5-fluorouracil, epirubicin, cyclophosphamide) before tamoxifen was associated with a 42% improvement in disease-free survival at 9 years compared to tamoxifen alone.

Since tamoxifen is potential toxicity, one example is that Melatonin is combined with it to improve the safety and efficacy of tamoxifen. Scientists at San Gerardo Hospital in Milan, Italy gave 14 women with metastatic breast cancer who had not responded to tamoxifen therapy, 20 mg of melatonin (in addition to tamoxifen) every evening. They found fewer side effects in these patients than those receiving tamoxifen alone, as well as significant tumor regression in 4 of the 14 patients receiving melatonin.

One of the side effect of taking tamoxifene is to have hot flashes .Paroxetine, an antidepressant commonly used to ease hot flashes that accompany treatment with tamoxifene.

To have a better clinical response, patients will took oral GLA in addition to tamoxifen. Inositol hexaphosphate (IP-6) also have the use in increasing the effectiveness of tamoxifen in blocking breast cancer cell growth.It was found that this combination is being particularly effective against ER alpha-negative cells and adriamycin-resistant cell lines.

Clinical trials

Adverse Reactions

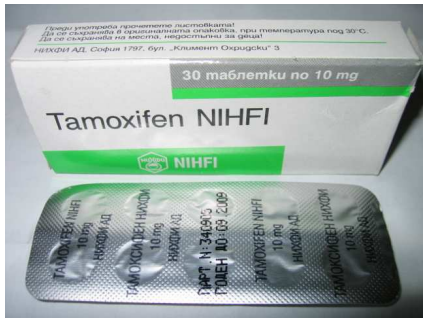
Adverse reactions to Tamoxifen are relatively mild and rarely severe enough to require discontinuation of treatment in breast cancer patients.Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with Tamoxifen as compared to placebo.

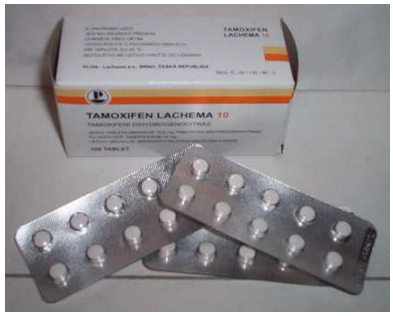
Metastatic Breast Cancer

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting Tamoxifen and generally subside rapidly.

In patients treated with Tamoxifen for metastatic breast cancer, the most frequent adverse reaction to Tamoxifen is hot flashes.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, lightheadedness, headache, hair thinning and/or partial hair loss, and vaginal dryness.





Reference

Medicine online
www.medicineonline.com/drugs/T/2941/TAMOXIFEN-CITRATE-TABLETS-USP.html
Wikipedia
http://en.wikipedia.org/wiki/Tamoxifen
PubMed
http://www.ncbi.nlm.nih.gov/pubmed/20091826
Alternativehealth
www.alternativehealth.co.nz/cancer/melatonin/chemo.htm
Anabolics
www.anabolics.ca/tamoxifen.php
Druglib
www.druglib.com/druginfo/nolvadex/side-effects_adverse-reactions
Drugs.com
www.drugs.com/sfx/nolvadex-side-effects.html
Journal of Organo metallic Chemistry
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