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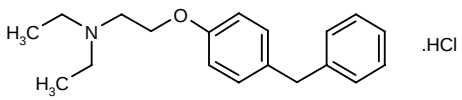
Tesmilifene Hydrochloride

Prop INNM; USAN

Antineoplastic Enhancing Agent
Antiestrogen
Histamine Antagonist

BMS-217380
BMY-33419
DPPE

2-(4-Benzylphenoxy)-*N*,*N*-diethylethylamine hydrochloride



$C_{19}H_{25}NO.HCl$

Mol wt: 319.8734

CAS: 092981-78-7

CAS: 098774-23-3 (as free base)

EN: 109897

Abstract

The antiestrogen tamoxifen has been the standard in the management and prevention of hormonally dependent breast cancer acting by antagonizing the estrogen receptor (ER), thus blocking estrogen-mediated mitogenic activity on breast cancer cells. The cytotoxic, antiproliferative effects of tamoxifen also involve ER-independent mechanisms such as targeting a high-affinity microsomal antiestrogen binding site (AEBS). Since tamoxifen also acts as a partial ER agonist, inducing beneficial hypolipidemic effects but increasing the risk of endometrial cancer, the search for antiestrogens with cytotoxic effects independent of the ER was initiated. One attractive antiestrogenic target is the AEBS, and the first specific and high-affinity AEBS ligand to emerge was the diphenylmethane antiestrogen tesmilifene, which is currently in phase III development as a chemotherapeutic enhancer in the treatment of breast and prostate cancer.

Synthesis

Tesmilifene hydrochloride can be obtained by reaction of *para*-benzylphenol (I) with 2-(diethylamino)ethyl chloride (II) by means of either NaOH in H_2O (1) or K_2CO_3 in DMF/acetone (2) at 60 °C in both cases, followed by treatment with HCl (1, 2). Scheme 1.

Introduction

Breast cancer is the most commonly diagnosed malignancy and the second highest cause of cancer death in women. One million new cases of breast cancer are reported each year throughout the world although the incidence varies with geographical location. Breast cancer is hormonally dependent with some forms requiring low levels of circulating estrogen. Withdrawal of estrogenic stimulation results in involution and shrinkage of tumors. Thus, research efforts have focused on discovering novel antiestrogens to block estrogenic mitogenic effects (3).

Tamoxifen, a triphenylethylenic antiestrogen, is one of the oldest and most effective antiestrogens that is a standard in the management and prevention of breast cancers and the second most widely used antitumoral drug. The agent was designed as an antagonist to the estrogen receptor (ER), competing with 17β-estradiol to block the steroid's mitogenic activity on breast cancer cells. Later, the cytotoxic, antiproliferative effects of tamoxifen were also found to involve ER-independent mechanisms such as producing adducts on DNA and proteins and targeting protein kinase C (PKC), calmodulin, histamine, prolactin receptors and a high-affinity microsomal antiestrogen binding site (AEBS) (4-11). Tamoxifen, however, is not only an antiestrogen but also acts as a partial estrogen agonist, inducing both beneficial hypolipidemic effects and increasing the risk of endometrial cancer. Thus, researchers have attempted to design antiestrogens with cytotoxic effects independent of the ER.

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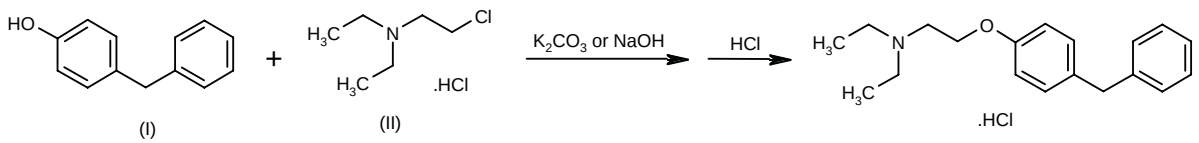
Scheme 1: Synthesis of Tesmilifene Hydrochloride



(I) (II)

One attractive antiestrogenic target is the AEBS, a membranous protein complex that specifically binds triphenylethylenic antiestrogens with high affinity (K_d = 1 nM) (5, 12, 13). The first specific and high-affinity AEBS ligand to emerge was 2-(4-benzylphenoxy)-*N*,*N*-diethylethylamine hydrochloride (tesmilifene; DPPE). The agent was shown to be a potent intracellular histamine antagonist inhibiting histamine binding to nuclear and microsomal sites, including cytochrome P450 (CYP) enzymes that mediate growth via regulation of lipid and prostanoid synthesis. Tesmilifene has no affinity for the ER (14, 15). The agent inhibited concanavalin A- and IL-3-induced mitogenic responses of normal spleen cells and myeloid progenitors, respectively. Moreover, tesmilifene was cytoprotective to bone marrow and gut while enhancing the cytotoxicity of chemotherapeutic agents in human malignant cells in vitro and increasing cure rates and reducing myelotoxicity in cancer patients treated with other antineoplastic agents (16-21). Tesmilifene was chosen for further development as a chemotherapeutic enhancer in the treatment of breast cancer and prostate cancer.

Pharmacological Studies

Results from competitive binding studies using rat liver microsomes showed that tesmilifene and tamoxifen bind with high affinity to the AEBS. In contrast to tamoxifen, tesmilifene at concentrations up to 10 μM did not significantly interact with the ER in experiments using rat uterine cytosol preparations. In addition, unlike tamoxifen, tesmilifene (10 nM) could not induce the progesterone receptor in MCF-7 cells. Tesmilifene also displayed concentration- and time-dependent cytotoxic activity against MCF-7 cells but had no detectable effects on the RTx6 variant which expresses ER but not AEBS. Other studies showed that tesmilifene had no effects on calmodulin or PKC activity of other cancer cell lines (15, 22-24).

Tesmilifene (4 mg/kg/day i.p. for 3 days) antagonized estradiol (100 μg/kg i.p. 1 h after tesmilifene for 3 days)-stimulated uterine growth in an *in vivo* study using ovariectomized immature rats. Rats treated with tesmilifene alone (0.1-75 mg/kg) had uterine size and weights below control levels as compared to tamoxifen (0.65 mg/kg i.p.)-treated animals. Animals treated with both tesmilifene (4 mg/kg) and low-dose tamoxifen (0.04 mg/kg) for 72 h had significantly smaller uteri and significantly more inhibition of estradiol-stimulated eosinophil migration and glandular proliferation in uteri as compared to controls and animals receiving either agent alone. In contrast to tamoxifen, tesmilifene had no effect on estradiol-stimulated luminal epithelial proliferation and, in fact, significantly reduced tamoxifen-induced hypertrophy (25).

The cytotoxic efficacy of tesmilifene was demonstrated *in vitro* in studies using ER-negative human ovarian cancer cells (KF, KFra, KK and MH). The IC_{50} values obtained for these cell lines were 1.66, 0.27, 19.72 and 18.57 μM, respectively. Tesmilifene was shown to time-dependently cause accumulation of cells in the G_2-M phase and inhibit phosphorylation of mitogen-activated protein kinase (MAPK) and cytosolic PKC (IC_{50} =3 μM) in KF cells. The antitumor and cisplatin-enhancing effects of tesmilifene were further demonstrated *in vivo* in experiments using nude mice inoculated with the KF cell line. Significant tumor growth delays were observed in animals treated with tesmilifene alone (50 mg/kg i.p. once weekly for 6 weeks) starting 7 days postinoculation; greater tumor growth delays were seen in animals treated with tesmilifene starting the day after inoculation. Tesmilifene at a dose of 25 mg/kg produced tumor growth delays comparable to those seen in animals treated with cisplatin alone (2 mg/kg). However, more pronounced antitumor activity and increased survival rates were noted in animals treated with a combination of tesmilifene and cisplatin. No significant adverse events were reported (25-27).

Tesmilifene was shown to act synergistically with cisplatin and cimetidine in studies using human melanoma cell lines (T-289, HT168). The IC_{50} values for cisplatin alone and in combination with tesmilifene obtained *in vitro* in T-289 cells were 2.45 ± 0.34 and 0.46 ± 0.22 μM, respectively; tesmilifene had no effects on a tamoxifen-resistant T-289 cell line. Both tesmilifene and cimetidine inhibited in vitro proliferation of HT168 cells and, when combined *in vivo*, markedly reduced tumor mass and increased survival of SCID mice bearing HT168 tumors. Combination treatment was also associated with increased infiltration of interferon-producing murine macrophages into the human tumor site (28, 29).

Pharmacokinetics and Metabolism

An *in vitro* study examined the interaction of tesmilifene with CYP isozymes using insect microsomes expressing human CYP1A1, CYP2B6, CYP2D6 or CYP3A4 cDNA. Tesmilifene was shown to bind to the substrate sites of CYP2D6, CYP3A4 and CYP1A1 with K_s values of 4.1 ± 0.4, 31 ± 15 and 40 ± 9 μM, respectively; no interaction was observed with CYP2B6. These results were further confirmed in metabolism experiments where tesmilifene was found to be metabolized by CYP2D6, CYP3A4 and CYP1A1 but not CYP2B6. Tesmilifene inhibited histamine (600 μM) binding to CYP2D6 (IC_{50} = 4 μM) and CYP1A1 (IC_{50} = 135 μM) but had no effect on histamine binding to CYP2B6. In contrast, the agent stimulated histaminne binding to CYP3A4 (EC_{50} = 155 μM) and was found to inhibit CYP3A4-mediated metabolism of testosterone biphasically (30% and 70% at the two respective sites; IC_{50} = 3 and 350 μM, respectively). It was concluded that tesmilifene is a substrate for CYP3A4, CYP2D6 and CYP1A1 but not CYP2B6 and was speculated that the enhancing effects of tesmilifene on the antitumor activity of other chemotherapeutics may be due to the agent's ability to inhibit CYP3A4-mediated metabolism and possibly Pgp-mediated efflux of antineoplastic agents (30).

The pharmacokinetics of tesmilifene (240 mg/m^2 [6 mg/kg] i.v. over 80 or 440 min once weekly) were examined in a phase I/II study involving 48 patients with advanced cancer (breast, colon, gastric, pancreatic, renal, adrenal, head and neck and prostate tumors and soft tissue sarcoma, melanoma, mesothelioma and lymphoma) receiving 5-fluorouracil (600-800 mg/m^2), cyclophosphamide (600-800 mg/m^2), dacarbazine (1500 mg/m^2) or vinblastine (7.5-10 mg/m^2) as an i.v. infusion during the last 20 min of tesmilifene infusion. Patients were also administered lorazepam to minimize the acute effects of tesmilifene on the CNS and ondansetron to minimize nausea and vomiting. The mean serum tesmilifene concentration at 80 min was 3.5 ± 0.3 μM, which decreased rapidly (75% in 2-3 h) in the distribution phase; this reduction correlated with recovery from acute CNS clinical effects. The elimination $t_{1/2}$ value for tesmilifene was 11 ± 2 h and the apparent volume of distribution was 800-1000 l, indicating a high level of tissue penetration. Analysis of 24-h pooled urine detected less than 1% of the unchanged compound. Mean serum tesmilifene concentration at 6 h from 16 patients receiving 1 mg/kg/h (i.v. over 80 min to 6 h) was 1.0 ± 0.4 μM. After a minimum of 4 cycles, 1 complete and 7 partial remissions were observed and 12, 12 and 16 patients improved, stabilized and progressed, respectively (21).

Clinical Studies

The efficacy and safety of tesmilifene (6 mg/kg i.v. over 80 min every 3 weeks for up to 7 cycles) combined with a standard schedule of doxorubicin (60 mg/m^2 i.v. over the last 20 min of tesmilifene infusion) were examined in a phase II pilot study involving 23 patients (16 with prior nonanthracycline chemotherapy) with metastatic breast cancer. The response rate reported in this study appeared to be higher than historical experience in patients treated with doxorubicin alone. There were 16 responders (7 complete and 9 partial responses), of whom 11 had received prior chemotherapy and 5 (2 complete and 3 partial responses) had a poor performance status (ECOG 3/4) at the study onset. The median duration of complete responses was 11 months. The incidence of nausea/vomiting/dyspepsia appeared to be higher than historical experience. However, most patients responded well to antiemetics, rantidine and/or dexamethasone. Incidence of hematological toxicity was low. Seventeen patients who had received 300 mg/m^2 or more doxorubicin experienced a mean 8% absolute drop in left ventricular ejection fraction (31).

The efficacy and toxicity of tesmilifene (6 mg/kg i.v. over 80 min every 21 days for a maximum of 7 cycles) in combination with doxorubicin (60 mg/m^2 i.v. over the last 20 min of tesmilifene infusion) were examined in a multicenter, phase II trial involving 42 women with anthracycline-naive metastatic breast cancer. All patients, of whom 35 were administered 4 or more cycles, were evaluable. Toxicities were similar to those historically observed in patients treated with doxorubicin alone with the exception of CNS adverse events, including motion sickness, mild hallucinations and cerebellar signs observed during infusion with tesmilifene. The CNS adverse events were generally manageable, not requiring hospitalization, and improved with subsequent cycles. Febrile neutropenia was reported in 4 patients. The overall response rate was 52.5% with 9.5%, 43% and 38% of the patients having complete responses, partial responses and stable disease, respectively (32).

A phase III study was conducted in 305 anthracycline-naive patients with metastatic/recurrent breast cancer to compare the efficacy and toxicity of tesmilifene (6 mg/kg i.v. over 80 min) combined with doxorubicin (60 mg/m^2 i.v. over the last 20 min of tesmilifene infusion) with doxorubicin alone. The study was closed to accrual due to the lack of an increased response rate and the presence of an increase in incidence of toxicity (particularly neurotoxicity) in the group treated with tesmilifene and doxorubicin as compared to patients treated with doxorubicin alone. Final analysis of toxicity, progression-free survival, response rate and response duration continues. It was concluded that further phase III trials in patients with metastatic breast cancer are required to corroborate phase II results (33).

The chemotherapeutic enhancing activity of tesmilifene has also been examined in patients with prostate cancer. The efficacy and toxicity of tesmilifene (6 mg/kg i.v. over 80 min once weekly for 4 weeks followed by 1-week rest period and subsequently once every 2/3 weeks) in combination with cyclophosphamide (600-800 mg/m^2 i.v. during the last 20 min of tesmilifene infusion) were evaluated in 20 patients with metastatic hormonally

unresponsive prostate cancer, of whom 19 were symptomatic. Partial remission was observed in 5 of 7 patients with measurable soft tissue disease. One complete and 2 partial remissions were observed in 3 of 16 patients with bone disease. Of the 18 patients with elevated serum prostate-specific antigen (PSA) levels, 9 had a more than 50% decrease in levels. Of the 13 patients with bone pain, 11 had partial or complete relief. Nausea/vomiting and ataxia at the time of tesmilifene infusion were seen in 6 and 20 patients, respectively, of 20 patients, and correlated with peak serum tesmilifene levels. Delayed adverse events reported at 24-48 h postinfusion included tiredness and mild nausea, with 1 patient developing hemorrhagic cystitis (34).

Tesmilifene (5.3 mg/kg i.v. over 80 min) was shown to enhance the anticancer effects (response rate and survival) of mitoxantrone (12 mg/m^2 i.v. weekly every 3 weeks starting during the last 20 min of the tesmilifene infusion) in a study involving 26 patients with symptomatic, progressive hormone-refractory prostate cancer (bone metastasis in 90%; median PSA = 220 ng/ml; 100% castrate testosterone levels) also receiving prednisone (5 mg p.o. b.i.d.). Improved pain and a reduction in analgesia was seen in 68% of the patients and 50% of the patients had a reduction in PSA of 50%. Mean survival for 16 patients was 18 months, with 38% surviving more than 2 years. With the exception of 3 cases of transient hallucinations, toxicities observed were similar to those observed in other studies in which mitoxantrone was adminsitered alone. A randomized trial in patients with hormone-refractory prostate cancer is planned to confirm the enhancing effects of tesmilifene on mitoxantrone which will include a cohort treated with mitoxantrone alone (35).

Tesmilifene continues to undergo active clinical development as a chemotherapeutic enhancer. A second phase III trial in patients with advanced metastatic/recurrent breast cancer has recently been approved by the FDA. The study will compare the overall survival of patients treated with a combination of tesmilifene and epirubicin/cyclophosphamide with patients treated with epirubicin/cyclophosphamide alone (36).

Source

YM BioSciences Inc. (US).

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