Cytotoxic Estrogens: Anilin Mustard Linked 1,1,2-Triphenylbut-1-enes with Mammary Tumor Inhibiting Activity

Martin R. Schneider*)**) and Michael L. Schuderer

Sonderforschungsbereich 234, Institut für Pharmazie, Lehrstuhl Pharmazeutische Chemie II, Universität Regensburg, Universitätsstraße 31, D-8400 Regensburg, F.R.G.

Received June 22, 1988

In order to develop cytotoxic estrogens with a specific effect on hormone-dependent mammary tumors, two 1,1,2-triphenylbut-1-enes with a 4-OH group at one C-1-phenyl ring and a chloro-[4] or bromo-[8] anilin mustard moiety at the other C-1-phenyl ring were synthesized. **4** and **8** exerted strong alkylating activity and an irreversible binding to the estrogen receptor. In spite of relatively low receptor affinities, both anilin mustards exhibited a better effect on a receptor-positive breast cancer cell line as well as on a hormone-dependent mammary carcinoma of the mouse than on a receptor-negative cell line and a hormone-independent mammary carcinoma. Therefore, a selective antitumor activity of **4** and **8** is likely.

Cytotoxische Östrogene: Anilin-Lost verknüpfte 1,1,2-Triphenyl-but-1-ene mit mammatumorhemmender Wirkung

Zur Entwicklung cytotoxischer Östrogene mit einer spezifischen Wirkung auf hormonabhängige Mammacarcinome wurden zwei 1,1,2-Triphenylbut-1-ene mit einer 4-OH Gruppe an einem C-1-Phenylrest und einem Chlor-[4] bzw. Brom-[8]-anilinlost-Rest am 2. C-1-Phenylrest synthetisiert. **4** und **8** zeigten starke alkylierende Aktivität und banden irreversibel an den Östrogenrezeptor. Trotz ihrer relativ geringen Rezeptoraffinitäten wiesen beide Anilinlost-Derivate eine bessere Wirkung an einer rezeptorpositiven Brustkrebszellinie und an einem hormonabhängigen Mammacarcinom der Maus auf als an einer rezeptornegativen Zellinie und einem hormonunabhängigen Mammacarcinom. Daher ist eine selektive Antitumorwirkung von **4** und **8** anzunehmen.

The advanced human mammary carcinoma is treated either by endocrine therapy with compounds like the antiestrogen tamoxifen or by chemotherapy[1]. Cytotoxic estrogens are a combination of both treatment modalities, in which a cytotoxic moiety is linked to a steroidal or nonsteroidal estrogen[2]. Background of the development of such compounds is the possible enrichment of cytotoxic estrogens in the mammary tumor due to their affinity for estrogen receptors, which are found in a high percentage of those tumors[3]. Because of this enrichment, an enhanced therapeutic efficiency and selectivity, but a reduced systemic toxicity of cytotoxic estrogens compared to usual cytotoxic drugs is possible[2,3].

Despite rather disappointing results in the development of such compounds[4], recent studies with chloroethylnitrosourea linked steroids[5], endocrine active diphenylethylenediamine platinum complexes[6] or cytotoxic esters of triphenylethylenes[7] showed the validity of this concept. In this study, chloro- and bromoanilin mustard groups were used as the cytotoxic moiety. These groups were linked at one C-1-phenylring of a 1,1,2-triphenylbut-1-ene with a 4-OH function at the second C-1-ring (Scheme I, **4**, **8**). 1,1,2-Triphenylbut-1-enes are a group of compounds having estrogen receptor affinities, estrogenic or antiestrogenic properties and mammary tumor inhibiting activities depending on their mode of aromatic substitutions[8,9]. The new compounds **4** and **8** were tested in an in vitro and in vivo biological test system[7] whether they are suitable for a selective treatment of mammary carcinomas.

Chemistry

For the preparation of both the chloro- and the bromoanilin mustard substituted compounds **4** and **8**, a route of synthesis as is outlined at the right panel of scheme I (**5** - **8**) was planned, i.e. synthesis of the corresponding N-morpholino-phenyl-derivative **7** and cleavage of the morpholino ring to the anilin mustards **4** and **8**.

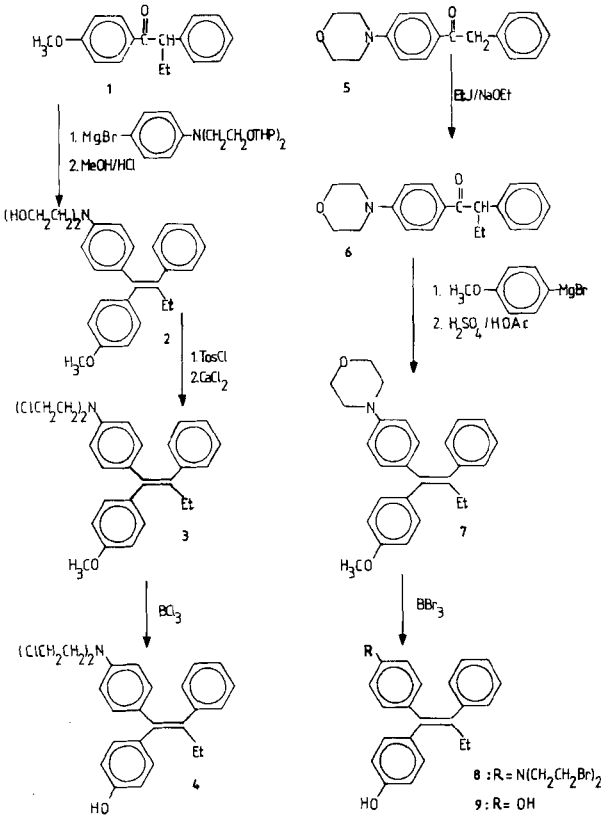
Compound **5** was obtained in a *Friedel-Crafts* acylation of 4- phenylmorpholine with phenylacetyl chloride. **5** was then alkylated with ethyl iodide to **6**[10]. The 1,1,2-triphenylbut-1-ene derivative **7** was prepared from **6** in a *Grignard* reaction with 4-methoxyphenylmagnesium chloride and subsequent dehydration with a mixture of sulfuric acid and acetic acid giving a mixture of the E- and Z-isomer. The bromoanilin mustard **8** was obtained by ether cleavage of the morpholino ring and the methoxy substituted phenyl ring with an excess of boron tribromide[9,10]. Separation of the E,Z-mixture of **8** was not possible.

Synthesis of **4** in a similar way by cleavage of the morpholino ring to the chloroanilin mustard was not possible. Neither treatment with boron trichloride, $ZnCl_2$/HCl at 180 °C, $ZnCl_2$/acetyl chloride nor $SOCl_2/TiCl_4$ resulted in the formation of **4**. Therefore, **4** was prepared in a different route which is outlined at the left panel of scheme I.

**) Present address: Schering AG, Institut für Pharmakologie, Experimentelle Andrologie und Onkologie, Postfach 650311, D-1000 Berlin 65

  0365-6233/89/0101-0059 $ 02.50/0

1-(4-Methoxyphenyl)-2-phenyl-butan-1-one **1**[9,10] was converted in a *Grignard* reaction with N,N-bis-(2-tetrahydropyranonyloxyethyl)-4-bromo-aniline to the corresponding tertiary carbinol. This carbinol was dehydrated with HCl/methanol to an E,Z-mixture of the 1,1,2-triphenylbut-1-ene **2**. Under these acidic conditions the protection groups were also removed[10]. The OH-groups were tosylated and then chlorinated with $CaCl_2$[11] to obtain the methoxy-substituted chloroanilin mustard derivative **3**, which was then converted to **4** by ether cleavage with BCl_3. Separation of this E,Z-mixture was not possible either. Therefore, 1:1 E,Z-mixtures were used in the biological tests.



Biological Properties

1,1-Bis-(4'-hydroxyphenyl)-2-phenylbut-1-ene (**9**) with a 4-OH group instead of an anilin mustard moiety and thus with *no* cytotoxic function was used as a reference in most of the biological tests[7]. Whereas this reference **9** has an affinity to the estrogen receptor of 6.2% that of estradiol with cytosol from calf uteri[7], both anilin mustards **4** and **8** exerted only low binding affinities (Table 1). Therefore, this moiety is not suitable for a good binding to this receptor. However, determination of the mode of binding revealed an irreversible binding of **4** and **8** as can be seen by the decrease in % bound ^{3}H-estradiol in assay II compared to assay I (Table 1). By way of contrast, **9** had a completely reversible mode of receptor binding as is demonstrated by an about tenfold increase in the % bound in assay II. Because of these different modes of binding, the RBA-values of **4** and **8** are not just comparable to that of **9**. In the in vitro NBP-(4-(p-nitrobenzyl)-pridine)-test, both anilin mustards exerted strong alkylating activities which equal that of the potent alkylating agent chlorambucile (E = 0.76)[7].

As endocrine effects can contribute to the tumor inhibiting potencies of cytotoxic estrogens, estrogenic and antiestrogenic properties were determined in the 3 day immature mouse uterine weight test[7]. Antiestrogenic activities of **4** and **8** (as well as of **9**[8]) were not given at various doses (data not shown). The estrogenic activities of **4** and to a lesser extent of **8** were lower than those of the reference **9** (Table 1).

As already mentioned, a cytotoxic estrogen should have a specific effect on hormone-dependent tumors by its possible enrichment in the tumor due to its receptor affinity[2,3]. Consequently it should have a superior effect on hormone-dependent, receptor-positive tumors compared to hormone-independent ones and exert a better effect than a structurally similar reference without a cytotoxic group like **9** (which acts just by its endocrine properties). **4** and to a stronger extent **8** inhibited in a dose-dependent manner the estrogen receptor-negative MDA MB231 breast cancer cell line in the same order as was determined for their alkylating activity. However, they exhibited a better effect on the estrogen receptor-positive MCF-7 breast cancer cell line, especially in the lower concentration (Table 1). Therefore, in vitro, a certain selectivity of antitumor action is obvious. In vivo, **4** and **8** exerted only low tumor inhibiting properties on the hormone-independent MXT OVEX mammary tumor of the mouse (Table 1). By way of contrast, the receptor-positive,

Table 1: Biological Properties of Compounds **4**, **8** and **9**

Compound	**4**	**8**	**9**
%RBA[a]	0.2	0.4	6.2
mode of binding	irrevers.	irrevers.	reversible
assay I/assay II[b]	45/39	47/14	3/22
alkylating acitvity[c]	0.60	0.76	- -
estrogenic acitvity, % of estrone (0.4 μg)[d]			
5 μg	0	29	73
25 μg	14	80	95
100 μg	65	94	- -
% inhibition of MDA MB 231 cells[e]			
log conc. -6/-5	24/45	25/84	0/0
MCF-7 cells			
log conc. -6/-5	58/88	74/96	2/0
MXT OVEX tumor[f]	26	19	0
MXT M 3.2 tumor[g]	82	83	56

a)Relative binding affinity to the estrogen receptor (estradiol = 100). b) %Bound ^{3}H-estradiol; conc. of **4** and **8**: 5 x 10^{-6}. c) Absorbance after incubation with NBP for 4 h at 50°. d) Effect = uterine dry weight/body weight related to estrone (= 100). e) Inhibition of cell numbers related to solvent control at day 2 (MDA) and at day 5 (MCF-7); mean of 12 dishes. f) Inhibition of tumor area related to control after 2 weeks of therapy (dosage: 3 times 4 x 10^{-5} mol(kg and week). g) Inhibition of tumor weight related to control after 6 weeks of therapy (dosage: 3 times 2 x 10^{-5} mol/kg and week).

hormone-dependent MXT M3.2 mammary tumor was inhibited by more than 80% by the anilin mustards **4** and **8**. The reference **9**, however, caused only 56% inhibition.

Because of the better effects of **4** and **8** on hormone-dependent tumors (MCF-7, MXT M3.2) compared to respective hormone-independent ones (MDA MB 231, MTX OVEX) and because of their superiority in antitumor action compared to the non-cytotoxic reference **9**, a selectivity of their mammary inhibiting activity seems to be given. However, the low estrogen receptor affinity is a disadvantage of these compounds so that relatively high concentrations are necessary to obtain good effects. An improvement of the receptor binding affinity and consequently of the selectivity of action is desirable.

The authors thank Prof. Dr. *H. Schönenberger* for helpful discussions, and the Deutsche Forschungsgemeinschaft (SFB 234) for financial support.

Experimental Part

MP: Büchi 510 melting point apparatus (uncorr.). – ^{1}H-NMR-spectra: Varian EM 360-A (60 MHz) and EM-390 A (90 MHz). – Elemental analysis: Mikroanal. Lab. Universität Regensburg.

Syntheses

E,Z-1-[4-(N,N-Bis-2-hydroxyethylamino)-phenyl]-1-(4-methoxy-phenyl) -2-phenyl-but-1-ene (**2**)

A *Grignard* reagent prepared from N,N-bis-(2-tetrahydropyranyl-oxyethyl)-4-bromoaniline (13.7 g, 0.04 mol) and Mg (9.7 g, 0.04 g-atom) in dry THF, and 1-(4-methoxyphenyl)-2-phenyl-butan-1-one (**1**) (2.5 g, 0.01 mol) were refluxed for 2 h. After decomposition with ice and 3N-H_2SO_4, the ethereal layer was separated, the aeq. layer was extracted with ether, the organic extracts were washed with saturated $NaHCO_3$-solution, and the solvents were removed. The crude product was dehydrated with MeOH/3N-HCl (v/v 1:1) for 12 h at room temp. After removal of the MeOH, the aeq. layer was extracted with ether, and the ether was removed. The crude product was purified by column chromatography on silica gel (10:1 $CHCl_3$/ethyl acetate) to give a yellow oil (48%). – ^{1}H-NMR (60 MHz, $CDCl_3$): δ (ppm) = 1.00 (t, J = 8 Hz, 3H, CH_3); 2.57 (q, J = 8 Hz, 2H, CH_2); 3.75 (m, 4H, $N(CH_2^-)_2$); 3.89 (s, 3H, OCH_3); 3.94 (m, 4H, CH_2O); 4.50 (s, 2H, OH); 6.62-7.43 (m, 13H, aromat. H).

E,Z-1-[4-)N,N-Bis-2-chloroethylamine)phenyl]-1-1(4-methoxy-phenyl)-2-phenyl-but-1-ene (**3**)

4-Toluenesulfonyl chloride (3.8 g, 0.02 mol) was added to a solution of **2** (3.0 g, 7.5 mmol) in 15 ml dry pyridine. After stirring for 1 h at -5°C, additional 3.8 g 4-toluenesulfonyl chloride were added and stirred for 2 h at room temp. After decomposition with water and extraction with $CHCl_3$, the solvent was removed. The crude material was heated with $CaCl_2$ (1.7 g, 15 mmol) in 20 ml of diethylene glycol for 15 min at 120 °C. After cooling, 30 ml of water were added, and the aeq. layer was extracted with $CHCl_3$. Removal of the solvent and purification by column chromatography on silica gel (10:1 $CHCl_3$/ethyl acetate) yielded **3** as a yellow oil (62%). - ^{1}H-NMR (60 MHz, $CDCl_3$): δ (ppm) = 0.88 (t, J = 8 Hz, 3H, CH_3); 2.42 (q, J = 8 Hz, 2H, CH_2); 3.49 (s, 3H, OCH_3); 3.62 (m, 8H, $N(CH_2CH_2Cl)_2$); 6.20-7.20 (m, 13H, aromat. H).

E,Z-1-[4-(N,N-Bis-2-chloroethylamino)-phenyl]-1-(4-hydroxy-phenyl)-2-phenyl-but-1-ene (**4**)

2.3 g (0.02 mol) of BCl_3 were added to **3** (4.5 g, 0.01 mol) in 50 ml of dry CH_2Cl_2, and the mixture was stirred for 3 h at room temp. After addition of 10 ml MeOH, the solvents were removed. The crude product was purified by column chromatography on silica gel (10:1 $CHCl_3$/ethyl acetate) and recrystallized from toluene to give **4** as colorless crystals (43%): mp 81-83 °C. - $C_{28}H_{27}Cl_2NO$ (440.4) Calcd C 70.9 H 6.19 N 3.2 Found C 70.5 H 6.33 N 3.1. - ^{1}H-NMR (60 MHz, $CDCl_3$): δ (ppm) = 0.85 (t, J = 8 Hz, 3H, CH_3); 2.29 (s, 1H, OH); 2.45 (q, J = 8 Hz, 2H, CH_2); 3.64 (m, 8H, $N(CH_2CH_2Cl)_2$); 6.32-7.28 (m, 13H, arom. H).

1-(4-N-Morpholinophenyl)-2-phenyl-ethanon (**5**)

To 11.4 g (0.07 mol) N-phenylmorpholine in 100 ml dichloroethane, 16.2 g (0.12 mol) $AlCl_3$ and 10.5 g (0.09 mol) phenylacetyl chloride were added. After stirring for 2 h at room temp., ice- water was added. The org. layer was separated and the aeq. layer was extracted with $CHCl_3$. The org. extracts were washed with 10% NaOH and H_2O, and the solvents were removed. The crude product was crystallized from EtOH to give **5** (34%): mp 135-137 °C. – $C_{18}H_{19}NO_2$ (281.4) Calcd C 76.8 H 6.82 N 5.0 Found C 76.8 H 6.95 N 5.. – ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 3.48 (t, 4H, $N(CH_2^-)_2$); 4.06 (t, 4H, $O(CH_2^-)_2$); 4.40 (s, 2H, CH_2); 7.04; 8.16 (AB, 4H, arom. H); 7.48 (s, 5H, arom. H).

1-(4-N-Morpholinophenyl)-2-phenyl-butan-1-one (**6**)

A solution of sodium (2.3 g, 0.10 g-atom) in 44 ml EtOH was added to a mixture of **5** (28.1 g, 0.10 mol) and ethyl iodide (15.6 g, 0.10 mol). The solution was refluxed for 10 min. A further quantity of sodium (1.15 g, 0.05 g-atom) in 22 ml EtOH and ethyl iodide (7.8 g, 0.05 mol) were added and the whole was refluxed for 4 h. EtOH was removed, and water was added. The aeq. layer was extracted with ether. The solvent was removed and the crude product was recrystallized from EtOH to give **6** as colorless crystals (74%): mp 82-84 °C. - $C_{20}H_{23}NO_2$ (309.4) Calcd C 77.6 H 7.51 N 4.5 Found C 77.7 H 7.57 N 4.5. - ^{1}H-NMR (90 MHz, $CDCl_3$) δ (ppm) = 0.80 (t, J = 8 Hz, 3H, CH_3); 1.57-2.28 (m, 2H, CH_2); 3.15 (t, 4H, $N(CH_2^-)_2$); 3.73 (t, 4H, $O(CH_2^-)_2$); 4.32 (t, J = 8 Hz, 1H, CH); 6.68-7.84 (m, 9H, arom. H).

E,Z-1-(4-N-Morpholinophenyl)-1-(4-methoxyphenyl)-2-phenyl-but-1-ene- (**7**)

A solution of **6** (7.7 g, 0.025 mol) in 25 ml dry THF was added dropwise to a solution of 4-methoxyphenylmagnesium bromide (15.8 g, 0.075 mol) in 40 ml dry THF. The mixture was refluxed for 2 h and then decomposed with ice and 3N-H_2SO_4. The ethereal layer was extracted with ether, and the org. extracts were washed with saturated $NaHCO_3$-solution. After removal of the solvent, the crude product was heated with H_2SO_4/acetic acid (v/v 8:2) on a water bath for 20 min. The mixture was cooled, water was added, and the reaction mixture was alkalized with 10% NaOH. The aeq. layer was extracted with ether and washed with water. After removal of the solvent, the product was recrystallized from EtOH to give **7** as colorless crystals (66%): mp 122-123 °C. – $C_{27}H_{29}NO_2$ (399.6) Calcd C 81.1 H 7.33 N 3.5 Found C 80.7 H 7.01 N 3.5. – ^{1}H-NMR (90 MHz, $CDCl_3$) δ (ppm) = 0.90 (t, J = 8 Hz, 3H, CH_3); 2.45 (q, J = 8 Hz, 2H, CH_2); 3.05 (m, 4H, $N(CH_2^-)_2$); 3.60 (s, 3H, OCH_3); 3.73 (m, 4H, $O(CH_2^-)_2$); 6.42-7.18 (m, 13H, arom. H).

E,Z-1-[4-(N,N-Bis-2-bromoethylamino)-phenyl]-1-(4-hydroxyphenyl)-2-phenyl-but-1-ene (**8**)

BBr_3 (12.5 g, 0.05 mol) was added dropwise to a solution of **7** (2.0 g, 0.005 mol) in 20 ml dry CH_2Cl_2. The whole was refluxed for 4 h. With cooling, 20 ml MeOH were added, and the solvents were removed. The product was dissolved in $CHCl_3$, washed with $NaHCO_3$, and purified by column chromatography on silica gel (10:1 $CHCL_3$(ethyl acetate). Recrystallization from toluene gave **8** as colorless crystals (42%): mp 80-81 °C. - $C_{26}H_{27}Br_2NO$ (529.4), Calcd C 59.0 H 5.15 N 2.6 Found C 59.1 H 5.51

N 2.6. – ^{1}H-NMR (90 MHz, CD_3OD) δ (ppm) = 0.90 (t, J = 8 Hz, 3H, CH_3); 2.44 (q, J = 8 Hz, 2H, CH_2); 3.54 (m, 8H, $N(CH_2CH_2Br)_2$); 6.20-7.08 (m, 13H, arom. H).

Biological Methods

All methods used were identical to those described[7].

Estradiol Receptor Binding Assay

The relative binding affinities (RBA) were determined by the displacement of ^{3}H-estradiol by the test compounds after incubation with cytosol from calf uteri at 4°C for 16 h (DCC- method).

Mode of Receptor Binding

To determine the reversibility or irreversibility of the receptor binding, the percentage of bound ^{3}H-estradiol was measured in two assays. Calf uterine cytosol was preincubated at 0 °C for 60 min with the test compound. ^{3}H-estradiol was added after preincubation for 120 min at 0 °C (assay I, 100%-value), or after preincubation and DCC-treatment (assay II). After centrifugation, the supernatants were incubated with ^{3}H-estradiol for 60 min at 0 °C, 25 min at 25 °C and for 60 min at 0 °C. Bound ^{3}H-estradiol was measured after charcoal adsorption. An increase of the amount of bound ^{3}H-estradiol in assay II compared with assay I indicates a reversible mode of binding to the estrogen receptor.

Alkylating activity in the NBP-assay

A solution of the test compounds (1 µmol/ml) in EtOH was incubated with 1 ml of NBP-solution (5% w/v 4-(p-nitrobenzyl)- pyridine in ethanol), 1 ml of 0.05 M potassium hydrogen phthalate buffer (pH 4.2) and 1 ml of ethanol for 4 h at 50 °C. After addition of 0.1 N KOH in 80% aqueous ethanol, absorptions were determined at 600 nm. The rate of alkylation is proportional to the measured absorption.

Estrogenic and antiestrogenic activity

Estrogenic and antiestrogenic properties were determined in the immature mouse uterine weight test by stimulation of the uterine growth or by inhibition of uterine growth stimulated by estrone, respectively.

Growth inhibition of hormone-independent MDA-MB 231 human breast cancer cells

The MDA-MB 231 cell line was provided by Dr. *M.E. Lippman*, NCI, Bethesda, USA. – Approximately $2x10^4$ cells in 2 ml McCoy 5 medium were plated in 6-well dishes (Costar). 2 days later, the medium was changed and the test compounds were added. After an incubation time of 2 days, the cells were washed with PBS and harvested with PBS/EDTA buffer. After centrifugation, the cell pellet was resuspended in PBS and the cell number was counted in a ZI Coulter Counter.

Growth inhibition of hormone-dependent MCF-7 human breast cancer cells

The MCF-7 cell line was provided by Dr. *M.E. Lippman*, NCI, Bethesda, USA. Cells were harvested with trypsine/EDTA in Richter's IMEM supplemented with 5% NCS. The cells were incubated with the test compounds for 5 days and proceeded as above.

Hormone-dependent transplantable MXT M 3.2 mammary tumor of the BDF1 mouse

The MXT tumor used in these studies was provided by Dr. *A.E. Bogden*, EG&G Bogden Laboratories, Worcester, USA. The tumor was transplanted in pieces of about 2 mm^3 subcutaneously into female BDF1 mice (Charles River Wiga, Sulzfeld, FRG). After transplantation, the mice were randomly distributed into groups of ten. Starting with the first day after transplantation, the test compounds were injected in olive oil s.c. 3 times a week for 6 weeks. Then the animals were killed and weighed. The tumors were removed and weighed and the average of tumor weight was calculated.

Hormone-independent transplantable MXT-OVEX mammary tumor of the BDF1 Mouse

The MXT-OVEX tumor used in these studies was provided by Dr. *A.E. Bodgen*, EG&G Bogden Laboratories, Worcester, USA. The tumor is propagated in ovariectomized BDF1 mice. Testing was performed in intact female BDF1 mice as described above. Duration of therapy was 14 days. At day 14, the animals were killed, tumor size was determined by caliper measurements. Tumor size = length + width / 2.

References

1 H.T. Mouridsen and R. Paridaens, Eur. J. Cancer Clin. Oncol. *24*, 99 (1988).
2 G. Leclercq, N. Devleeschouwer, and J.C. Heuson, J. steroid Biochem. *19*, 75 (1983).
3 J.A. Katzenellenbogen and B.S. Katzenellenbogen, Breast Cancer Res. Treat. *2*, 347 (1982).
4 R.J. Paridaens, G. Leclercq, and J.C. Heuson in H.M. Pinedo and B.A. Chabner, Cancer Chemotherapy Annual 6, p. 170, Elsevier, Amsterdam 1984.
5 G. Eisenbrand, M.R. Berger, J. Fischer, M.R. Schneider, W. Zeller, and W. Tang, Cancer Treat. Rev. *14*, 285 (1987).
6 J. Karl, R. Gust, T. Spruss, M.R. Schneider, H. Schönenberger, J. Engel, K.H. Wrobel, F. Lux, and S. Trebert-Haeberlin, J. Med. Chem. *31*, 72 (1988).
7 M.L. Schuderer and M.R. Schneider, J. Cancer Res. Clin. Oncol. *113*, 230 (1987).
8 M.R. Schneider, J. Cancer Res. Clin. Oncol. *112*, 119 (1986).
9 M.R. Schneider, E. von Angerer, H. Schönenberger, R.T. Michel, and H.P. Fortmeyer, J. Med. Chem. *25*, 1070 (1982).
10 M.L. Schuderer, Diss. Univ. Regensburg 1986.
11 W. Werner, J. prakt. Chem. *314*, 577 (1972).

[Ph522]