

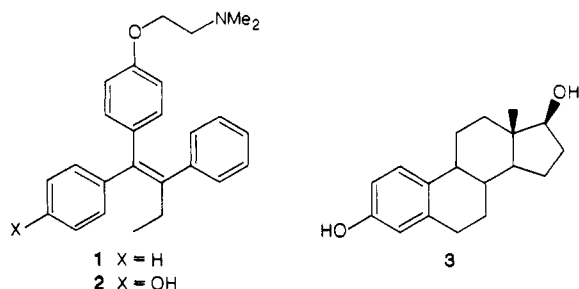
Derivatives of Tamoxifen. Dependence of Antiestrogenicity on the 4-Substituent

Raymond McCague,*† Guy Leclercq,‡ Nicole Legros,‡ Joyce Goodman,§ G. Michael Blackburn,§ Michael Jarman,† and Allan B. Foster†

Drug Development Section, Institute of Cancer Research, Sutton, Surrey SM2 5NG, U.K., Laboratoire de Cancerologie Mammaire, Service de Médecine, Institut Jules Bordet, 1000 Bruxelles, Belgium, and Chemistry Department, University of Sheffield, Sheffield S3 7HF, U.K. Received October 12, 1988

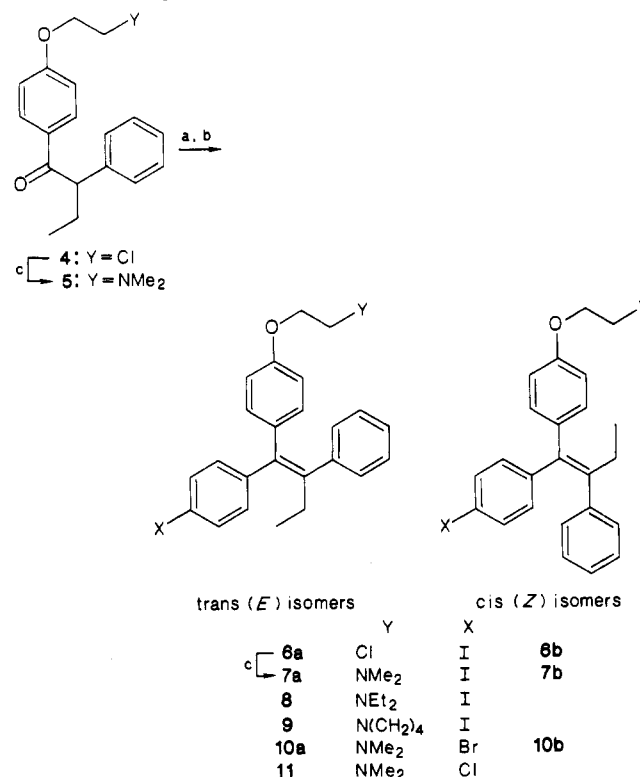
A range of tamoxifen derivatives substituted in the 4-position of the 1-phenyl ring are described. The key steps in the synthesis of 4-iodo-, 4-bromo-, and 4-(methylthio)tamoxifen were reactions of 1,2-diarylbutanones with the (4-halogenophenyl)lithium or [4-(methylthio)phenyl]magnesium bromide. Oxidized precursors of 4-(methylthio)tamoxifen were used to prepare the methylsulfinyl and methylsulfonyl derivatives. Further derivatives (formyl, hydroxymethyl, oxirane, mercapto) were prepared from 4-lithiotamoxifen via the 4-lithio derivative. Several of the derivatives (Br, I, SMe, SO₂Me, oxirane, CHO, CH₂OH) displayed a higher affinity for estrogen receptors (ER) of calf uterine cytosol than did tamoxifen, but there was no relationship between affinity to ER and the ability to inhibit the growth of the MCF-7 breast cancer cell line in vitro.

For the treatment of hormone-dependent advanced breast cancer, tamoxifen [1, *trans*-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1,2-diphenyl-1-butene, ICI-Nolvadex] is an excellent drug frequently giving a period of freedom from disease with a low incidence of side effects.^{1,2} It displaces the growth-promoting natural hormone estradiol from its protein receptor, and consequently its principal mode of action has been thought to be as an antiestrogen.³ Metabolism of tamoxifen may play a significant role in mediating its overall activity,⁴ and of the metabolites that have been detected in the plasma of patients,⁵ the hydroxylated derivative 2 (4-hydroxytamoxifen) has much greater potency in vitro than the parent drug.⁶⁻⁸ Thus, whereas tamoxifen binds to the estrogen receptor with an affinity about 1% of that of estradiol, 4-hydroxytamoxifen has an affinity comparable to that of estradiol and has a correspondingly increased potency for inhibition of the growth of the MCF-7 human breast cancer cell line. Although the greater potency observed for 2 in vitro corresponds to a greater effect in the rat uterine weight assay,⁶ 2 is a weaker agent than tamoxifen against the dimethylbenzanthracene-induced mammary tumor in rats,^{9,10} and this has been attributed to rapid clearance of 2¹¹ by way of deactivating metabolic conjugation of the hydroxyl group, most probably to form a glucuronide. Indeed, plasma concentrations attained for 2 in patients on treatment with tamoxifen are low (~5 ng/mL; compare ca. 200 ng/mL for tamoxifen).⁵



We have sought to replace the hydroxyl group in 2 by a function were high affinity for the estrogen receptor is retained but there is not the propensity for metabolic conjugate formation. Of the few 4-substituted derivatives of tamoxifen apart from 2 that are known, the 4-chloro,

Scheme I. Preparation of 4-Iodo- and 4-Bromotamoxifen^a



^a Reagents: (a) 4-X-C₆H₄-X, *n*-BuLi (1 equiv), THF, -70–20 °C; (b) HCl (aqueous), EtOH, 80 °C; (c) Me₂NH, EtOH, 80 °C.

fluoro, and methyl derivatives have a similar potency to tamoxifen,^{12,13} and although the amino derivative has a

* Address correspondence to this author at the Cancer Research Campaign Laboratory, Institute of Cancer Research, Sutton, Surrey SM2 5NG, U.K.

† Institute of Cancer Research.

‡ Institut Jules Bordet.

§ University of Sheffield.

- Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. *Drugs* 1978, 16, 1.
- Furr, B. J. A.; Jordan, V. C. *Pharmacol. Ther.* 1984, 25, 127.
- Nicholson, R. I.; Daniel, P.; Gaskell, S. J.; Syne, J. S.; Davies, P.; Griffiths, K. *Antihormones* 1979, 253.
- Jordan, V. C. *Breast Cancer Res. Treat.* 1982, 2, 123.
- Daniel, C. P.; Gaskell, S. J.; Bishop, H.; Nicholson, R. I. *J. Endocrinol.* 1979, 83, 401.
- Jordan, V. C.; Collins, M.; Rowsby, L.; Prestwich, G. J. *Endocrinol.* 1977, 75, 305.
- Binart, N.; Catelli, M. G.; Geynet, C.; Puri, V.; Hahnel, R.; Mester, J.; Baulieu, E. E. *Biochem. Biophys. Res. Commun.* 1979, 91, 812.
- Wakeling, A. E.; Slater, S. R. *Cancer Treat. Rep.* 1980, 64, 741.
- Jordan, V. C.; Naylor, K. E. *Proc. Br. Pharmacol. Soc.* 1978, 376p.
- Jordan, V. C.; Allen, K. E. *Eur. J. Cancer* 1980, 16, 239.
- Jordan, V. C.; Allen, K. E. *Antihormones* 1979, 235.

greater affinity to the estrogen receptor than tamoxifen,¹³ the amino function is likely to be highly susceptible to metabolism. A further reason for studying 4-substituted tamoxifen derivatives is to establish, through structure-activity studies, some insight into the nature of the high-affinity binding interaction with the estrogen receptor and its role in determining antitumor activity. Hence a variety of 4-substituted tamoxifen derivatives were prepared.

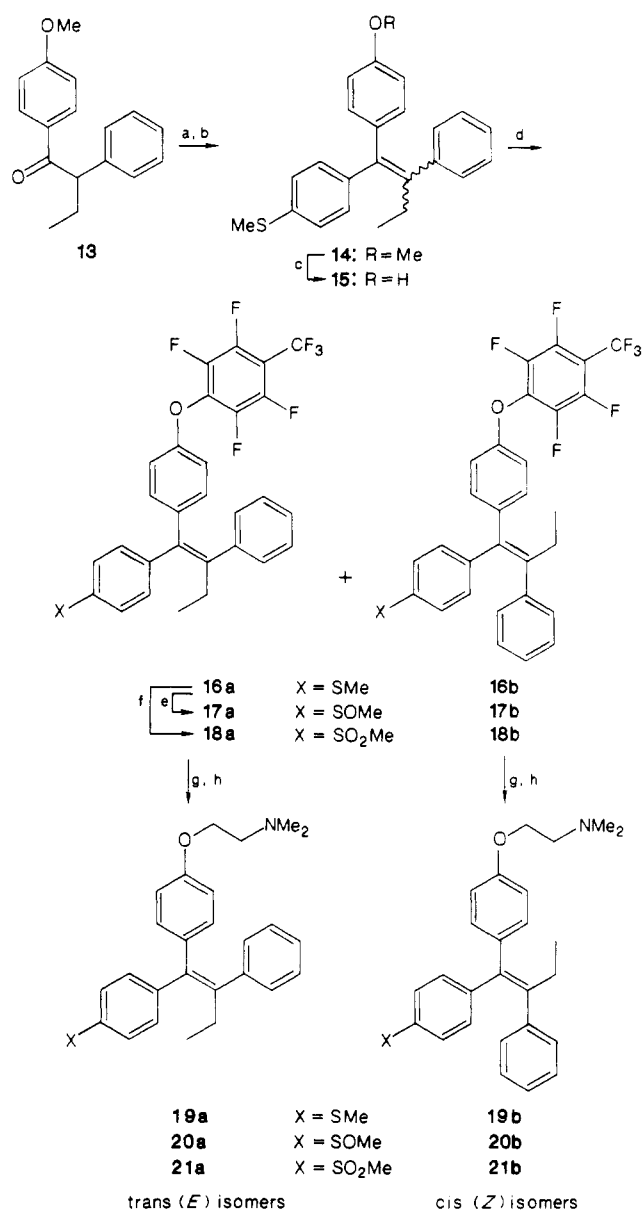
We report that, for a variety of 4-substituted derivatives of tamoxifen, whether the growth of breast tumor cells in culture is inhibited is not related to binding affinity for the estrogen receptor.

Results and Discussion

Synthesis. 4-Halogenotamoxifens. The synthesis of iodo and bromo derivatives of tamoxifen is outlined in Scheme I. The procedure essentially follows that reported in a synthesis of tamoxifen,¹⁴ substituting the appropriate (halophenyl)lithium for phenylmagnesium bromide. The required reagents were readily generated by treatment of a dihalobenzene with 1 equiv of *n*-butyllithium. Hence from the ketone 5 and 1,4-diiodobenzene, 4-iodotamoxifen was formed as a mixture of *E* (7a) and *Z* (7b) geometric isomers, from which it was possible to isolate the *E* (trans) isomer by chromatography on silica. (Trans and cis are used in this paper to designate the relative positions of the ethyl group and the ring bearing the basic side chain. Whether a compound of given configuration by this nomenclature is *Z* or *E* depends on the 4-substituent.) However, the preferred procedure employed the chloroethoxy ketone 4 and (4-iodophenyl)lithium to give compounds 6a and 6b, which were separable by fractional crystallization from 2-propanol. Treatment of the *E* (trans) isomer 6a with dimethylamine then gave 4-iodotamoxifen. Advantages of this route are that other alkylamine functions can be introduced and pure isomers are obtained. Thus, diethylamine and pyrrolidine gave respectively the derivatives 8 and 9. 4-Bromotamoxifen was prepared from the ketone 5 and 1,4-dibromobenzene. By careful control of the conditions for the dehydration of the intermediate tertiary alcohol, the *E*-trans isomer 10a was the predominant product (1.6:1) and could be isolated pure by fractional crystallization. 3-Iodotamoxifen (11) was similarly prepared from the ketone 5 and 1,3-diiodobenzene. The known 4-chlorotamoxifen (11) was prepared from the ketone 4 and (4-chlorophenyl)magnesium bromide.

Tamoxifen Analogues Bearing a Sulfur Substituent. The preparation of tamoxifen derivatives bearing SMe, SMe, and SO₂Me groups in the 4-position is outlined in Scheme II. The route employs the isomeric perfluorotolyl ethers 16a and 16b as common intermediates. As with previously described perfluorotolyl ethers of 1,1,2-triarylbutenes,^{15,16} the *Z* and *E* isomers 16a and 16b were easy to separate, in this case by a combination of fractional crystallization and chromatography. The isomers were individually converted into the methylthio derivatives of tamoxifen 19a and 19b by cleavage of the perfluorotolyl function with sodium methoxide in dimethylformamide followed by (dimethylamino)ethylation of the liberated phenol. Tamoxifen derivatives having the

Scheme II. Preparation of Sulfur-Substituted Tamoxifen Derivatives^a



sulfur atom in a higher oxidation state were prepared by oxidation of the intermediate ethers 16a and 16b. Direct oxidation of 4-(methylthio)tamoxifen was not used because there would be a problem of simultaneous *N*-oxide formation. Hydrogen peroxide gave the sulfoxides 17a/17b, and peroxyacetic acid gave the sulfone 18a/18b. These products were then converted into the tamoxifen derivatives as described for the methylthio analogue. Attempts to prepare the derivative bearing a thiol substituent by demethylation of 19a were not successful, but a route to the thiol is given below.

Tamoxifen Analogues Prepared from 4-Bromotamoxifen. Since 4-bromotamoxifen (10a) can be prepared on a large scale in pure geometric configuration, it is ideal as a common precursor for the preparation of a range of 4-substituted tamoxifen analogues (see Scheme III). Treatment of 4-bromotamoxifen with either *n*- or *tert*-butyllithium at low temperature generated an aryllithium species. For the preparation of the thiol 23, sulfur was

- (12) Allen, K. E.; Clark, E. R.; Jordan, V. C. *Br. J. Pharmacol.* 1980, 68, 171p.
- (13) Shani, J.; Gazit, A.; Livshitz, T.; Biran, S. *J. Med. Chem.* 1985, 28, 1504.
- (14) McCague, R. *J. Chem. Soc., Perkin Trans. 1* 1987, 1011.
- (15) Jarman, M.; McCague, R. *J. Chem. Res., Synop.* 1985, 116; *J. Chem. Res., Miniprint* 1985, 1342.
- (16) McCague, R. *J. Chem. Res., Synop.* 1986, 58; *J. Chem. Res., Miniprint* 1986, 771.

Table I. Receptor Binding Affinities (RBA) and Effect on Growth of the MCF-7 Cell Line

compound	4-Substituent	RBA calf uterine cytosol (estradiol = 100)	MCF-7 cell growth, ^{a-c} % of control \pm SD			DNA amts in controls ^d
			10 ⁻⁸ M	10 ⁻⁷ M	10 ⁻⁶ M	
trans isomers						
1 (<i>trans</i> -tamoxifen)	H	1	119 \pm 6**	100 \pm 6 (ns)	70 \pm 8***	A
7a	I	5	115 \pm 6**	42 \pm 6***	26 \pm 6***	B
8	I	5	101 \pm 7 (ns)	35 \pm 5***	23 \pm 2***	B
9	I	5	84 \pm 5***	27 \pm 3***	20 \pm 2***	C
10a	Br	5	130 \pm 10**	101 \pm 8 (ns)	63 \pm 8***	D
11	Cl	1	116 \pm 3*	119 \pm 8*	56 \pm 5***	E
12	(3-I)	2	100 \pm 8 (ns)	68 \pm 2***	27 \pm 5***	A
19a	SMe	3	154 \pm 9***	66 \pm 7***	54 \pm 5***	F
20a	SOMe	3	177 \pm 8***	237 \pm 15***	238 \pm 7***	G
21a	SO ₂ Me	6	125 \pm 6**	75 \pm 10**	29 \pm 3***	G
23	SH	1	94 \pm 4 (ns)	110 \pm 7 (ns)	147 \pm 10*	H
24	CHO	20	62 \pm 2***	38 \pm 7***	42 \pm 6***	I
25	CH ₂ OH	80	164 \pm 10***	145 \pm 7***	150 \pm 3***	C
26	CH(O)CH ₂	3	113 \pm 12 (ns)	42 \pm 5***	19 \pm 3***	C
cis isomers						
cis-tamoxifen	H	0.1	135 \pm 5***	140 \pm 5***	137 \pm 8***	A
7b	I	0.2	99 \pm 13 (ns)	126 \pm 6***	120 \pm 3***	B
10b	Br	0.2	110 \pm 3*	163 \pm 4***	174 \pm 8***	D
19b	SMe	0.1	102 \pm 4*	117 \pm 3***	69 \pm 4***	J
20b	SOMe	0.3	112 \pm 9 (ns)	135 \pm 7***	67 \pm 5***	G
21b	SO ₂ Me	0.6	88 \pm 12 (ns)	114 \pm 5**	140 \pm 7***	G

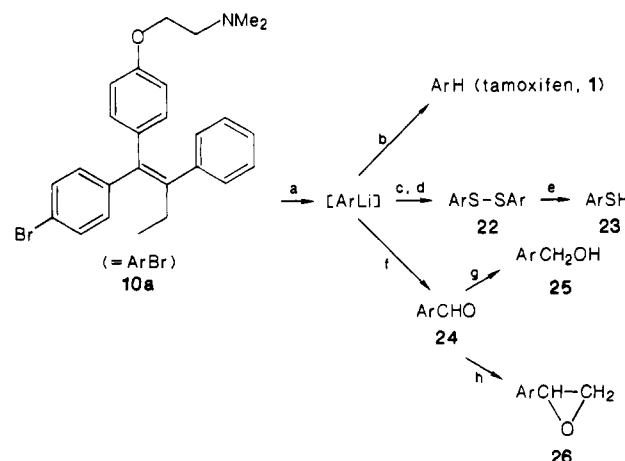
^a The indicator phenol red, a weak estrogen, was present in the culture medium and may have influenced the results obtained. ^b Previously recorded values for tamoxifen: 10⁻⁷ M, 82% of control; 10⁻⁶ M, 55%, and for 4-hydroxytamoxifen, 10⁻⁸ M, 48%; 10⁻⁷ M, 38%; 10⁻⁶ M, 15%. N.B. A value over 100% implies a greater rate of growth than that of the control. ^c One-way variance analysis showed that all compounds produce a significant effect on cell growth; the Newman-Keuls test showed that they are effective at either 10⁻⁸, 10⁻⁷, or 10⁻⁶ M. (*) $p < 0.05$; (**) $p < 0.01$; (***) $p < 0.001$. "ns" indicates no significant effect on cell growth at the concentration given. ^d DNA amounts in controls (100% reference) (μ g of DNA \pm SD): A = 20.7 \pm 1.9; B = 15.3 \pm 0.5; C = 13.0 \pm 1.1; D = 14.5 \pm 0.7; E = 11.6 \pm 1.4; F = 12.6 \pm 0.9; G = 15.4 \pm 0.9; H = 14.1 \pm 0.7; I = 16.2 \pm 0.9; J = 21.4 \pm 0.8. SD values for effects of compounds at 10⁻⁸–10⁻⁶ M do not take into account the SD of control data.

added. It was necessary, in this case, to use *tert*-butyllithium rather than *n*-butyllithium since with the latter reagent the aryl thiolate would undergo alkylation by the liberated bromobutane. Isolation of the thiol directly from the resulting product mixture proved impractical. It was preferable to oxidize the product mixture and isolate the easily purified disulfide (22). The thiol was then readily obtained by reduction with triphenylphosphine in aqueous dioxane.

Attachment of a carbon atom to give the aldehyde 24 was accomplished by treatment of the aryllithium with *N*-formylpiperidine.¹⁷ The aldehyde group could then be modified by standard procedures. Thus, reduction with sodium borohydride gave the benzylic alcohol 25, and treatment with trimethylsulfonium iodide¹⁸ in the presence of base gave the epoxide 26, which might have alkylating activity.

Assignment of Configuration. The products were readily assigned as *trans* or *cis* configuration by proton NMR spectroscopy. In all of the tamoxifen derivatives studied, there was no exception to the rule¹⁹ that only in the *trans* isomers do the OCH₂ protons of the side chain have a chemical shift (δ) of less than 4.0 ppm owing to the through-space shielding influence of the vicinal 2-phenyl substituent.

Apart from the NMR evidence, the configurations of the 4-substituted derivatives could be related to (*Z*)- or (*E*)-tamoxifen. Protonation of the aryllithium intermediate generated from 10a gave (*Z*)-tamoxifen. If the disulfide 22 was reduced in the presence of methanol instead of dioxane as cosolvent, the *trans* methylthio derivative 19a was a byproduct. The *cis* methylthio derivative 19b

Scheme III. Synthesis of Various 4-Substituted Tamoxifen Derivatives from 4-Bromotamoxifen^a

^a Reagents: (a) *n*-BuLi or *t*-BuLi, THF, -78 °C; (b) H₂O; (c) S₈; (d) H₂O₂; (e) PPh₃, H₂O, dioxane; (f) (CH₂)₅NCHO; (g) NaBH₄, EtOH; (h) Me₃S⁺I⁻, NaH, Me₂SO.

has been shown independently to have the expected configuration by X-ray crystallography.²⁰

Endocrinological Properties and General Discussion. Table I gives values for relative binding affinity (RBA) to estrogen receptors in calf uterine cytosol. As for tamoxifen, the *trans* derivatives displayed higher binding affinities than the corresponding *cis* isomers. Most of the derivatives studied possessed a slightly higher binding affinity than the parent drug. Exceptions are 4-chlorotamoxifen (11) and the thiol 23, which had an identical RBA to tamoxifen, and compounds 24 (CHO) and 25 (CH₂OH), which had a markedly increased affinity

(17) Olah, G. H.; Arvanaghi, M. *Angew. Chem., Int. Ed.* **1981**, *20*, 878.

(18) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(19) Collins, D. J.; Hobbs, J. J.; Emmens, C. W. *J. Med. Chem.* **1971**, *14*, 952.

(20) Blackburn, G. M.; Goodman, J.; Smith, A. J. *Acta Crystallogr.* **1988**, *C44*, 1629.

(RBA = 20 and 80, respectively).

Binding affinity values alone do not give information on whether compounds are estrogen agonists or antagonists. A distinction can be made by determining the effect on the growth of the MCF-7 human breast tumor cell line in vitro,^{21,22} and the results of such an assay are given also in Table I. Depending on the 4-substituent, the tamoxifen derivatives having trans stereochemistry displayed a striking variance in their profiles of activity against the MCF-7 cell line that certainly could not have been predicted from the RBA data. At the concentrations tested (10^{-8} – 10^{-6} M) some derivatives produced a marked growth inhibition whereas others produced a strong stimulation. On the contrary, the *cis*-tamoxifen derivatives were essentially estrogen agonists lacking any tumor inhibition at 10^{-7} M, paralleling data for *cis*-tamoxifen. Yet the *cis* methylthio and methyl sulfoxide derivatives did show some inhibition at 10^{-6} M, which for the latter is especially unexpected in view of the contrasting strong estrogenic activity of its trans isomer.

The profile of activity on proceeding through the series of halogen-substituted tamoxifens was unusual. Fluoro- and chlorotamoxifen are reported to be antiestrogens having similar potencies as tamoxifen,^{12,13} and we can confirm this result for 4-chlorotamoxifen. Substitution by the larger halogens, bromine and iodine, gave a 5-fold increase in RBA. Despite its higher RBA, 4-bromotamoxifen was less effective than tamoxifen at inhibiting the growth of the MCF-7 cell line; indeed, its action at 10^{-8} M was as an agonist. On the other hand, 4-iodotamoxifen had improved inhibitory potency when compared with tamoxifen at 10^{-7} and 10^{-6} M as did the 3-iodo isomer. This improved potency brought about by the incorporation of iodine could be due to an ability of iodine to form a polar interaction to the site of the receptor protein that binds the hydroxyl hydrogen of 2. Relatively strong directional interactions between iodine (and other heavier p-block elements) with nucleophilic sites have been revealed by analysis of crystal structures;²³ an example of an intermolecular iodine–oxygen association has been found in the crystal structure of the thyroxine–prealbumin complex.²⁴ Known iodinated tamoxifen derivatives in radiolabeled form have been proposed for use in imaging or site-selective radiotherapy.^{25,26} For these purposes, 4-iodotamoxifen may be more suitable because of its higher affinity for the estrogen receptor.

Very marked differences were also seen in the series of sulfur-substituted tamoxifen analogues. The strong growth stimulation by the methyl sulfoxide and weaker stimulation by the thiol contrasted the growth inhibition by the methyl sulfide and methyl sulfone. This behavior could not have been predicted from values of relative binding affinity (RBA) to the estrogen receptor (ER), which differed only 2-fold between the sulfoxide and sulfone. The

MCF-7 cell growth stimulation by the hydroxymethyl derivative was also surprising in view of its comparable RBA value to that of the strong inhibitor 4-hydroxytamoxifen. For this hydroxymethyl compound, a relative binding affinity was also determined in MCF-7 whole cells. The whole cell assay has been shown to correlate with ER activation and processing and gives a measure of estrogen agonism.^{27,28} Since both 4-hydroxytamoxifen (whole cell RBA = 2.9) and the hydroxymethyl derivative (whole cell RBA = 1.5) are, according to this assay, comparably estrogenic, the difference in tumor growth inhibitory ability must be due to inability of the hydroxymethyl derivative to bring about a necessary interaction that gives rise to tumor inhibition. Unlike the hydroxymethyl compound, the aldehyde did inhibit MCF-7 cell growth.

The derivative bearing the epoxide group gave a similar growth inhibitory profile to other antiestrogens, and there was no evidence to indicate cytotoxicity arising from alkylation of ER. Steroidal estrogens bearing epoxide groups have similarly been found to not have any specific alkylating activity toward ER.²⁹

To conclude, we have described a series of tamoxifen derivatives in which the abilities to inhibit MCF-7 cell growth do not correlate with the binding affinities for the estrogen receptor. In this respect, it is noteworthy that several targets apart from the estradiol binding site of the estrogen receptor, upon which tamoxifen might act in exerting its antitumor action, have been identified.^{30–36} For further biological studies aimed to determine the importance of possible proposed mechanisms of tumor growth inhibition by the triarylethylene antiestrogens, the 4-substituted tamoxifen derivatives described should prove valuable.

Experimental Section

Chemical Methods. General Procedures. ¹H NMR spectra (internal Me₄Si) were obtained with Bruker AC250 and AM250 spectrometers and 220-MHz spectra with a Perkin-Elmer R34 instrument. Mass spectra (electron impact, 70 eV) were obtained with a VG 7070H spectrometer and VG 2235 data station or a Kratos MS80RF spectrometer with a Kratos DS55 data station. Melting points were determined on a Kofler hot stage. Chromatography refers to column chromatography on silica gel (Merck 15111) with the eluant indicated applied at a positive pressure of 0.5 atm. THF refers to tetrahydrofuran. When *E* and *Z* geometric isomers were separated, it was carried out to the point where none of the other isomer could be detected by proton NMR spectroscopy.

(E)- and (Z)-1-[4-(2-Chloroethoxy)phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (6a and 6b). To a stirred solution of 1,4-diiodobenzene (21.8 g, 66 mmol) in dry THF (100 mL) under N₂ at ca. –75 °C was introduced *n*-butyllithium (41.2 mL of a 1.6 M solution in hexane, 66 mmol) over 5 min. After 10 min, a solution of 1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butanone (4)¹⁸ (20.0 g, 66 mmol) in dry THF was added and the mixture allowed

- (21) Leclercq, G.; Devleeschouwer, N.; Heuson, J.-C. *J. Steroid Biochem.* **1983**, *19*, 75.
- (22) Foster, A. B.; Jarman, M.; Leung, O.-T.; McCague, R.; Leclercq, G.; Devleeschouwer, N. *J. Med. Chem.* **1985**, *28*, 1491.
- (23) Murray-Rust, P.; Motherwell, W. D. S. *J. Am. Chem. Soc.* **1979**, *101*, 4374.
- (24) Blaney, J. M.; Jorgensen, E. C.; Connolly, M. L.; Ferrin, T. E.; Langridge, R.; Oatley, S. J.; Burrige, J. M.; Blake, C. C. F. *J. Med. Chem.* **1982**, *25*, 785.
- (25) Bloomer, W. D.; McLaughlin, W. H.; Weichselbaum, R. R.; Tonnesen, G. L.; Hellman, S.; Seitz, D. E.; Hanson, R. N.; Adelstein, S. J.; Rosner, A. L.; Burnstein, N. A.; Nove, J. J.; Little, J. B. *Int. J. Radiat. Biol.* **1980**, *38*, 197.
- (26) Hunter, D. H.; Payne, N. C.; Rahman, A.; Richardson, J. F.; Ponce, Y. Z. *Can. J. Chem.* **1983**, *61*, 421.

- (27) Stoessel, S.; Leclercq, G. *J. Steroid Biochem.* **1986**, *25*, 677.
- (28) Gyling, M.; Leclercq, G. *J. Steroid Biochem.* **1988**, *29*, 1.
- (29) Gill, J. C.; Lockey, P. M.; Marples, B. A.; Traynor, J. R. *J. Med. Chem.* **1986**, *29*, 1537.
- (30) Martin, P. M.; Berthois, Y.; Jensen, E. V. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 2533.
- (31) Vignon, F.; Bouton, M.-M.; Rochefort, H. *Biochem. Biophys. Res. Commun.* **1987**, *146*, 1502.
- (32) Su, H. D.; Mazzei, G. J.; Vogler, W. R.; Kuo, J. F. *Biochem. Pharmacol.* **1985**, *34*, 3649.
- (33) O'Brian, C. A.; Liskamp, R. M.; Solomon, D. H.; Weinstein, I. B. *Cancer Res.* **1985**, *45*, 2462.
- (34) Lam, H. Y. P. *Biochem. Biophys. Res. Commun.* **1984**, *118*, 27.
- (35) Sutherland, R. L.; Watts, C. K. W.; Hall, R. E.; Ruenitz, P. C. *J. Steroid Biochem.* **1987**, *27*, 891.
- (36) Brandes, L. J.; Bogdanovic, R. P.; Cawker, M. D.; Bose, R. *Cancer Chemother. Pharmacol.* **1986**, *18*, 21.

to attain ambient temperature. After 20 h, the mixture was partitioned between Et₂O (200 mL) and H₂O (200 mL). The Et₂O solution was concentrated and the residual oil dissolved in EtOH (300 mL). Concentrated HCl (100 mL) was added, and the mixture was heated under reflux for 4 h and then cooled and poured into water (300 mL). The products were extracted with Et₂O (2 × 150 mL), and the combined extracts were washed with H₂O (200 mL), dried with Na₂SO₄, and concentrated to give a brown oil which was dissolved in EtOH (200 mL). Crystals of mainly the desired *E*-trans isomer **6a** were deposited, and recrystallization from EtOH gave the pure isomer (12.92 g, 40%): mp 96–97 °C; δ_{H} (CDCl₃) 0.91 (t, *J* = 7.4 Hz, 3, CH₃CH₂), 2.44 (q, *J* = 7.4 Hz, 2, CH₃CH₂), 3.73 (t, *J* = 5.9 Hz, 2, CH₂CH₂Cl), 4.10 (t, *J* = 5.9 Hz, 2, CH₂CH₂Cl), 6.55 (d, *J* = 8.8 Hz, 2, ArH ortho to OCH₂), 6.75 (d, *J* = 8.8 Hz, 2, ArH meta to OCH₂), 6.98 (d, *J* = 8.3 Hz, 2, ArH meta to I), 7.07–7.22 (m, 5, Ph), 7.67 (d, *J* = 8.3 Hz, 2, ArH ortho to I). Anal. (C₂₄H₂₂ClIO) C, H, Cl, I.

Concentration of the original mother liquors gave the *Z*-cis isomer **6b** (7.03 g, 22%): mp 110–112 °C; δ_{H} (CDCl₃) 0.93 (t, *J* = 7.4 Hz, 3, CH₃CH₂), 2.47 (q, *J* = 7.4 Hz, 2, CH₃CH₂), 3.84 (t, *J* = 5.9 Hz, 2, CH₂CH₂Cl), 4.25 (t, *J* = 5.9 Hz, 2, CH₂CH₂Cl), 6.59 (d, *J* = 8.4 Hz, 2, ArH meta to I), 6.90 (d, *J* = 8.7 Hz, 2, ArH ortho to OCH₂), 7.06–7.21 (m, 7, ArH), 7.32 (d, *J* = 8.4 Hz, 2, ArH ortho to I). Anal. (C₂₄H₂₂ClIO) C, H, Cl, I.

(E)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (4-Iodotamoxifen, 7a). A solution of **6a** (3.05 g) in 33% HNMe₂ in EtOH (60 mL) was heated under reflux. After 20 h, the mixture was concentrated, a further 33% HNMe₂ in EtOH (60 mL) added, and reflux continued for a further 20 h. The mixture was then again concentrated and the residue partitioned between Et₂O (50 mL) and NaOH (1 M; 50 mL). The Et₂O solution was concentrated and the residue applied to a column of silica gel (Merck 15111; 40 g). Elution with 1:20:20 NEt₃-Et₂O-petroleum ether (bp 60–80 °C) gave **7a** (2.60 g, 84%): mp 112–114 °C (from petroleum ether, bp 40–60 °C); δ_{H} (CDCl₃) 0.91 (t, *J* = 7.4 Hz, 3, CH₃CH₂), 2.28 (s, 6, NMe₂), 2.43 (q, *J* = 7.4 Hz, 2, CH₃CH₂), 2.64 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 3.92 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 6.55 (d, *J* = 8.8 Hz, 2, ArH ortho to OCH₂), 6.73 (d, *J* = 8.8 Hz, 2, ArH meta to OCH₂), 6.98 (d, *J* = 8.3 Hz, 2, ArH meta to I), 7.04–7.22 (m, 5, Ph), 7.66 (d, *J* = 8.3 Hz, 2, ArH ortho to I); *m/z* 497 (M⁺, 36%), 380 (3%), 252 (13%), 72 (100%), and 58 (100%). Anal. (C₂₆H₂₈INO) C, H, N, I.

(Z)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (7b). **6b** (1.01 g) was heated with HNMe₂ by the method described above for the conversion of **6a** into **7a** to give **7b** (0.80 g, 77% yield): mp 71–72 °C (from cold petroleum ether, bp 40–60 °C); δ_{H} (CDCl₃) 0.92 (t, *J* = 7.4 Hz, 3, CH₃CH₂), 2.35 (s, 6, NMe₂), 2.48 (q, *J* = 7.4 Hz, 2, CH₃CH₂), 2.75 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 4.08 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 6.60 (d, *J* = 8.5 Hz, 2, ArH meta to I), 6.89 (d, *J* = 8.7 Hz, 2, ArH ortho to O), 7.05–7.25 (m, 7, ArH), 7.31 (d, *J* = 8.5 Hz, 2, ArH ortho to I). Anal. (C₂₆H₂₈INO) C, H, N, I.

(E)-1-[4-[2-(Diethylamino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (8). **6a** (1.069 g) in Et₃NH (20 mL) and EtOH (20 mL) was heated under reflux for 2 days. Workup and chromatography as described in the preparation of **7a** gave **8** (1.03 g, 93%): mp 58–59 °C (from cold petroleum ether, bp 40–60 °C). Anal. (C₂₈H₃₂INO) C, H, N, I.

(E)-1-[4-[2-(N-Pyrrolidino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (9). A solution of **6a** (1.748 g) in pyrrolidine (10 mL) and EtOH (30 mL) was heated under reflux for 2 h. The mixture was concentrated and partitioned between Et₂O (30 mL) and NaOH (1 M; 30 mL). Concentration of the Et₂O layer and recrystallization of the residue from petroleum ether (bp 80–100 °C) gave **9** (1.72 g, 92%): mp 108–109 °C. Anal. (C₂₈H₃₀INO) C, H, N, I.

(E)- and (Z)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-(4-bromophenyl)-2-phenyl-1-butene (4-Bromotamoxifen, 10a and 10b). A stirred solution of 1,4-dibromobenzene (6.88 g, 19.15 mmol) in dry THF (30 mL) was cooled under N₂ to –75 °C and *n*-BuLi (15.1 mL of a 1.55 M solution in hexane; 24 mmol) added over 2 min. After 10 min, a solution of **5** (6.09 g, 19.43 mmol) in THF (15 mL) was added and the mixture allowed to attain ambient temperature. After 16 h the mixture was partitioned between Et₂O (100 mL) and H₂O (100 mL). The Et₂O solution

was concentrated and the crude tertiary alcohol dissolved in EtOH (100 mL). Concentrated HCl (60 mL) was added, and the mixture was heated under gentle reflux for 20 h and then cooled and partitioned between Et₂O (200 mL) and NaOH (5 M; 200 mL). The Et₂O solution was concentrated and the residue dissolved in hot petroleum ether (bp 80–100 °C) (40 mL). Cooling gave crystals of **10a** (2.78 g, 32% yield): mp 114–116 °C; δ_{H} (CDCl₃) 0.91 (t, *J* = 7.4 Hz, 3, CH₃CH₂), 2.28 (s, 6, NMe₂), 2.44 (q, *J* = 7.4 Hz, 2, CH₃CH₂), 2.64 (t, *J* = 5.7 Hz, 2, OCH₂CH₂N), 3.92 (t, *J* = 5.7 Hz, 2, OCH₂CH₂N), 6.56 (d, *J* = 8.8 Hz, 2, ArH ortho to O), 6.73 (d, *J* = 8.8 Hz, 2, ArH meta to O), 7.08–7.26 (m, 7, ArH), 7.46 (d, *J* = 8.3 Hz, 2, ArH ortho to Br). Anal. (C₂₆H₂₈BrNO) C, H, N, Br.

The mother liquors from the crystallization were concentrated, and the residue was applied to a column of silica gel (60 g). Elution with 20:20:1 petroleum ether (bp 40–60 °C)-Et₂O-Et₃N gave further 4-bromotamoxifen (4.94 g, total yield 88%) as a mixture of *Z* and *E* isomers, which on recrystallization from petroleum ether (bp 80–100 °C) gave further **10a** (0.19 g) and then **10b** (1.10 g): mp 77–78 °C; δ_{H} (CDCl₃) 0.92 (t, *J* = 7.4 Hz, 3, CH₃CH₂), 2.34 (s, 6, NMe₂), 2.48 (q, *J* = 7.4 Hz, 2, CH₃CH₂), 2.74 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 4.08 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 6.72 (d, *J* = 8.4 Hz, 2, ArH meta to Br), 6.89 (d, *J* = 8.5 Hz, 2, ArH ortho to O), 7.05–7.20 (m, 9, ArH). Anal. (C₂₆H₂₈BrNO) C, H, N, Br.

The proportion of isomers in the crude product was estimated as 1.2:1 **10a**:**10b**. In a subsequent reaction a milder dehydration procedure (25 mL of concentrated HCl, 200 mL of EtOH, reflux 30 min) was employed. The isomer ratio was improved to 1.6:1 **10a**:**10b**, but the yield was lower (72%; 35% of **10a** isolated after recrystallization).

(E)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-(4-chlorophenyl)-2-phenyl-1-butene (4-Chlorotamoxifen, 11). The method for the preparation of 4-iodotamoxifen, **4** → **6a** → **7a**, was followed but with treatment of **4** (7.63 g, 25 mmol) with 4-(chlorophenyl)magnesium bromide (1 M solution in Et₂O, 30 mL, 30 mmol) in Et₂O (50 mL). The chloroethoxy-substituted triarylbutene obtained (8.74 g, 88% yield) was a 1.9:1 mixture of *E* and *Z* isomers from which pure *E* isomer (4.03 g, 40%) was obtained on recrystallization from 2-propanol. Conversion to the amine **11** proceeded in 86% yield: mp 112.5–113.5 °C (lit.¹⁰ mp 112 °C); δ_{H} (CDCl₃) 0.91 (t, *J* = 7.4 Hz, 3, CH₃CH₂), 2.28 (s, 6, NMe₂), 2.44 (q, *J* = 7.4 Hz, 2, CH₃CH₂), 2.64 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 3.92 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 6.55 (d, *J* = 8.9 Hz, 2, ArH ortho to OCH₂), 6.73 (d, *J* = 8.9 Hz, 2, ArH meta to OCH₂), 7.0–7.19 (m, 7, ArH), 7.31 (d, *J* = 8.5 Hz, 2, ArH ortho to Cl).

(E)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-(3-iodophenyl)-2-phenyl-1-butene (3-Iodotamoxifen, 12). The method for the preparation of 4-iodotamoxifen, **4** → **6a** → **7a**, was followed, but 1,3-diiodobenzene was substituted for 1,4-diiodobenzene. The chloroethoxy-substituted triarylbutene, obtained as an oil (80% yield), was a mixture of isomers, converted without separation into the amine **12** which, when dissolved in cyclohexane, gave the *E* isomer as needles (27% yield): mp 60–62 °C; δ_{H} (CDCl₃) 0.91 (t, *J* = 7.4 Hz, 3, CH₃CH₂), 2.29 (s, 6, NMe₂), 2.43 (q, *J* = 7.4 Hz, 2, CH₃CH₂), 2.65 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 3.93 (t, *J* = 5.8 Hz, 2, OCH₂CH₂N), 6.56 (d, *J* = 8.8 Hz, 2, ArH ortho to OCH₂), 6.74 (d, *J* = 8.8 Hz, 2, ArH meta to OCH₂), 7.05–7.24 (m, 7, ArH), 7.58–7.63 (m, 2, ArH ortho to I); *m/z* 497 (M⁺, 10%), 72 (53%), and 58 (100%). Anal. (C₂₆H₂₈INO) C, H, N, I.

1-(4-Methoxyphenyl)-1-[4-(methoxythio)phenyl]-2-phenylbut-1-ene (14). Magnesium turnings (1.35 g, 56 mmol) were covered with a solution of 4-(bromothio)anisole (5.7 g, 25 mmol) in Et₂O (50 mL). The mixture was stirred and heated to reflux while a solution of BrCH₂CH₂Br (5.28 g, 28 mmol) in Et₂O was added dropwise over 4 h. A solution of 1-(4-methoxyphenyl)-2-phenylbutan-1-one (**13**)²⁷ (6.7 g, 26 mmol) in Et₂O (50 mL) was added over 1 h and reflux maintained for 12 h. The mixture was then cooled and Mg residues destroyed with dilute HCl (1 M). The organic and aqueous layers were separated. The aqueous layer was extracted with ether (100 mL) and the extract dried over MgSO₄. Concentration under reduced pressure gave crude tertiary alcohol which was dissolved in EtOH. Concentrated H₂SO₄ (10 equiv) was then added, and the mixture was stirred at room temperature for 1 h and then neutralized with saturated NaHCO₃ solution. The mixture was extracted with CHCl₃ and

the extract dried over MgSO_4 . Concentration under reduced pressure gave **14** as a 1:1 mixture of *Z* and *E* isomers (6.43 g, 68%): mp 101–103 °C (from EtOH); δ_{H} (CDCl_3) 0.89 (t, 3), 2.33 (s) + 2.47 (s) + 2.40–2.54 (m) (5), 3.66 (s) + 3.70 (s) (3), 6.53 (d) + 6.77 (d) + 6.86 (d) + 7.05–7.25 (m) (13); m/z 360 (M^+). Anal. ($\text{C}_{24}\text{H}_{24}\text{OS}$) C, H, S.

1-(4-Hydroxyphenyl)-1-[4-(methylthio)phenyl]-2-phenylbut-1-ene (15). Concentrated HCl (aqueous) (5.5 mL) was added rapidly to pyridine (5 mL), and then water was distilled from the mixture until an internal temperature of 210 °C was reached. The reaction vessel was purged with N_2 , **14** (0.2 g, 0.5 mmol) added, and the mixture heated at 200 °C for 2 h. The mixture was then allowed to cool to below 100 °C, diluted with warm water (5 mL), and poured into hot water (40 mL). The solution was cooled and extracted with Et_2O , and the combined extracts were dried over MgSO_4 and concentrated to give **15** as an oil, which solidified on trituration under petroleum ether. It was a 1:1 mixture of *Z* and *E* isomers (0.14 g, 73%): mp 86–88 °C; ν_{max} 3590, 3400–3200 cm^{-1} ; δ_{H} (CDCl_3) 0.89 (t, 3), 2.32 (s) + 2.46 (s) + 2.40–2.52 (m) (5), 4.8–5.0 (bs, 1), 6.44 (d) + 6.68–7.25 (m) (13); m/z 346 (M^+). Anal. ($\text{C}_{23}\text{H}_{22}\text{OS}$) C, H, S.

(E)- and (Z)-1-[4-(Methylthio)phenyl]-1-[4-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]phenyl]-2-phenylbut-1-ene (16a and 16b). A mixture of **15** (4.69 g, 13.5 mmol), octafluorotoluene (3.72 g, 14 mmol), and $\text{Bu}_4\text{N}^+\text{HSO}_4^-$ (2.4 g, 7 mmol) in CH_2Cl_2 (40 mL) and NaOH (1 M; 40 mL) was shaken at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (40 mL). The combined CH_2Cl_2 solutions were washed with water (50 mL) and dried over Na_2SO_4 . Concentration gave a mixture of **16a** and **16b** as an oil which solidified on standing (5.17 g, 81%). Recrystallization twice from petroleum ether (bp 60–80 °C) gave *Z* isomer (1.2 g): mp 143–145 °C; δ_{H} (CDCl_3) 0.9 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.34 (s, 3, SMe), 2.46 (q, $J = 7$ Hz, 2, CH_3CH_2), 6.74 (d, $J = 9$ Hz, 2, ArH ortho to O), 6.88 (d, $J = 9$ Hz, 2, ArH meta to O), 6.97 (d, $J = 9$ Hz, 2, ArH ortho to S), 7.05–7.20 (m, 5, Ph), 7.21 (d, $J = 9$ Hz, 2, ArH meta to S); δ_{F} –56.4 (t, $J = 22$ Hz, F para to CF_3), –141 (m, 2, F ortho to CF_3), –152 (m, 2, F meta to CF_3); m/z 562 (M^+). Anal. ($\text{C}_{30}\text{H}_{21}\text{F}_7\text{OS}$) C, H, S.

The residue from the mother liquors of the crystallizations was applied to a column of silica gel which was eluted with 2% EtOAc in petroleum ether (bp 60–80 °C). Concentration of appropriate fractions gave the *E* isomer **16a** (0.41 g): mp 81–82 °C; δ_{H} (CDCl_3) 0.93 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.49 (s, 3, SMe), 2.49 (q, $J = 7$ Hz, 2, CH_3CH_2), 6.63 (d, $J = 9$ Hz, 2, ArH ortho to S), 6.85 (d, $J = 9$ Hz, 2, ArH meta to S), 7.12 (m, 7), 7.25 (d, $J = 7$ Hz, 2, ArH meta to O); m/z 562 (M^+). Anal. ($\text{C}_{30}\text{H}_{21}\text{F}_7\text{OS}$) C, H, S.

(E)- and (Z)-1-[4-(Methylsulfinyl)phenyl]-1-[4-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]phenyl]-2-phenylbut-1-ene (17a and 17b). To a suspension of **16a** (0.76 g, 1.35 mmol) in HOAc (15 mL) was added H_2O_2 (30 volumes; 0.49 mL), and the mixture was heated under reflux for 2 h. The solution was then poured into water, neutralized with saturated aqueous NaHCO_3 , and extracted into CHCl_3 . The combined extracts were dried over MgSO_4 , and the solvent was evaporated. Chromatography of the residue on silica gel gave, on elution with 2% MeOH in CH_2Cl_2 , **17a** (0.4 g, 51%) as crystals: mp 37–41 °C; δ_{H} (CDCl_3) 0.95 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.48 (q, $J = 7$ Hz, 2, CH_3CH_2), 2.78 (s, 3, SOMe), 6.68 (d, $J = 9$ Hz, 2, ArH ortho to O), 6.86 (d, $J = 9$ Hz, 2, ArH meta to O), 7.1–7.25 (m, 5, Ph), 7.44 (d, $J = 9$ Hz, 2, ArH meta to S), 7.68 (d, $J = 9$ Hz, 2, ArH ortho to S); m/z 578 (M^+).

Similar treatment of **16b** (0.56 g) gave **17b** (0.5 g, 87%): mp 155–156 °C (from petroleum ether, bp 60–80 °C); δ_{H} (CDCl_3) 0.93 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.57 (q, $J = 7$ Hz, 2, CH_3CH_2), 2.61 (s, 3, SOMe), 7.0–7.35 (m, 13, ArH); m/z 578 (M^+). Anal. ($\text{C}_{30}\text{H}_{21}\text{F}_7\text{O}_2\text{S}$) C, H, S.

(E)- and (Z)-1-[4-(Methylsulfonyl)phenyl]-1-[4-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]phenyl]-2-phenylbut-1-ene (18a and 18b). Peroxylauric acid (0.44 g, 95%; 2.5 equiv) was added to a solution of **16a** (0.44 g, 0.8 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The solution was stirred at room temperature for 2 h and then concentrated under reduced pressure. Chromatography of the residue on basic alumina gave **18a** (0.35 g, 75%): mp 171 °C (from EtOH); δ_{H} (CDCl_3) 0.95 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.48 (q, $J = 7$ Hz, 2, CH_3CH_2), 3.09 (s, 3, SO_2Me),

6.68 (d, $J = 9$ Hz, 2, ArH ortho to O), 6.85 (d, $J = 9$ Hz, 2, ArH meta to O), 7.1–7.27 (m, 5, Ph), 7.47 (d, $J = 9$ Hz, 2, ArH meta to S), 7.96 (d, $J = 9$ Hz, 2, ArH ortho to S); m/z 594.1123, calcd for $\text{C}_{30}\text{H}_{21}\text{F}_7\text{O}_3\text{S}$ 594.1099.

Similar treatment of **16b** (1.0 g, 1.8 mmol) gave **18b** (0.71 g, 67%): mp 149 °C (from EtOH); δ_{H} (CDCl_3) 0.93 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.51 (q, $J = 7$ Hz, 2, CH_3CH_2), 2.95 (s, 3, SO_2Me), 7.0–7.27 (m, 11, ArH) 7.69 (d, $J = 9$ Hz, 2, ArH ortho to S); m/z (positive ion FAB) 594 (M^+). Anal. ($\text{C}_{30}\text{H}_{21}\text{F}_7\text{O}_3\text{S}$) C, H, S.

(E)- and (Z)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-[4-(methylthio)phenyl]-2-phenylbut-1-ene [4-(Methylthio)-tamoxifen, 19a and 19b]. To a solution of **16a** (0.41 g, 0.73 mmol) in dry Me_2NCHO (4 mL) was added NaOMe (0.23 g, 4.5 mmol), and the mixture was stirred at 40 °C for 2 h. The mixture was then portioned between Et_2O (20 mL) and diluted H_2SO_4 (0.05 M; 20 mL). The Et_2O layer was dried over MgSO_4 and concentrated. The crude phenol was dissolved in dry Me_2NCHO (4 mL) under N_2 , NaH (0.28 g, 11 mmol) was added, and the mixture was stirred and heated to 40 °C. Then $\text{Me}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{Cl}\cdot\text{HCl}$ (0.53 g, 3.7 mmol) was added in small portions over 30 min, and the mixture was maintained at 40 °C for a further 30 min. Excess NaH was destroyed by the addition of water and the resulting solution partitioned between Et_2O and water (20 mL each). The aqueous layer was further extracted with Et_2O , the combined Et_2O solutions were dried over MgSO_4 , and the solvent was evaporated. Chromatography of the residue gave on elution with methanol **19a** (0.16 g, 52%): mp 79–80 °C (from petroleum ether, bp 60–80 °C); δ_{H} (CDCl_3) 0.92 (t, $J = 7.4$ Hz, 3, CH_3CH_2), 2.29 (s, 6, NMe_2), 2.47 (q, $J = 7.4$ Hz, 2, CH_3CH_2), 2.51 (s, 3, SMe), 2.65 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 3.93 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.56 (d, $J = 8.8$ Hz, 2, ArH ortho to O), 6.76 (d, $J = 8.8$ Hz, 2, ArH meta to O), 7.07–7.12 (m, 5, Ph), 7.16 (d, $J = 8.4$ Hz, 2), 7.24 (d, $J = 8.4$ Hz, 2); m/z 417 (M^+). Anal. ($\text{C}_{27}\text{H}_{31}\text{NOS}$) C, H, N, S.

Similar treatment of **16b** (1.1 g, 1.9 mmol) gave **19b** (0.24 g, 29%): mp 92–93 °C (from petroleum ether, bp 60–80 °C); δ_{H} (CDCl_3) 0.92 (t, $J = 7.4$ Hz, 3, CH_3CH_2), 2.35 (s, 6, NMe_2), 2.36 (s, 3, SMe), 2.48 (q, $J = 7.4$ Hz, 2, CH_3CH_2), 2.74 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 4.04 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.77 (d, $J = 8.4$ Hz, 2, $\text{C}_6\text{H}_4\text{S}$), 6.88 (d, $J = 8.4$ Hz, 2, $\text{C}_6\text{H}_4\text{S}$), 6.89 (d, $J = 8.7$ Hz, 2, ArH ortho to O), 7.06–7.20 (m, 7, remaining ArH); m/z 417 (M^+). Anal. ($\text{C}_{27}\text{H}_{31}\text{NOS}$) C, H, N, S.

(E)- and (Z)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-[4-(methylsulfinyl)phenyl]-2-phenylbut-1-ene [4-(Methylsulfinyl)-tamoxifen, 20a and 20b]. The title compounds **19a** and **19b** were prepared from **17a** and **17b** in 32% and 17% yield, respectively, by the method described above for the conversion of **16a** and **18a**.

The *E* isomer **20a** was a solid: mp 88–90 °C (from petroleum ether, bp 60–80 °C); δ_{H} (CDCl_3) 0.93 (t, $J = 7.4$ Hz, 3, CH_3CH_2), 2.29 (s, 6, NMe_2), 2.45 (q, $J = 7.4$ Hz, 2, CH_3CH_2), 2.64 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 2.77 (s, 3, SOMe), 3.94 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.58 (d, $J = 8.8$ Hz, 2, ArH ortho to O), 6.76 (d, $J = 8.8$ Hz, 2, ArH meta to O), 7.1–7.2 (m, 5, Ph), 7.42 (d, $J = 8.4$ Hz, 2, ArH meta to S), 7.65 (d, $J = 8.4$ Hz, 2, ArH ortho to S); m/z 433 (M^+). Anal. ($\text{C}_{27}\text{H}_{31}\text{NO}_2\text{S}$) C, H, N, S.

The *Z* isomer **20b** was a solid: mp 116–118 °C (from petroleum ether, bp 60–80 °C); δ_{H} (CDCl_3) 0.93 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.34 (s, 6, NMe_2), 2.52 (q, $J = 7$ Hz, 2, CH_3CH_2), 2.60 (s, 3, SOMe), 2.74 (t, $J = 5$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 4.10 (t, $J = 5$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.91 (d, $J = 9$ Hz, 2), 7.09 (m, 9), 7.28 (d, $J = 9$ Hz, 2, ArH ortho to S); m/z 433.2077, calcd for $\text{C}_{27}\text{H}_{31}\text{NO}_2\text{S}$ 433.2075.

(E)- and (Z)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-[4-(methylsulfonyl)phenyl]-2-phenylbut-1-ene [4-(Methylsulfonyl)-tamoxifen, 21a and 21b]. The title compounds **21a** and **21b** were prepared from **18a** and **18b** in 30% and 6% yield, respectively, by the method described above for the conversion of **16a** to **19a**.

The *E* isomer **21a** was an oil: δ_{H} (CDCl_3) 0.9 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.26 (s, 6, NMe_2), 2.42 (q, $J = 7$ Hz, 2, CH_3CH_2), 2.62 (t, $J = 5$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 3.07 (s, 3, SO_2Me), 3.93 (t, $J = 5$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.57 (d, $J = 9$ Hz, 2, ArH ortho to O), 6.72 (d, $J = 9$ Hz, 2, ArH meta to O), 7.13 (m, 5, Ph), 7.44 (d, $J = 9$ Hz, 2, ArH meta to S), 7.92 (d, $J = 9$ Hz, 2, ArH ortho to S); m/z 449.2001, calcd for $\text{C}_{27}\text{H}_{31}\text{NO}_3\text{S}$ 449.2025.

The *Z* isomer **21b** was a solid: mp 46–48 °C (from EtOH); δ_{H} (CDCl_3) 0.93 (t, $J = 7$ Hz, 3, CH_3CH_2), 2.38 (s, 6, NMe_2), 2.52 (q,

$J = 7$ Hz, 2, CH_3CH_2), 2.72 (t, $J = 5$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 2.92 (s, 3, SO_2Me), 4.13 (t, $J = 5$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.94 (d, $J = 10$ Hz, 2, ArH ortho to O), 7.04–7.20 (m, 9), 7.56 (d, $J = 10$ Hz, 2, ArH ortho to S); m/z 449 (M^+). Anal. ($\text{C}_{27}\text{H}_{31}\text{NO}_3\text{S}$) C, H, N, S.

Bis[4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]phenyl] Disulfide (22). A stirred solution of 4-bromotamoxifen (10a) (501 mg, 1.1 mmol) in dry THF (6 mL) was cooled under N_2 to -75°C , and then $t\text{-BuLi}$ (1.7 M solution; 1.18 mL, 2 mmol) was added. The mixture was allowed to warm to 0°C , and then sulfur (53 mg, 1.66 mmol) was added in one portion. After 5 min the deep yellow solution was poured into H_2O (40 mL) and Et_2O (30 mL). To the two-phase system was added H_2O_2 (100 volumes; 1 mL), and the mixture was shaken. The Et_2O layer was washed with H_2O (30 mL), dried (Na_2SO_4), and concentrated. Chromatography of the residue (3:7 $\text{NET}_3\text{-Et}_2\text{O}$) gave the disulfide 22 as crystals (289 mg, 65%): mp $121\text{--}123^\circ\text{C}$ (from petroleum ether, bp $80\text{--}100^\circ\text{C}$); δ_{H} (CDCl_3) 0.91 (s, $J = 7.4$ Hz, 3, CH_3CH_2), 2.28 (s, 6, NMe_2), 2.45 (q, $J = 7.4$ Hz, 2, CH_3CH_2), 2.64 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 3.92 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.55 (d, $J = 8.8$ Hz, 2, ArH ortho to OCH_2), 6.74 (d, $J = 8.8$ Hz, 2, ArH meta to OCH_2), 7.0–7.2 (m, 7, ArH), 7.48 (d, $J = 8.3$ Hz, ArH ortho to S). Anal. ($\text{C}_{52}\text{H}_{56}\text{N}_2\text{S}_2\text{O}_2$) C, H, N.

4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]phenyl Mercaptan (23). A solution of the disulfide 22 (500 mg) and triphenylphosphine (1.0 g) in dioxane (40 mL) and H_2O (10 mL) was heated under reflux for 2 h and then partitioned between Et_2O (30 mL) and H_2O (30 mL). The Et_2O layer was dried (Na_2SO_4) and concentrated. Chromatography of the residue (1:50 MeOH-CHCl_3) gave the thiol 23 (426 mg, 85%): mp $102\text{--}104^\circ\text{C}$; ν_{max} (film from CH_2Cl_2) 2780 cm^{-1} (S–H str); δ_{H} (CDCl_3) 0.91 (t, $J = 7.4$ Hz, 3, CH_3CH_2), 2.29 (s, 6, NMe_2), 2.45 (q, $J = 7.4$ Hz, 2, CH_3CH_2), 2.65 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 3.93 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.54 (d, $J = 8.8$ Hz, 2, ArH ortho to OCH_2), 6.72 (d, $J = 8.8$ Hz, 2, ArH meta to OCH_2), 7.0–7.2 (m, 7, ArH), 7.24 (d, $J = 8.3$ Hz, 2, ArH ortho to SH). Anal. ($\text{C}_{26}\text{H}_{29}\text{NOS}$) C, H, N. Found S, 7.45%; required S, 7.94%.

4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]benzaldehyde (4-Formyltamoxifen, 24). To a stirred solution of 4-bromotamoxifen (10a) (1.794 g, 3.98 mmol) in dry THF (20 mL) at -75°C under N_2 was added a solution of $n\text{-BuLi}$ in hexane (1.6 M; 2.5 mL, 4.0 mmol) followed after 5 min by $N\text{-formylpiperidine}$ (1.0 g, 8.8 mmol). The mixture was allowed to attain room temperature and then partitioned between Et_2O (60 mL) and H_2O (60 mL). The Et_2O layer was concentrated. Chromatography of the residue (1:10:10 $\text{NET}_3\text{-Et}_2\text{O}\text{-petroleum ether}$, bp $60\text{--}80^\circ\text{C}$) gave 4-formyltamoxifen (24) as crystals (1.392 g, 87.5%): mp $77\text{--}79^\circ\text{C}$ (from petroleum ether, bp $80\text{--}100^\circ\text{C}$); δ_{H} (CDCl_3) 0.94 (t, $J = 7.4$ Hz, 3, CH_3CH_2), 2.29 (s, 6, NMe_2), 2.45 (q, $J = 7.4$ Hz, 2, CH_3CH_2), 2.64 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 3.93 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.57 (d, $J = 8.7$ Hz, 2, ArH ortho to OCH_2), 6.74 (d, $J = 8.7$ Hz, 2, ArH meta to OCH_2), 7.05–7.25 (m, 5, Ph), 7.41 (d, $J = 8.1$ Hz, 2, ArH meta to CHO), 7.87 (d, $J = 8.1$ Hz, 2, ArH ortho to CHO), 10.02 (s, 1, CHO); m/z 399 (M^+ , 4%), 72 (12%), and 58 (100%). Anal. ($\text{C}_{27}\text{H}_{29}\text{NO}_2$) C, H, N.

[4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-phenylbut-1-enyl]phenyl]methanol [4-(Hydroxymethyl)tamoxifen, 25]. NaBH_4 (100 mg, 2.64 mmol) was added to a stirred solution of 4-formyltamoxifen (24) (142 mg, 0.36 mmol) in EtOH (10 mL) at 20°C . After 10 min the mixture was partitioned between Et_2O (50 mL) and H_2O (50 mL). The Et_2O solution was dried (Na_2SO_4) and concentrated. Crystallization of the residue from petroleum ether (bp $80\text{--}100^\circ\text{C}$) gave 25 (120.5 mg, 84%) as crystals: mp $118\text{--}119^\circ\text{C}$; δ_{H} (CDCl_3) 0.92 (t, $J = 7.4$ Hz, 3, CH_3CH_2), 2.36 (s, 6, NMe_2), 2.45 (q, $J = 7.4$ Hz, 2, CH_3CH_2), 2.76 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 3.97 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 4.70 (s, 2, CH_2OH), 6.53 (d, $J = 8.7$ Hz, ArH ortho to OCH_2), 6.75 (d, $J = 8.7$ Hz, ArH meta to OCH_2), 7.0–7.2 (m, 5, Ph), 7.22 (d, $J = 8.0$ Hz, ArH meta to CH_2OH), 7.34 (d, $J = 8.0$ Hz, ArH ortho to CH_2OH). Anal. ($\text{C}_{27}\text{H}_{31}\text{NO}_2$) C, H, N.

2-[4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]phenyl]oxirane (26). A stirred suspension of NaH (96 mg, 4 mmol) in dry Me_2SO (5 mL) was heated at 70°C under N_2 for 1 h and then cooled to 20°C and diluted to 10 mL with

dry THF. One milliliter of this solution of dimethyl sodium (0.4 mmol) was added to a stirred solution of trimethylsulfonium iodide (81.6 mg, 0.4 mmol) in dry DMSO (1 mL) under N_2 , followed, after 5 min, by a solution of 4-formyltamoxifen (24) (135 mg, 0.34 mmol) in dry THF (0.5 mL). After 15 min, the mixture was partitioned between Et_2O (20 mL) and H_2O (20 mL). The Et_2O solution was dried (NaSO_4) and concentrated. Crystallization of the residue from petroleum ether (bp $80\text{--}100^\circ\text{C}$) gave the epoxide 26 (75.4 mg, 54%) as crystals: mp $94\text{--}95^\circ\text{C}$; δ_{H} (CDCl_3) 0.91 (t, $J = 7.4$ Hz, 3, CH_3CH_2), 2.28 (s, 6, NMe_2), 2.44 (q, $J = 7.4$ Hz, 2, CH_3CH_2), 2.64 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 2.87 [dd, $J = 2.5, 5.4$ Hz, 1, $\text{ArCH}(\text{O})\text{CH}_2$], 3.17 [dd, $J = 4.1, 5.4$ Hz, 1, $\text{ArCH}(\text{O})\text{CH}_2$], 3.88 [dd, $J = 2.5, 4.1$ Hz, 1, $\text{ArCH}(\text{O})\text{CH}_2$], 3.92 (t, $J = 5.8$ Hz, 2, $\text{OCH}_2\text{CH}_2\text{N}$), 6.55 (d, $J = 8.7$ Hz, 2, ArH ortho to OCH_2), 6.74 (d, $J = 8.7$ Hz, 2, ArH meta to OCH_2), 7.03–7.30 (m, 9, ArH). Anal. ($\text{C}_{28}\text{H}_{31}\text{NO}_2$) C, H, N.

Determination of Relative Binding Affinity.³⁷ Calf uterine cytosol was incubated at 18°C for 30 min with 5×10^{-9} M [^3H]estradiol in the absence and presence of increasing amounts ($10^{-9}\text{--}10^{-5}$ M) of the tamoxifen derivative or unlabeled estradiol (control). Unbound compounds were then removed by dextran-coated charcoal, and the amounts of estrogen receptor bound [^3H]estradiol were measured. The relative concentrations of estradiol and tamoxifen derivative required to achieve 50% inhibition of [^3H]estradiol binding is the RBA; i.e., $\text{RBA} = ([I_{50}] \text{ of estradiol} / [I_{50}] \text{ of test compound}) \times 100$. This procedure gives values of the same order of magnitude with cytosol from rat immature uterus, human breast tumours, or MCF-7 cells.

An MCF-7 whole-cell assay^{27,38} was additionally carried out on the hydroxymethyl derivative 25. MCF-7 cells were incubated at 37°C for 50 min with 10^{-9} M [^3H]estradiol in the absence or presence of increasing amounts ($10^{-10}\text{--}10^{-5}$ M) of 25 or unlabeled estradiol (control). Bound compounds were then extracted with ethanol, and the amounts of estrogen receptor bound [^3H]estradiol were measured. The RBA value was calculated as for the cytosol assay.

Effect on MCF-7 Cell Growth. The action of tamoxifen and derivatives on MCF-7 cell growth was determined by measuring the amounts of DNA after 120 h of culture according to the protocol described previously.^{21,22}

Acknowledgment. This work was funded by grants from the Cancer Research Campaign and Medical Research Council to the Institute of Cancer Research and from the Caisse Générale d'Epargne et de Retraite de Belgique to the Institut Jules Bordet and by a SERC CASE Studentship (to J.G.).

Registry No. 1, 10540-29-1; 4, 103628-22-4; 5, 68047-07-4; 6a, 116057-73-9; 6b, 116057-74-0; 7a, 116057-66-0; 7b, 116057-68-2; (E)-8, 116083-97-7; (E)-9, 116057-75-1; 10a, 116057-69-3; 10b, 116057-71-1; (E)-11, 77588-46-6; (E)-12, 116057-76-2; 13, 78423-10-6; (E)-14, 121887-38-5; (Z)-14, 121887-47-6; (E)-15, 121887-39-6; (Z)-15, 121887-48-7; 16a, 121887-49-8; 16b, 121887-50-1; 17a, 121887-51-2; 17b, 121887-52-3; 18a, 121887-53-4; 18b, 121887-54-5; 19a, 121887-55-6; 19b, 117332-14-6; 20a, 121887-56-7; 20b, 121887-57-8; 21a, 121887-58-9; 21b, 121887-59-0; (E,E)-22, 121887-42-1; (E)-23, 121887-43-2; (E)-24, 121887-44-3; (E)-25, 121887-45-4; (E)-26, 121887-46-5; $\text{Br}(\text{CH}_2)_2\text{Br}$, 106-93-4; $\text{Me}_2\text{N}(\text{CH}_2)_2\text{Cl}\cdot\text{HCl}$, 4584-46-7; 1,4-diiodobenzene, 624-38-4; 1,4-dibromobenzene, 106-37-6; (4-chlorophenyl)magnesium bromide, 873-77-8; (E)-1-[4-(2-chloroethoxy)phenyl]-(4-chlorophenyl)-2-phenyl-1-butene, 121887-40-9; (Z)-1-[4-(2-chloroethoxy)phenyl]-(4-chlorophenyl)-2-phenyl-1-butene, 121887-41-0; m -diiodobenzene, 626-00-6; (E)-1-[4-(2-chloroethoxy)phenyl]-(3-iodophenyl)-2-phenyl-1-butene, 116057-78-4; (Z)-1-[4-(2-chloroethoxy)phenyl]-(3-iodophenyl)-2-phenyl-1-butene, 116057-79-5; 4-(bromothio)anisole, 104-95-0; octafluorotoluene, 434-64-0; *cis*-tamoxifen, 13002-65-8.

(37) Leclercq, G.; Deboel, M. C.; Heuson, J. C. *Int. J. Cancer* 1976, 18, 750.

(38) Olea-Serrano, N.; Devleeschouwer, N.; Leclercq, G.; Heuson, J.-C. *Eur. J. Cancer Clin. Oncol.* 1985, 21, 1965.