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

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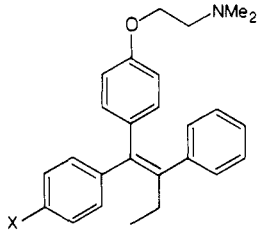
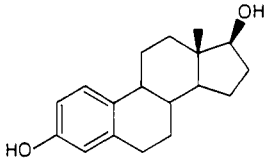
A range of tamoxifen derivatives substituted in the 4-position of the 1-phenyl ring are described. The key steps in the synthesis of 4-iodo-, 4-bromo-, and 4-(methylthio)tamoxifen were reactions of 1,2-diarylbutanones with the (4-halogenophenyl)lithium or [4-(methylthio)phenyl]magnesium bromide. Oxidized precursors of 4-(methylthio)tamoxifen were used to prepare the methylsulfinyl and methylsulfonyl derivatives. Further derivatives (formyl, hydroxymethyl, oxirane, mercapto) were prepared from 4-bromotamoxifen via the 4-lithio derivative. Several of the derivatives (Br, I, SMe, SOMe, SO_2Me, oxirane, CHO, CH_2OH) 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 **2**[11] 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]



1 X = H
2 X = OH



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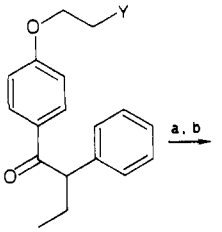
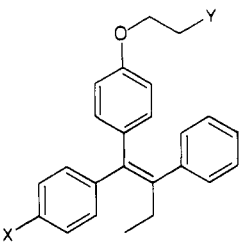
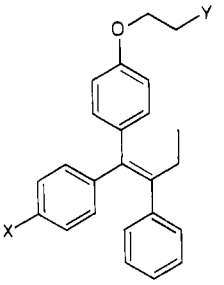
We have sought to replace the hydroxyl group in **2** by a function were high affinity for the estrogen receptor is retained but there is not the propensity for metabolic conjugate formation. Of the few 4-substituted derivatives of tamoxifen apart from **2** that are known, the 4-chloro, fluoro, and methyl derivatives have a similar potency to tamoxifen,[12,13] and although the amino derivative has a

Scheme I. Preparation of 4-Iodo- and 4-Bromotamoxifen[a]



c → **4**: Y = Cl
c → **5**: Y = NMe_2





	trans (*E*) isomers		cis (*Z*) isomers
	Y	X	
c → **6a**	Cl	I	**6b**
c → **7a**	NMe_2	I	**7b**
6	NEt_2	I	
9	$N(CH_2)_4$	I	
10a	NMe_2	Br	**10b**
11	NMe_2	Cl	

[a] Reagents: (a) 4-X-C_6H_4-X, *n*-BuLi (1 equiv), THF, −70–20 °C; (b) HCl (aqueous), EtOH, 80 °C; (c) Me_2NH, EtOH, 80 °C.

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

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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.

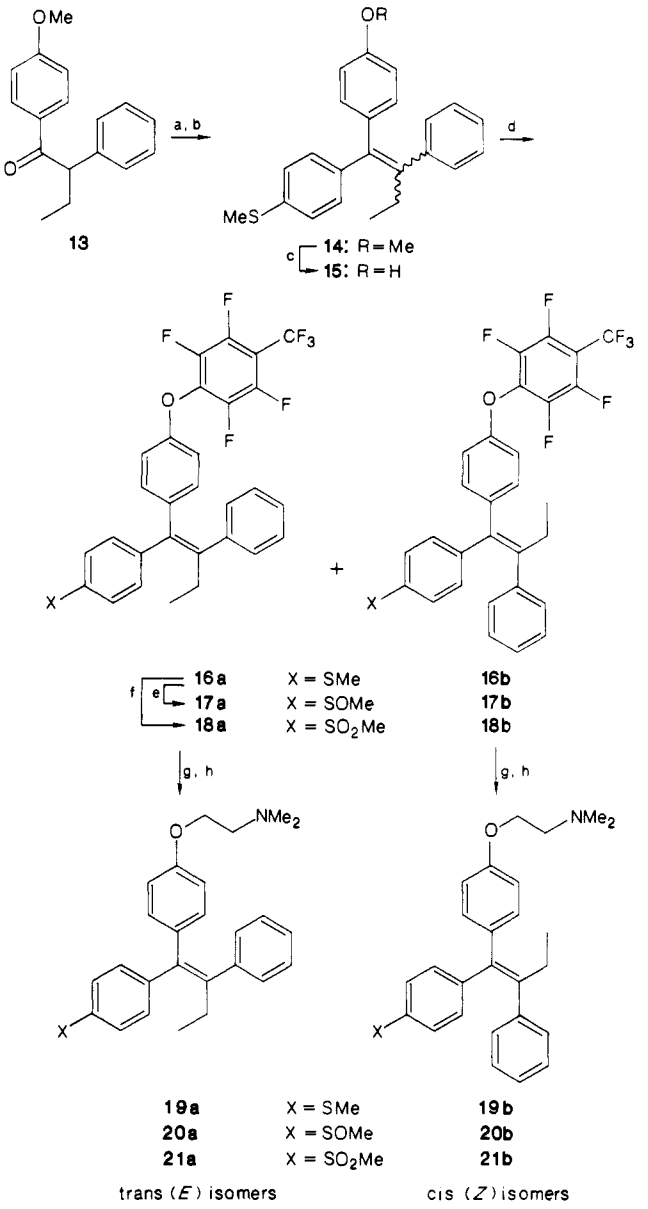
We report that, for a variety of 4-substituted derivatives of tamoxifen, whether the growth of breast tumor cells in culture is inhibited is not related to binding affinity for the estrogen receptor.

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, SOMe, and SO_2Me 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 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 peroxylauric 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.

Scheme II. Preparation of Sulfur-Substituted Tamoxifen Derivatives[a]



[a] Reagents: (a) $MeSC_6H_4MgBr$; (b) EtOH, H_2SO_4; (c) pyridine hydrochloride, 220 °C; (d) C_7F_8, CH_2Cl_2, NaOH (aqueous), $Bu_4N^+HSO_4^-$; (e) H_2O_2, HOAc; (f) $CH_3(CH_2)_{10}CO_3H$, CH_2Cl_2; (g) NaOMe, Me_2NCHO; (h) NaH, Me_2NCHO, $Me_2NCH_2CH_2Cl$·HCl.

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 ± SD			DNA amts in controls[d]
			10^{-8} M	10^{-7} M	10^{-6} M	
trans isomers						
1 (*trans*-tamoxifen)	H	1	119 ± 6**	100 ± 6 (ns)	70 ± 8***	A
7a	I	5	115 ± 6**	42 ± 6***	26 ± 6***	B
8	I	5	101 ± 7 (ns)	35 ± 5***	23 ± 2***	B
9	I	5	84 ± 5***	27 ± 3***	20 ± 2***	C
10a	Br	5	130 ± 10**	101 ± 8 (ns)	63 ± 8***	D
11	Cl	1	116 ± 3*	119 ± 8*	56 ± 5***	E
12	(3-I)	2	100 ± 8 (ns)	68 ± 2***	27 ± 5***	A
19a	SMe	3	154 ± 9***	66 ± 7***	54 ± 5***	F
20a	SOMe	3	177 ± 8***	237 ± 15***	238 ± 7***	G
21a	SO_2Me	6	125 ± 6**	75 ± 10**	29 ± 3***	G
23	SH	1	94 ± 4 (ns)	110 ± 7 (ns)	147 ± 10*	H
24	CHO	20	62 ± 2***	38 ± 7***	42 ± 6***	I
25	CH_2OH	80	164 ± 10***	145 ± 7***	150 ± 3***	C
26	$CH(O)CH_2$	3	113 ± 12 (ns)	42 ± 5***	19 ± 3***	C
cis isomers						
cis-tamoxifen	H	0.1	135 ± 5***	140 ± 5***	137 ± 8***	A
7b	I	0.2	99 ± 13 (ns)	126 ± 6***	120 ± 3***	B
10b	Br	0.2	110 ± 3*	163 ± 4***	174 ± 8***	D
19b	SMe	0.1	102 ± 4*	117 ± 3***	69 ± 4***	J
20b	SOMe	0.3	112 ± 9 (ns)	135 ± 7***	67 ± 5***	G
21b	SO_2Me	0.6	88 ± 12 (ns)	114 ± 5**	140 ± 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 that 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) (μg of DNA ± SD): A = 20.7 ± 1.9; B = 15.3 ± 0.5; C = 13.0 ± 1.1; D = 14.5 ± 0.7; E = 11.6 ± 1.4; F = 12.6 ± 0.9; G = 15.4 ± 0.9; H = 14.1 ± 0.7; I = 16.2 ± 0.9; J = 21.4 ± 0.8. SD values for effects of compounds at 10^{-8}–10^{-6} M do not take into account the SD of control data.

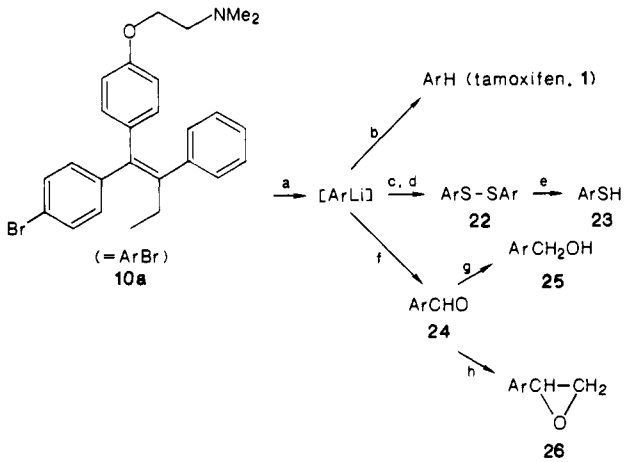
added. It was necessary, in this case, to use *tert*-butyllithium rather than *n*-butyllithium since with the latter reagent the aryl thiolate would undergo alkylation by the liberated bromobutane. Isolation of the thiol directly from the resulting product mixture proved impractical. It was preferable 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 iodide[18] 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 rule[19] that only in the trans isomers do the OCH_2 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** has been shown independently to have the expected configuration by X-ray crystallography.[20]

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) H_2O; (c) S_8; (d) H_2O_2; (e) PPh_3, H_2O, dioxane; (f) $(CH_2)_5NCHO$; (g) $NaBH_4$, EtOH; (h) $Me_3S^+I^-$, NaH, Me_2SO.

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** (CH_2OH), 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 studied 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 to 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. ^{1}H NMR spectra (internal Me_4Si) 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 N_2 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.; Burridge, 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. Radiol. 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 Et_2O (200 mL) and H_2O (200 mL). The Et_2O 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 Et_2O (2 × 150 mL), and the combined extracts were washed with H_2O (200 mL), dried with Na_2SO_4, 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 ($CDCl_3$) 0.91 (t, J = 7.4 Hz, 3, CH_3CH_2), 2.44 (q, J = 7.4 Hz, 2, CH_3CH_2), 3.73 (t, J = 5.9 Hz, 2, CH_2CH_2Cl), 4.10 (t, J = 5.9 Hz, 2, CH_2CH_2Cl), 6.55 (d, J = 8.8 Hz, 2, Ar*H* ortho to OCH_2), 6.75 (d, J = 8.8 Hz, 2, Ar*H* meta to OCH_2), 6.98 (d, J = 8.3 Hz, 2, Ar*H* meta to I), 7.07–7.22 (m, 5, Ph), 7.67 (d, J = 8.3 Hz, 2, Ar*H* ortho to I). Anal. ($C_{24}H_{22}ClIO$) 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 ($CDCl_3$) 0.93 (t, J = 7.4 Hz, 3, CH_3CH_2), 2.47 (q, J = 7.4 Hz, 2, CH_3CH_2), 3.84 (t, J = 5.9 Hz, 2, CH_2CH_2Cl), 4.25 (t, J = 5.9 Hz, 2, CH_2CH_2Cl), 6.59 (d, J = 8.4 Hz, 2, Ar*H* meta to I), 6.90 (d, J = 8.7 Hz, 2 Ar*H* ortho to OCH_2), 7.06–7.21 (m, 7, Ar*H*), 7.32 (d, J = 8.4 Hz, 2, Ar*H* ortho to I). Anal. ($C_{24}H_{22}ClIO$) 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% $HNMe_2$ in EtOH (60 mL) was heated under reflux. After 20 h, the mixture was concentrated, a further 33% $HNMe_2$ in EtOH (60 mL) added, and reflux continued for a further 20 h. The mixture was then again concentrated and the residue partitioned between Et_2O (50 mL) and NaOH (1 M; 50 mL). The Et_2O solution was concentrated and the residue applied to a column of silica gel (Merck 15111; 40 g). Elution with 1:20:20 NEt_3–Et_2O–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 ($CDCl_3$) 0.91 (t, J = 7.4 Hz, 3, CH_3CH_2), 2.28 (s, 6, NMe_2), 2.43 (q, J = 7.4 Hz, 2, CH_3CH_2), 2.64 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 3.92 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.55 (d, J = 8.8 Hz, 2, Ar*H* ortho to OCH_2), 6.73, (d, J = 8.8 Hz, 2, Ar*H* meta to OCH_2), 6.98 (d, J = 8.3 Hz, 2, Ar*H* meta to I), 7.04–7.22 (m, 5, Ph), 7.66 (d, J = 8.3 Hz, 2, Ar*H* ortho to I); m/z 497 (M^+, 36%), 380 (3%), 252 (13%), 72 (100%), and 58 (100%). Anal. ($C_{26}H_{28}INO$) 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 $HNMe_2$ 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 ($CDCl_3$) 0.92 (t, J = 7.4 Hz, 3, CH_3CH_2), 2.35 (s, 6, NMe_2), 2.48 (q, J = 7.4 Hz, 2, CH_3CH_2), 2.75 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 4.08 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.60 (d, J = 8.5 Hz, 2, Ar*H* meta to I), 6.89 (d, J = 8.7 Hz, 2, Ar*H* ortho to O), 7.05–7.25 (m, 7, Ar*H*), 7.31 (d, J = 8.5 Hz, 2, Ar*H* ortho to I). Anal. ($C_{26}H_{28}INO$) C, H, N, I.

(*E*)-1-[4-[2-(Diethylamino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (8). **6a** (1.069 g) in Et_2NH (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. ($C_{28}H_{32}INO$) 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 Et_2O (30 mL) and NaOH (1 M; 30 mL). Concentration of the Et_2O layer and recrystallization of the residue from petroleum ether (bp 80–100 °C) gave **9** (1.72 g, 92%): mp 108–109 °C. Anal. ($C_{28}H_{30}INO$) 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 N_2 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 Et_2O (100 mL) and H_2O (100 mL). The Et_2O 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 Et_2O (200 mL) and NaOH (5 M; 200 mL). The Et_2O 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 ($CDCl_3$) 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 = 5.7 Hz, 2, OCH_2CH_2N), 3.92 (t, J = 5.7 Hz, 2, OCH_2CH_2N), 6.56 (d, J = 8.8 Hz, 2, Ar*H* ortho to O), 6.73 (d, J = 8.8 Hz, 2, Ar*H* meta to O), 7.08–7.26 (m, 7, Ar*H*), 7.46 (d, J = 8.3 Hz, 2, Ar*H* ortho to Br). Anal. ($C_{26}H_{28}BrNO$) 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)–Et_2O–Et_3N 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 ($CDCl_3$) 0.92 (t, J = 7.4 Hz, 3, CH_3CH_2), 2.34 (s, 6, NMe_2), 2.48 (q, J = 7.4 Hz, 2, CH_3CH_2), 2.74 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 4.08 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.72 (d, J = 8.4 Hz, 2, Ar*H* meta to Br), 6.89 (d, J = 8.5 Hz, 2, Ar*H* ortho to O), 7.05–7.20 (m, 9, Ar*H*). Anal. ($C_{26}H_{28}BrNO$) 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]-(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 Et_2O, 30 mL, 30 mmol) in Et_2O (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 ($CDCl_3$) 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, OCH_2CH_2N), 3.92 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.55 (d, J = 8.9 Hz, 2, Ar*H* ortho to OCH_2), 6.73 (d, J = 8.9 Hz, 2, Ar*H* meta to OCH_2), 7.0–7.19 (m, 7, ArH), 7.31 (d, J = 8.5 Hz, 2, Ar*H* 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 ($CDCl_3$) 0.91 (t, J = 7.4 Hz, 3, CH_3CH_2), 2.29 (s, 6, NMe_2), 2.43 (q, J = 7.4 Hz, 2, CH_3CH_2), 2.65 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 3.93 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.56 (d, J = 8.8 Hz, 2, Ar*H* ortho to OCH_2), 6.74 (d, J = 8.8 Hz, 2, Ar*H* meta to OCH_2), 7.05–7.24 (m, 7, ArH), 7.58–7.63 (m, 2, Ar*H* ortho to I); m/z 497 (M^+, 10%), 72 (53%), and 58 (100%). Anal. ($C_{26}H_{28}INO$) C, H, N, I.

1-(4-Methoxyphenyl)-1-[4-(methylthio)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 Et_2O (50 mL). The mixture was stirred and heated to reflux while a solution of $BrCH_2CH_2Br$ (5.28 g, 28 mmol) in Et_2O was added dropwise over 4 h. A solution of 1-(4-methoxyphenyl)-2-phenylbutan-1-one (**13**)[27] (6.7 g, 26 mmol) in Et_2O (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 $MgSO_4$. Concentration under reduced pressure gave crude tertiary alcohol which was dissolved in EtOH. Concentrated H_2SO_4 (10 equiv) was then added, and the mixture was stirred at room temperature for 1 h and then neutralized with saturated $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$ 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. ($C_{24}H_{24}OS$) 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. ($C_{23}H_{22}OS$) 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 $Bu_4N^+HSO_4^-$ (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, Ar*H* ortho to O), 6.88 (d, *J* = 9 Hz, 2, Ar*H* meta to O), 6.97 (d, *J* = 9 Hz, 2, Ar*H* ortho to S), 7.05–7.20 (m, 5, Ph), 7.21 (d, *J* = 9 Hz, 2, Ar*H* 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. ($C_{30}H_{21}F_7OS$) 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, Ar*H* ortho to S), 6.85 (d, *J* = 9 Hz, 2, Ar*H* meta to S), 7.12 (m, 7), 7.25 (d, *J* = 7 Hz, 2, Ar*H* meta to O); *m/z* 562 (M^+). Anal. ($C_{30}H_{21}F_7OS$) 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, Ar*H* ortho to O), 6.86 (d, *J* = 9 Hz, 2, Ar*H* meta to O), 7.1–7.25 (m, 5, Ph), 7.44 (d, *J* = 9 Hz, 2, Ar*H* meta to S), 7.68 (d, *J* 9 Hz, 2, Ar*H* 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, Ar*H*); *m/z* 578 (M^+). Anal. ($C_{30}H_{21}F_7O_2S$) 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, Ar*H* ortho to O), 6.85 (d, *J* = 9 Hz, 2, Ar*H* meta to O), 7.1–7.27 (m, 5, Ph), 7.47 (d, *J* = 9 Hz, 2, Ar*H* meta to S), 7.96 (d, *J* = 9 Hz, 2, Ar*H* ortho to S); *m/z* 594.1123, calcd for $C_{30}H_{21}F_7O_3S$ 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, Ar*H*) 7.69 (d, *J* = 9 Hz, 2, Ar*H* ortho to S); *m/z* (positive ion FAB) 594 (M^+). Anal. ($C_{30}H_{21}F_7O_3S$) 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 $Me_2NCH_2CH_2Cl$·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, OCH_2CH_2N), 3.93 (t, *J* = 5.8 Hz, 2, OCH_2CH_2N), 6.56 (d, *J* = 8.8 Hz, 2, Ar*H* ortho to O), 6.76 (d, *J* = 8.8 Hz, 2, Ar*H* 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. ($C_{27}H_{31}NOS$) 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, OCH_2CH_2N), 4.04 (t, *J* = 5.8 Hz, 2, OCH_2CH_2N), 6.77 (d, *J* = 8.4 Hz, 2, C_6H_4S), 6.88 (d, *J* = 8.4 Hz, 2, C_6H_4S), 6.89 (d, *J* = 8.7 Hz, 2, Ar*H* ortho to O), 7.06–7.20 (m, 7, remaining Ar*H*); *m/z* 417 (M^+). Anal. ($C_{27}H_{31}NOS$), 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, OCH_2CH_2N), 2.77 (s, 3, SOMe), 3.94 (t, *J* = 5.8 Hz, 2, OCH_2CH_2N), 6.58 (d, *J* = 8.8 Hz, 2, Ar*H* ortho to O), 6.76 (d, *J* = 8.8 Hz, 2, Ar*H* meta to O), 7.1–7.2 (m, 5, Ph), 7.42 (d, *J* = 8.4 Hz, 2, Ar*H* meta to S), 7.65 (d, *J* = 8.4 Hz, 2, Ar*H* ortho to S); *m/z* 433 (M^+). Anal. ($C_{27}H_{13}NO_2S$), 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, OCH_2CH_2N), 4.10 (t, *J* = 5 Hz, 2, OCH_2CH_2N), 6.91 (d, *J* = 9 Hz, 2), 7.09 (m, 9), 7.28 (d, *J* = 9 Hz, 2, Ar*H* ortho to S); *m/z* 433.2077, calcd for $C_{27}H_{13}NO_2S$ 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 the 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, OCH_2CH_2N), 3.07 (s, 3, SO_2Me), 3.93 (t, *J* = 5 Hz, 2, OCH_2CH_2N), 6.57 (d, *J* = 9 Hz, 2, Ar*H* ortho to O), 6.72 (d, *J* = 9 Hz, 2 Ar*H* meta to O), 7.13 (m, 5, Ph), 7.44 (d, *J* = 9 Hz, 2, Ar*H* meta to S), 7.92 (d, *J* = 9 Hz, 2, Ar*H* ortho to S); *m/z* 449.2001, calcd for $C_{27}H_{31}NO_3S$ 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, OCH_2CH_2N), 2.92 (s, 3, SO_2Me), 4.13 (t, J = 5 Hz, 2, OCH_2CH_2N), 6.94 (d, J = 10 Hz, 2, Ar*H* ortho to O), 7.04–7.20 (m, 9), 7.56 (d, J = 10 Hz, 2, Ar*H* ortho to S); m/z 449 (M^+). Anal. ($C_{27}H_{31}NO_3S$) 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*-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 NEt_3–Et_2O) gave the disulfide **22** as crystals (289 mg, 65%): mp 121–123 °C (from petroleum ether, bp 80–100 °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, OCH_2CH_2N), 3.92 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.55 (d, J = 8.8 Hz, 2, Ar*H* ortho to OCH_2), 6.74 (d, J = 8.8 Hz, 2, Ar*H* meta to OCH_2), 7.0–7.2 (m, 7, Ar*H*), 7.48 (d, J = 8.3 Hz, Ar*H* ortho to S). Anal. ($C_{52}H_{56}N_2S_2O_2$) 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 102–104 °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, OCH_2CH_2N), 3.93 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.54 (d, J = 8.8 Hz, 2, Ar*H* ortho to OCH_2), 6.72 (d, J = 8.8 Hz, 2, Ar*H* meta to OCH_2), 7.0–7.2 (m, 7, Ar*H*), 7.24 (d, J = 8.3 Hz, 2, Ar*H* ortho to SH). Anal. ($C_{26}H_{29}NOS$) 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*-BuLi in hexane (1.6 M; 2.5 mL, 4.0 mmol) followed after 5 min by *N*-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 NEt_3–Et_2O–petroleum ether, bp 60–80 °C) gave 4-formyltamoxifen (**24**) as crystals (1.392 g, 87.5%): mp 77–79 °C (from petroleum ether, bp 80–100 °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, OCH_2CH_2N), 3.93 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.57 (d, J = 8.7 Hz, 2, Ar*H* ortho to OCH_2), 6.74 (d, J = 8.7 Hz, 2, Ar*H* meta to OCH_2), 7.05–7.25 (m, 5, Ph), 7.41 (d, J = 8.1 Hz, 2, Ar*H* meta to CHO), 7.87 (d, J = 8.1 Hz, 2, Ar*H* ortho to CHO), 10.02 (s, 1, CHO); m/z 399 (M^+, 4%), 72 (12%), and 58 (100%). Anal. ($C_{27}H_{29}NO_2$) 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 80–100 °C) gave **25** (120.5 mg, 84%) as crystals: mp 118–119 °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, OCH_2CH_2N), 3.97 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 4.70 (s, 2, CH_2OH), 6.53 (d, J = 8.7 Hz, Ar*H* ortho to OCH_2), 6.75 (d, J = 8.7 Hz, Ar*H* meta to OCH_2), 7.0–7.2 (m, 5, Ph), 7.22 (d, J = 8.0 Hz, Ar*H* meta to CH_2OH), 7.34 (d, J = 8.0 Hz, Ar*H* ortho to CH_2OH). Anal. ($C_{27}H_{31}NO_2$) 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 dimsyl 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 80–100 °C) gave the epoxide **26** (75.4 mg, 54%) as crystals: mp 94–95 °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, OCH_2CH_2N), 2.87 [dd, J = 2.5, 5.4 Hz, 1, $ArCH(O)CH_2$], 3.17 [dd, J = 4.1, 5.4 Hz, 1, $ArCH(O)CH_2$], 3.88 [dd, J = 2.5, 4.1 Hz, 1, $ArCH(O)CH_2$], 3.92 (t, J = 5.8 Hz, 2, OCH_2CH_2N), 6.55 (d, J = 8.7 Hz, 2, Ar*H* ortho to OCH_2), 6.74 (d, J = 8.7 Hz, 2, Ar*H* meta to OCH_2), 7.03–7.30 (m, 9, Ar*H*). Anal. ($C_{28}H_{31}NO_2$) 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 [^{3}H]estradiol in the absence and presence of increasing amounts (10^{-9}–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 [^{3}H]estradiol were measured. The relative concentrations of estradiol and tamoxifen derivative required to achieve 50% inhibition of [^{3}H]estradiol binding is the RBA; i.e., RBA = ($[I_{50}]$ of estradiol/$[I_{50}]$ of test compound) × 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 [^{3}H]estradiol in the absence or presence of increasing amounts (10^{-10}–10^{-5} M) of **25** or unlabeled estradiol (control). Bound compounds were then extracted with ethanol, and the amounts of estrogen receptor bound [^{3}H]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]

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(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.