Antiestrogens. 2.[1] Structure–Activity Studies in a Series of 3-Aroyl-2-arylbenzo[*b*]thiophene Derivatives Leading to [6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone Hydrochloride (LY156758), a Remarkably Effective Estrogen Antagonist with Only Minimal Intrinsic Estrogenicity

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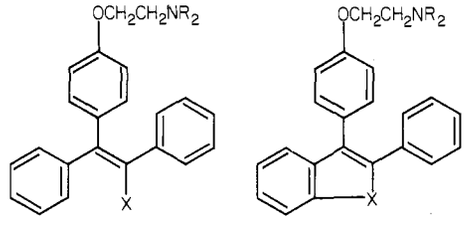
In an effort to prepare nonsteroidal antiestrogens demonstrating greater antagonism and less intrinsic estrogenicity than those currently available, a series of 3-aroyl-2-arylbenzo[*b*]thiophene derivatives was synthesized. These compounds were prepared by Friedel–Crafts aroylation of appropriate O-protected 2-arylbenzo[*b*]thiophene nuclei with basic side-chain-bearing benzoyl chlorides followed by removal of the protective groups to provide the desired compounds containing both hydroxyl and basic side-chain functionality. A particularly useful method for the cleavage of aryl methoxy ethers without removal of (dialkylamino)ethoxy side chain functionality elsewhere in the molecule was found to be $AlCl_3$/EtSH. The benzothiophene derivatives were tested for their ability to inhibit the growth-stimulating action of estradiol on the immature rat uterus. Seemingly minor changes in the side-chain amine moiety were found to have profound effects on the ability of the compounds to antagonize estradiol. Analogues having basic side chains containing cyclic (pyrrolidine, piperidine, and hexamethyleneamine) moieties were found to have less intrinsic estrogenicity and to antagonize estradiol action more completely than their noncyclic counterparts. The most effective antiestrogen in the series, compound **44**, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, elicited a modest uterotropic activity that did not increase with increasing dose. In antagonism of estradiol, **44** exhibited a degree of inhibition surpassing that of tamoxifen at any dose tested. The new benzothiophene antiestrogen was also shown to have high affinity for rat uterine cycloplasmic estrogen receptor and to be an inhibitor of the growth of DMBA-induced rat mammary tumors.

A part of the ongoing program in our laboratories to obtain nonsteroidal compounds that prevent the action of natural steroid hormones on target tissue is concerned with the discovery of novel antiestrogens. Most investigators searching in the area of nonsteroidal antiestrogens have been primarily interested in compounds conforming to the classical triarylethylene nucleus **1**, its cyclic counterpart **2**, or reduced versions of these.



1 **2**

Many years of synthetic effort in this area have produced a wide range of structures possessing pharmacological effects consistent with mixed agonist–antagonist estrogenic activity.[2] The more important structural classes include noncyclic derivatives (**1**) bearing X = alkyl[3] (e.g., tamoxifen), chloro[4] (clomiphene), or nitro[5] (nitromifene) groups as well as heterocyclic or carbocyclic examples (**2**) such as 2,3-diarylindenes,[6] -indoles,[7] -benzofurans,[8] -benzothiophenes,[8] 1,2-diaryl-3,4-dihydronaphthalenes,[9] and 3,4-diarylchromenes[8,10] and related compounds. In the aforementioned compounds, basic side chains that have received most attention have been the (dimethylamino)- (R = CH_3), the (diethylamino)- (R = Et), and the pyrrolidinoethoxy moieties [R_2 = $(CH_2)_4$].

Tamoxifen (ICI-46,474, Nolvadex), the best known of the above nonsteroidal antiestrogens, is widely used in treating estrogen-dependent metastatic mammary carcinoma.[11] In recent years it has also been applied, with varying degrees of success, to a number of other endocrine disorders including prostatic,[12] renal,[13] ovarian,[14] and en-

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(11) For reviews of the clinical application of tamoxifen to metastatic breast cancer, see: (a) H. Mouridsen, T. Palshof, J. Patterson, and L. Battersby, *Cancer Treat. Rev.*, **5**, 131 (1978); (b) R. C. Heel, R. N. Brogden, T. M. Speight, and G. S. Avery, *Drugs*, **16**, 1 (1978); (c) B. J. Furr, J. S. Patterson, D. N. Richardson, S. R. Slater, and A. E. Wakeling in "Pharmacological and Biochemical Properties of Drug Substances", M. E. Goldberg, Ed., American Pharmaceutical Association, Washington, DC, 1979, Vol. 2, pp 335–99.
(12) (a) J. H. Glick, A. Wein, K. Padavic, W. Negendank, D. Harris, and H. Brodovsky, *Cancer Treat. Rep.*, **64**, 813 (1980); (b) J. H. Glick, A. Wein, K. Padavic, W. Negendank, D. Harris, and H. Brodovsky, *Cancer*, **49**, 1367 (1982); (c) E. Spremulli, P. DeSimone, and J. Durant, *Am. J. Clin. Oncol.-Cancer Clin. Trials*, **5**, 149 (1982).

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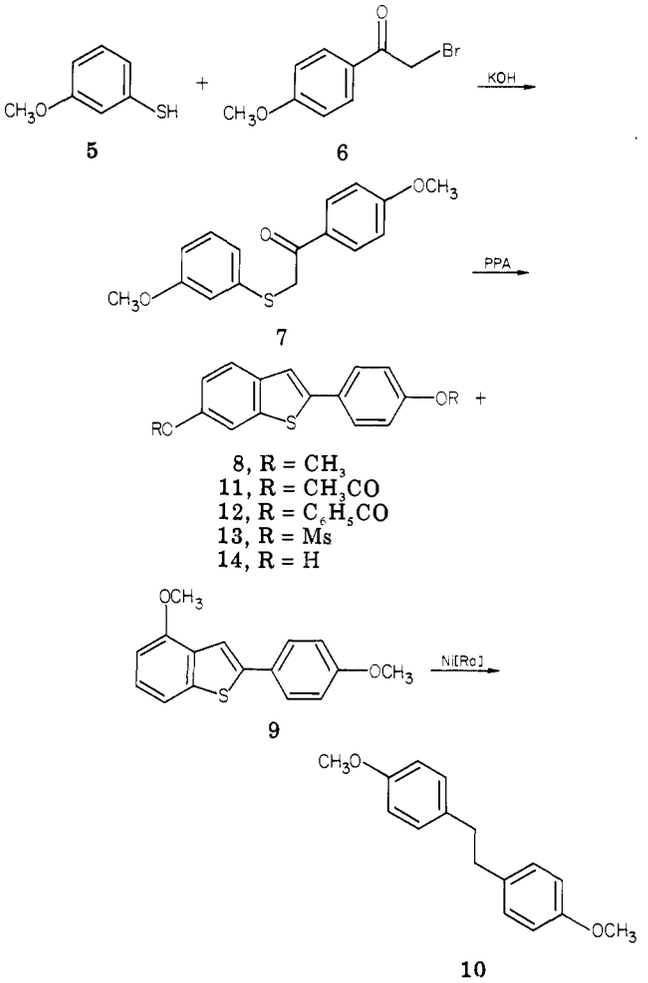
dometrial cancer;[15] malignant melanoma;[16] as well as benign breast disease,[17] anovulation,[18] gynecomastia,[19] and oligospermia.[20]

Although tamoxifen and other closely related triphenylethylene derivatives are generally considered to be antiestrogens, they are also known to have intrinsic estrogen agonist properties. It is believed that such intrinsic estrogenic effects restrict the ability of a given compound to inhibit biological responses to exogenous or endogenous estrogens.[21] Thus, it would appear that although antiestrogens may eventually prove applicable to a variety of disease states comprising a large total patient population, better compounds are needed particularly for use in those situations where only a low degree of intrinsic estrogenicity can be tolerated. Therefore, a major goal in our work has been to find antiestrogens demonstrating greater antagonism and less intrinsic estrogenicity than those currently available.

Efforts by other investigators to obtain compounds with greater affinity than tamoxifen for cytoplasmic estrogen receptors led to the investigation of hydroxylated derivatives in the triphenylethylene series. A metabolite of tamoxifen in the rat, 4-hydroxytamoxifen, was found to have an affinity for estrogen receptor approaching that of estradiol and to possess a profile of in vivo activity similar to that of tamoxifen.[22] Although it appears that in man 4-hydroxytamoxifen may not be responsible for the majority of tamoxifen's biological effect,[23] such hydroxylated structure compounds continue to be of high interest.

However, in the tamoxifen and other noncyclic triphenylethylene series, the hydroxy compounds are known to exhibit isomerization instability concerning the ethylene double bond. This equilibration is particularly facile when at least one hydroxy group is para to the carbon–carbon ethylene double bond.[24] The interconversion of *E* and *Z* isomers, which probably follows a prototropic equilibrium similar to that exhibited by cis and trans diethylstilbestrol isomers[25] renders the synthesis, purification, and pharmaceutical handling of the pure isomers more difficult. A second goal of our work, therefore, is to obtain antiestrogenic structures with a high degree of chemical stability which are not prone to *E–Z* isomerization.

Scheme I



In contrast to most other investigators, we have concentrated on ketonic structures of type **3** in which a carbonyl group is formally inserted into the triarylethylene nucleus. An initial clue that ketones of this general type could retain hormonal activity may be found in the literature concerning a series of acrylophenone derivatives published by Iyer et al.[26] in 1969. However, it has only been in recent years that the viability of this approach to antiestrogens was confirmed through the discovery of trioxifene mesylate **4**.[1] This compound, which reflects the general structure **3** (X = CH_2CH_2), provided the first example of a ketonic structure with in vivo antiestrogenic activity,[1] in vitro binding affinity,[1] and human antitumor effects[27,28] approaching or exceeding those of tamoxifen.

Following the discovery of trioxifene, we extended our work to other carbocyclic and heterocyclic ketonic nuclei. We now report the synthesis and antiestrogenic activity of a series of 3-aroylbenzothiophenes (**3**, X = S) incorporating both the basic ether side-chain and hydroxy func-

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(14) P. E. Schwartz, G. Keating, N. MacLusky, F. Naftolin, and A. Eisenfeld, *Obstet. Gynecol. (Amsterdam)*, **59**, 583 (1982).
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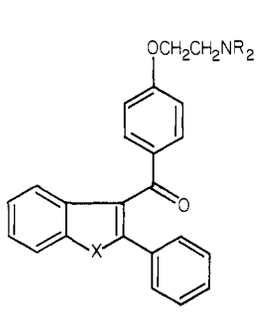
(27) A. U. Buzdar, K. C. Powell, S. S. Legha, G. N. Hortobagyi, H. Y. Yap, and G. R. Blumenschein, *Proc. Am. Assoc. Cancer Res.*, **22**, 448 (1981).
(28) B. T. Pruitt, D. C. Tormey, D. P. Rose, R. S. Witte, and G. Falkson, *Clin. Res.*, **29**, 736A (1981).



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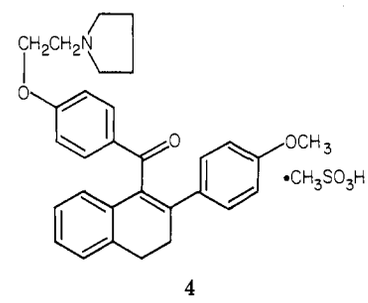

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tionality. A number of analogues that vary in the basic side-chain amine moiety have been prepared and included for comparative purposes. Preliminary accounts of the in vitro and in vivo activity of the lead compound in the series (**38**, LY117018) have already appeared in the biological literature.[21,29a,b,30,31]

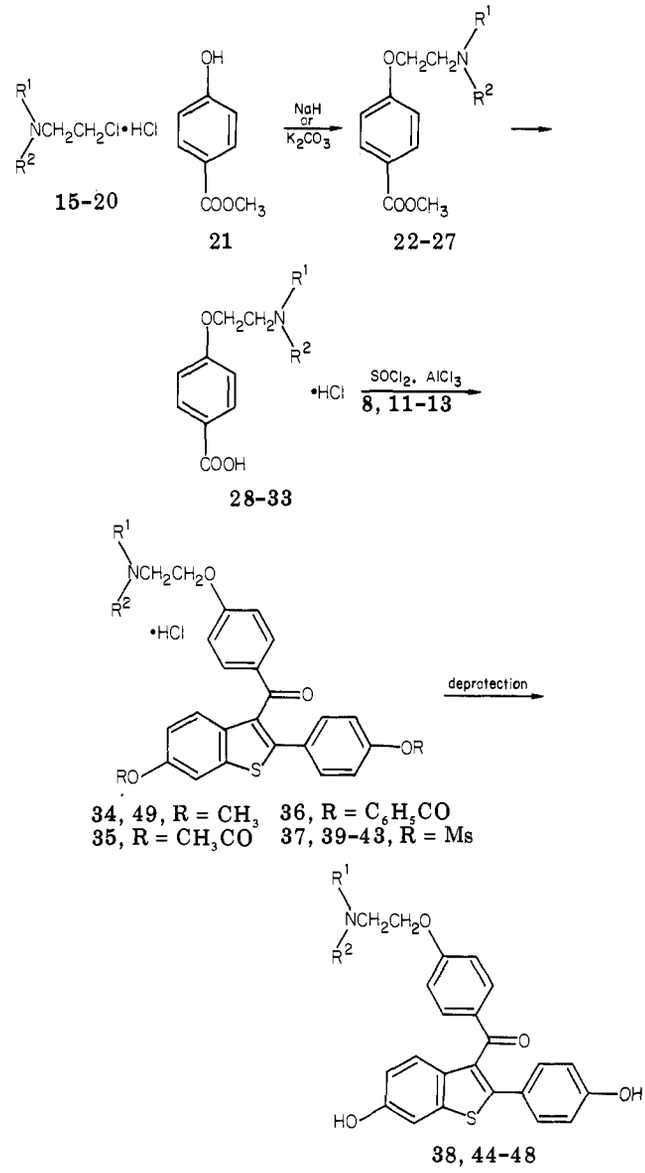
Chemistry

Synthesis of Benzo[*b*]thiophene Intermediates. The key intermediate 6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophene (**8**) was prepared by the cyclization–rearrangement induced by polyphosphoric acid (PPA) as depicted in Scheme I. This rearrangement has been described in the literature by Kost[32] and the product **8** was clearly a 2-arylbenzo[*b*]thiophene on the basis of its UV spectrum. Nevertheless, it was desirable in this case to unequivocally demonstrate that the aryl group was at the 2-position rather than 3. This was done by Raney nickel (Ni[Ra]) desulfurization to produce the 1,2-diarylethane **10**. That the cyclization occurred predominantly at the position para to OCH_3 was demonstrated by the 270-MHz NMR spectrum of **8**, as well as the isolation of the ortho-cyclized product **9**, which also exhibited NMR and UV data consistent with its structure. Cleavage of the methoxy groups in **8** could be done conveniently with pyridine hydrochloride. Subsequently **11–13** could be prepared by using conventional methods of acylation or sulfonation.

Synthesis of 4-(Aminoethoxy)benzoic Acids (Scheme II). The intermediate basic ether side chain containing benzoate esters **22–27** were prepared by alkylation of methyl *p*-hydroxybenzoate with appropriate amino halides in DMF by means of NaH (method A) or K_2CO_3 (method B) (see Table I). The latter method gave better yields and purer products. In most cases, without prior purification, the intermediate esters were taken on to the corresponding acids, which were easily isolated as HCl salts **28–33** (Table I).

Synthesis of 3-Aroylbenzo[*b*]thiophenes. With the requisite 4-(aminoethoxy)benzoic acids and benzo[*b*]-thiophenes in hand, we next examined Friedel–Crafts aroylation (also shown in Scheme II) as a means to produce the desired benzo[*b*]thien-3-yl ketones. Aroylation of the methoxy-protected benzothiophene **8** with the acid chlorides derived from **28–33** proceeded normally. However, preliminary experiments to cleave the methoxy protective

Scheme II



15, 22, 28, 34-38, $R^1, R^2 = (CH_2)_4$
16, 23, 29, 39, 44, 49, $R^1, R^2 = (CH_2)_5$
17, 24, 30, 40, 45, $R^1, R^2 = (CH_2)_6$
18, 25, 31, 41, 46, $R^1, R^2 = CH_3$
19, 26, 32, 42, 47, $R^1, R^2 = C_2H_5$
20, 27, 33, 43, 48, $R^1, R^2 = i\text{-}C_3H_7$

groups of compound **34** with conventional demethylation agents (BBr_3, NaSEt, pyridine hydrochloride) failed to provide products containing both basic side-chain and aromatic hydroxy functions.

In considering what protective groups to try in place of methyl, a primary consideration was the desire to avoid formation of Fries rearrangement[33] products. For this reason the substrate **13** was chosen since it was expected that a process analogous to Fries rearrangement involving the mesyl (Ms = CH_3SO_2) groups would not be likely. This expectation proved true as utilization of **13** allowed the synthesis of the desired **37**, **39–43** (Table II) in excellent yields provided a sufficient excess of $AlCl_3$ was used. Trifluoromethanesulfonic acid in refluxing CH_2Cl_2 proved to also be an effective catalyst for the aroylation of dimesylate **13**, as evidenced by the high-yield preparation of compound **39** (see Experimental Section). The mesylate

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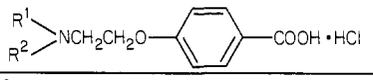
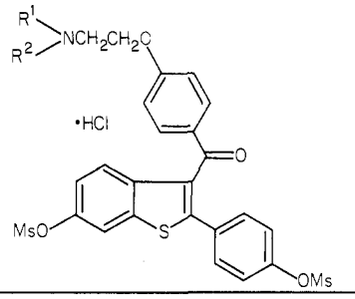
Table I. N-Substituted (Aminoethoxy)benzoic Acid Hydrochlorides



no.	R^1, R^2	method of ester prep	mp, °C	yield, %	formula	anal.
28	$(CH_2)_4$	A	235–237	67[b]	$C_{13}H_{18}ClNO_3$	C, H, N
29	$(CH_2)_5$	A	276–277	82[b]	$C_{14}H_{20}ClNO_3$	C, H, N
30	$(CH_2)_6$	B[a]	243–245	72[c]	$C_{15}H_{22}ClNO_3$	C, H, N, Cl
31	CH_3	B	156–261	92[c]	$C_{11}H_{16}ClNO_3$	C, H, N
32	C_2H_5	B[a]	171–174	67[c]	$C_{13}H_{20}ClNO_3$	C, H, N, Cl
33	i-C_3H_7	A	208–209	66[b]	$C_{15}H_{24}ClNO_3$	C, H, N, Cl

[a] Intermediate ester compound **24**: bp 160–180 °C (0.05 mm), yield 29%. Ester **26**: bp 117–25 °C (0.1 mm), yield 37%. [b] Overall yield from compound **21**. [c] Yield based on the corresponding ester **24**, **25**, or **26**.

Table II. [6-[(Methylsulfonyl)oxy]-2-[4-[(methylsulfonyl)oxy]phenyl]benzo[*b*]thien-3-yl][4-[2-(*N*-substituted-amino)-ethoxy]phenyl]methanone Hydrochlorides[a]



no.	R^1, R^2	mp, °C	yield, %	crystn solvent	formula	anal.
37	$(CH_2)_4$	207–207.5	92	EtOH	$C_{29}H_{30}ClNO_8S_3$	C, H, N
39	$(CH_2)_5$	133–135	84	MeOH	$C_{30}H_{32}ClNO_8S_3$	C, H, N
40	$(CH_2)_6$	(oil)[b]	73			
41	CH_3	204–206	86	EtOH	$C_{27}H_{28}ClNO_8S_3$	C, H, N, Cl
42	C_2H_5	172–174	80	EtOH	$C_{29}H_{32}ClNO_8S_3$	C, H, N
43	i-C_3H_7	192–201	76	EtOH	$C_{31}H_{36}ClNO_8S_3$	C, H, N

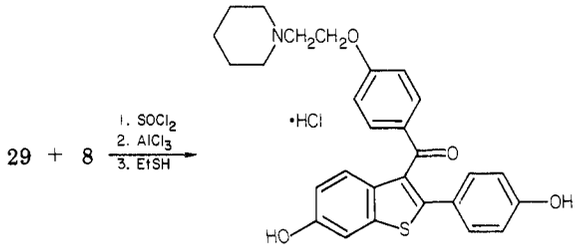
[a] All compounds were prepared via method 1 with use of $AlCl_3$ as described for compound **39**. [b] Isolated as an oil used without further purification.

groups were easily cleaved by alkaline hydrolysis and the final products **38**, **44–48** were isolated as stable, frequently crystalline free bases. This aroylation and subsequent mesylate hydrolysis sequence was used for most of the SAR work described on this paper. Later in the work, it was found that simple acyl protective groups (e.g., acetate, benzoate) were sufficiently stable during the $AlCl_3$-catalyzed aroylation process to provide good yields of the desired **35** and **39** without significant complication by the formation of Fries-type products.

Once compound **44** was selected for further development, a more efficient route for its preparation was sought. In order to eliminate the necessity for protection–deprotection protocols, the problem of selective cleavage of arylmethoxy groups in the presence of a basic ether side chain was reexamined. By this time a report[34] had appeared concerning the use of a hard acid (AlX_3) combined with a soft nucleophile (EtSH) to easily cleave aliphatic and aromatic ethers. Although this combination had failed to demethylate the basic alkaloid asimilobine, we attempted demethylation of compound **49** (Scheme II). When **49** was treated with excess $AlCl_3$/EtSH, the methyl ether groups were cleanly cleaved, the basic side chain remained intact, and the desired **50** (the HCl salt of **44**) was obtained in greater than 75% yield.

The synthesis of **50** was streamlined further when it was found that the $AlCl_3$-catalyzed aroylation and the

Scheme III



50

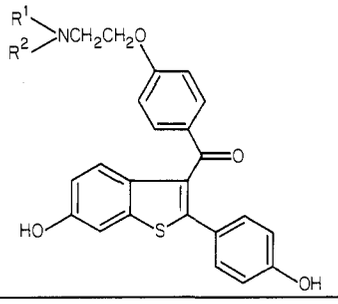
$AlCl_3$/EtSH demethylation could be combined. Thus, **50** can be obtained directly from aroylation of **8** by the acid chloride of **29** in the presence of $AlCl_3$ followed by addition of EtSH (Scheme III). This one-pot process conveniently provides multigram quantities of **50** in a yield exceeding that of the stepwise procedures described above.

Biological Results and Discussion

The synthetic benzothiophene derivatives bearing basic side-chain and aromatic hydroxyl functions were tested for estrogenic and antiestrogenic activity in the immature rat uterotropic assay. Results of these assays are presented in Table III. All of the compounds tested demonstrated estrogen antagonist activity; however, their relative ability to do so varied over a wide range. The data indicate a difference in biological profile between the cyclic (pyrrolidine, piperidine, and hexamethyleneamine) and noncyclic (dimethyl, diethyl, and diisopropyl) amine containing compounds. The noncyclic examples (**46–48**) increased

(34) M. Node, K. Nishide, K. Fuji, and E. Fujita, *J. Org. Chem.*, 45, 4275 (1980).

Table III. Uterotropic and Antiuterotropic Activity of 3-Acyl-2-arylbenzo[*b*]thiophene Derivatives in Immature Rats



compd	structure (R^1, R^2)	dose,[a] μg	uterotropic N[b]	uterotropic mean uterine wt, mg	antiuterotropic[c] N[b]	antiuterotropic[c] mean uterine wt, mg
control			24	26.1 ± 1.0		
estradiol		0.1	24	82.3 ± 2.5		
38	$(CH_2)_4$	1	6	55.1 ± 1.7	12	61.7 ± 3.2
38		10	18	46.6 ± 1.1	18	44.5 ± 1.4
38		100	18	43.9 ± 1.6	18	42.7 ± 1.4
38		1000	18	40.7 ± 1.2	18	36.1 ± 1.0
44	$(CH_2)_5$	1	12	48.6 ± 1.9	24	48.7 ± 1.6
44		10	12	42.2 ± 1.7	24	36.7 ± 1.1
44		100	12	42.7 ± 1.0	24	32.5 ± 0.8
44		1000	12	35.4 ± 0.8	24	28.9 ± 0.8
45	$(CH_2)_6$	1	6	52.7 ± 2.8	6	56.3 ± 2.6
45		10	6	46.6 ± 1.2	6	52.7 ± 3.5
45		100	6	43.9 ± 2.2	6	39.7 ± 1.5
45		1000	6	40.1 ± 2.4	6	36.7 ± 1.5
46	CH_3	1	18	44.6 ± 1.7	18	54.7 ± 2.4
46		10	18	55.0 ± 2.6	18	54.3 ± 2.5
46		100	18	66.0 ± 2.0	18	64.7 ± 1.9
46		1000	18	71.5 ± 2.3	18	70.8 ± 2.9
47	C_2H_5	1	18	45.4 ± 1.2	12	56.2 ± 2.4
47		10	18	53.6 ± 1.7	12	61.3 ± 1.5
47		100	18	67.6 ± 2.1	12	66.4 ± 1.6
47		1000	18	66.5 ± 2.4	12	66.0 ± 1.9
48	i-C_3H_7	1	6	37.3 ± 2.0	6	60.1 ± 2.1
48		10	6	50.0 ± 2.0	6	58.7 ± 3.3
48		100	6	62.1 ± 3.6	6	69.5 ± 2.1
48		1000	6	60.4 ± 2.3	6	70.2 ± 2.2
tamoxifen		1	6	38.9 ± 1.9	6	64.1 ± 4.6
tamoxifen		10	6	64.8 ± 2.0	6	62.1 ± 3.8
tamoxifen		100	6	65.6 ± 1.7	6	72.1 ± 3.0
tamoxifen		1000	6	70.1 ± 2.3	6	74.1 ± 3.8

[a] Per rat per day; subcutaneously in corn oil. [b] Number of determinations. [c] Every rat received 1 μg of estradiol/day sc in corn oil.

uterine weight in relation to the dose administered. Since antagonist effectiveness is limited by agonist activity, their ability to inhibit the action of estradiol was restricted, especially so at the 100- and 1000-μg doses of the antagonists. By contrast, the cyclic antagonists (**38**, **44**, and **45**) exhibited weak uterotropic activity that did not increase in relation to dose. Thus, they produced a more complete dose-related antiestrogenic response. A major conclusion that can be drawn from this study is that seemingly minor changes in the basic side-chain moiety can have profound effects on the agonist–antagonist profile.

The biological properties of compound **44** (LY139481) were remarkable. Compound **44** evoked its maximum uterotropic effect at 1 μg and no further increase in uterotropic action was observed with up to a 1000-fold increase in the dose. Accordingly, **44** (1000 μg) suppressed the uterotropic effect of estradiol in a dose dependent manner and elicited >90% inhibition. This degree of inhibition surpassed that demonstrated by tamoxifen at any dose in the range (1–1000 μg) tested. Therefore, compound **44** in the form of its hydrochloride salt **50** (LY156758) is a candidate for further investigations against estrogen-dependent disease conditions. A more detailed account of the above and some added biological findings for **44** may be found elsewhere.[35,36]

An examination of the literature immediately revealed that the high degree of antiestrogenic activity demonstrated by **44** is not achieved simply by incorporating cyclic basic side-chain moieties into other antiestrogenic series. In the tamoxifen series, the analogues bearing pyrrolidine- or piperidine-containing side chains do not give estrogenic/antiestrogenic dose response curves for the immature rat assay much different from tamoxifen itself.[37]

At the present time, the reason for the great difference between agonist/antagonist profiles for the cyclic and noncyclic basic side-chain compounds in the benzothiophene series remains elusive. In view of a recent study[37] of various side chains in the tamoxifen series, it appears unlikely that the relatively small pK_a differences expected for the compounds of this study would account for the large biological differences we see. More likely, it

(35) L. J. Black, C. D. Jones, J. H. Clark, and J. A. Clemens, "Breast Cancer Research and Treatment", Martinus Nijhoff: The Hague, Netherlands, Abstract No. 12, 1982, Vol. 2, No. 3, p 279.
(36) L. J. Black, C. D. Jones, and J. F. Falcone, *Life Sci.*, **32**, 1031 (1983).
(37) D. W. Robertson, J. A. Katzenellenbogen, J. R. Hayes, and B. S. Katzenellenbogen, *J. Med. Chem.*, **25**, 167 (1982).

Table IV. Effects of Compound **50** on the Growth of Mammary Tumors in Rats

treatment	duration of treatment, days	N^a	tumor area, mm² start	tumor area, mm² finish	serum prolactin levels, mg/mL	serum LH levels,[g] ng/mL
			Experiment I			
control[b]	21	8	47.6 ± 4.0[d]	496.7 ± 81.7	886 ± 754.6	10.5 ± 1.6
50, 1 mg/kg[c]	21	7	33.3 ± 3.5	77.3 ± 31.9 ($p < 0.001$)[e]	204.1 ± 45.6	30.8 ± 8.7 ($p < 0.05$)
50, 10 mg/kg[c]	21	6	41.4 ± 5.9	197.9 ± 82.6 ($p < 0.05$)	711.2 ± 113.5	27.7 ± 3.4 ($p < 0.001$)
ovariectomy	21	8	56.1 ± 9.4	108.9 ± 74.9[f]	16.7 ± 2.6	295.4 ± 12.7 ($p < 0.001$)
			Experiment II			
control[b]	21	8	52.1 ± 4.9	836.6 ± 154.4	86.2 ± 24.7	
50, 10 mg/kg[c]	21	8	33.8 ± 6.8	175.0 ± 112.9 ($p < 0.01$)	72.4 ± 39.0	
tamoxifen, 10 mg/kg[c]	21	8	43.4 ± 9.2	46.4 ± 42.5 ($p < 0.01$)	126.0 ± 39.0	

[a] Number of rats. [b] Vehicle (polyethylene glycol 400:water, 1:1), 0.4 mL po twice a day). [c] po, twice a day. [d] Mean ± standard error. [e] Parentheses indicate level of significance vs. control. [f] Group had rat with one tumor that grew etremely rapidly, causing mean to be artificially elevated when in fact 7/9 tumors regressed. [g] Vaginal smears were diestrus in rats treated with antiestrogens. Control rats were cycling and the smears were a mixture of stages. The animals were killed in the morning, however, before any of the afternoon surges normally occur.

Table V. Effects of Compound **50** on Additional Parameters of Tumor Growth

compd	dose, mg/kg	no. of tumors start	no. of tumors finish	no. of tumors with[b] CR	PR	NC	P	% change of tumor area
			Experiment I					
control	0	9	16	0	0	0	9	+943
50	1	9	9	1	2	4	2	+132
50	10	9	13	1	2	2	4	+378
ovariectomy	0	9	7	4	3	1	1	+41
			Experiment II					
control	0	14	16	0	0	0	14	+1506
50	10	9	5	4	2	1	2	+417
tamoxifen	10	11	7	3	3	2	3	+7

[a] The group shown in this table are the same groups shown in Table IV. [b] CR = complete remission, PR = partial remission (> than 30% area decrease), NC = no change; P = progression. Values are based on number of tumors at start of study.

would appear that in the benzothiophene series there are subtle steric receptor interactions or possibly metabolic pathway differences between the cyclic and noncyclic structures that will account for the differences in profile. Further studies will be required to address these possibilities.

Binding affinities relative to that of estradiol for compounds **38** and **44** were determined with use of cytoplasmic estrogen receptors as described in the Experimental Section. The relative binding affinity of the piperidine analogue **44** increased with increasing temperature in a manner similar to that of the pyrrolidine lead compound **38** (Figure 1). However, much greater affinity was seen quantitatively with compound **44** such that it demonstrated greater affinity than estradiol itself at all three temperatures. This increase in competition with respect to temperature may be related to a slow rate of dissociation from the cytosol estrogen receptor relative to the dissociation rate of estradiol.[21,29b]

Compound **50** was evaluated for antitumor effects in the DMBA-induced rat mammary tumor model as described in the Experimental Section. Weekly measurements of tumor areas revealed that both doses (1 mg/kg and 10 mg/kg) of **50** significantly inhibited tumor growth (Tables IV and V). The degree of growth inhibition was similar to that produced by ovariectomy. This indicates that **50** is effective as an antiestrogen at the level of the mammary gland. Serum prolactin levels were variable, and no significant effect was observed, while a small but significant elevation of serum LH levels was seen. Possibly, **50** partially antagonizes the negative feedback effects of estradiol on LH release.

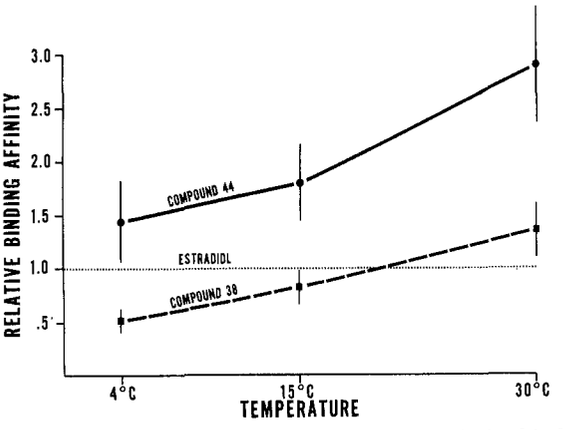


Figure 1. Rat uterine cytosol estrogen receptor relative binding affinity of **38** and **44** (estradiol = 1.0). Various concentrations (1–1000 nM of test compound were incubated 1 h at 4 or 15 °C and 0.5 h at 30 °C with 10 nM [2,4,6,7-^{3}H]estradiol. The concentration on the binding curve corresponding to 50% inhibition of specific [^{3}H]estradiol binding was used to calculate RBA. Results are the mean ± standard error of at least 10 determinations.

Vaginal smear patterns indicated that the rats receiving the antiestrogens were in persistent diestrous while the control animals demonstrated cycles. Thus hormonal measurements were performed in diestrous treated animals while the control rats were in various stages of the cycle.

The rats were sacrificed early in the morning, however, when the prolactin and LH levels are low in all stages of the cycle.

Overall, the benzo[*b*]thien-3-yl ketones of this report provide an interesting point of departure for further investigations in the area of nonsteroidal antiestrogens.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 10MX Fourier transform spectrometer and ultraviolet spectra were taken on a Cary 118 instrument. Proton NMR spectra were determined at 60 MHz on a Varian T-60 NMR spectrometer, at 90 MHz on a JEOL FX-90Q spectrometer, at 100 MHz on a Varian HA-100 instrument, or at 270 MHz on a Bruker WM270 machine using tetramethylsilane as internal standard. Mass spectra were obtained on a Finnegan MAT731 spectrometer in the EI mode with samples introduced directly into the ion source or in the FD mode using carbon dendrite emitters for the spectral determination. Although only selective spectral data are presented herein, all new compounds exhibited IR, UV, and NMR spectra consistent with the structures assigned them. Microanalyses were performed at Eli Lilly and Co. and results are within 0.4% of the calculated values except as noted.

4-Methoxy-α-[(3-methoxyphenyl)thio]acetophenone (7). To a freshly prepared solution of 75 mL of EtOH, 30 mL of water, and 4.7 g of KOH (85% purity; 0.071 mol) at room temperature was added 3-methoxybenzenethiol (10.0 g, 0.071 mol) in one portion, and the solution was cooled to between 5 and 10 °C. A solution of the bromo compound 6 (16.4 g, 0.071 mol) in 25 mL of EtOAc was added at a rate such that the temperature did not exceed 25 °C. The reaction mixture was allowed to stir overnight at room temperature and was then evaporated in vacuo to a solid. The solid was dissolved in water and EtOAc, the layers were separated, and the aqueous layer was extracted once with EtOAc. The combined organic layers were washed with 1 N HCl solution, water, saturated aqueous $NaHCO_3$, water again, and saturated NaCl solution. The organics were dried ($MgSO_4$), filtered, and evaporated in vacuo to 22.8 g of a golden oil. The oil was taken up in 25 mL of hot MeOH and, with stirring, was allowed to cool to 25 °C and then kept in a refrigerator overnight. The following day 7 was collected by filtration, washing with 20 mL of cold (−25 °C) MeOH. The product was then slurried in hexane and refiltered. The white crystalline 7 was then dried in vacuo at or below 40 °C, yielding 16.5 g (80.4%), mp 51–53 °C. Anal. ($C_{16}H_{16}O_3S$) C, H, S, O.

6-Methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (8). A 250-mL beaker was fitted with a mechanical stirrer and was placed on a steam bath. Into the beaker was placed 38 g of polyphosphoric acid. The acid was heated, with stirring, to 85 °C. Then 7 (6.42 g, 0.0223 mol) was added portionwise at a rate such that the temperature never exceeded 100 °C. The solution turned dark red as 7 was added. After the addition was complete, the reaction mixture was stirred between 85 and 90 °C for 1 h and allowed to cool to 70 °C and was then slowly poured into rapidly stirring ice water. The crude product precipitated as a tan solid, which was collected by vacuum filtration and was washed with water. The solid was air-dried overnight to yield 5.95 g of material that consisted of the desired product (8) and a lesser amount of the corresponding 4-methoxy isomer (9).

The ratio of 8 to 9 in the mixture was determined by HPLC (Dupont Zorbax C-18, 7 μm, 4.6 mm × 25 cm column, MeOH:water:NH_4OAc (80:19:1) eluant at 2.0 mL/min) to be approximately 3:1. The mixture of materials was then slurried in refluxing acetone for 1 h and then allowed to cool to room temperature. The bulk of the 4-methoxy isomer remained in the acetone solution. The off-white crystals of 8 were collected via vacuum filtration, washed with acetone, and dried in vacuo at 60 °C. The purity of the product was determined by HPLC to be >95% and the yield was 4.16 g (69% overall) for the purified material. An analytical sample of 8 was recrystallized from EtOAc: mp 193–194 °C; NMR (270 MHz, Me_2SO-d_6) δ 3.83 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 6.98 (1 H, q, J_{H4-H5} = 9 Hz, J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 7.04 (2 H, d, J = 9 Hz, aromatic ortho to OCH_3), 7.53 (1 H, d, J = 2 H, H7 of benzothiophene ring), 7.61 (1 H, s, H3 of benzothiophene ring), 7.65 (2 H, d, J = 9 Hz, H4 of benzothiophene ring); UV (EtOH) λ_{max} 236 nm (ε 22000), 262 (11750), 273 (11600), 310 (sh) (29000), 317 (30000). Anal. ($C_{16}H_{14}O_2S$) C, H, O, S.

4-Methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (9). The combined acetone slurries from purification of several different lots of compound 8 were concentrated to dryness. The resulting solid was slurried in refluxing MeOH and filtered hot. The solid on the filter was slurried twice more as above to give the 4-methoxy isomer 9: mp 112–114 °C; NMR (270 MHz, Me_2SO-d_6) δ 3.92 (s, 3 H, OCH_3), 3.98 (3 H, s, OCH_3), 6.91 (1 H, d, J = 9 Hz, H5 of benzothiophene ring), 7.02 (2 H, d, J = 9 Hz, aromatic ortho to OCH_3), 7.29 (1 H, t, J = 9 Hz, H6 of benzothiophene ring), 7.50 (1 H, d, J = 9 Hz, H7 of benzothiophene ring), 7.69 (1 H, s, H3 of benzothiophene ring), 7.71 (2 H, d, J = 9 Hz, aromatic meta to OCH_3); UV (EtOH) λ_{max} 215 nm (ε 31000), 236 (17000), 258 (12500), 304 (sh) (23500), 312 (23800), 327 (20000), 340 (12000). Anal. ($C_{16}H_{14}O_2S$) C, H, O, S.

6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophene (14). A mixture of 16.5 g (0.061 mol) of 8 and 50 g of pyridine hydrochloride was heated under a N_2 atmosphere at 220 °C for 6 h. The resulting yellow solution was then poured with stirring into an ice–water mixture. The tan solid that precipitated was collected by filtration, washed thoroughly with water, and air-dried. Recrystallization from MeOH provided 10.5 g (71%) of the desired 14: mp 305–306 °C; NMR (270 MHz, Me_2SO-d_6) δ 7.84 (2 H, d, J = 9 Hz, aromatic ortho to OH), 7.85 (1 H, m, J_{H4-H5} = 9 Hz, J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 7.24 (1 H, d, J = 2 Hz, H7 of benzothiophene ring), 7.46–7.54 (3 H, m, H3 of benzothiophene ring and aromatic meta to OH), 7.64 (1 H, d, J = 9 H, H4 of benzothiophene ring). Anal. ($C_{14}H_{10}O_2S$) C, H, S.

Structure Proof for Compound 8 by Desulfurization of 6-Methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene; 1,2-Bis(4-methoxyphenyl)ethane (10). A 200-mg (0.078 mmol) sample of compound 8 was desulfurized by refluxing with 4 g of W-2 Raney nickel[38] in 75 mL of EtOH for 30 min. The hot alcohol solution was filtered through filtercel and the filter cake was washed with 25 mL of warm EtOH. The clear, colorless filtrate was evaporated to dryness to provide 175 mg (100%) of 1,2-bis(4-methoxyphenyl)ethane: mp 123–124 °C (lit.[39] mp 125 °C), the identity of which was established by NMR spectroscopy: δ 2.83 (4 H, s, CH_2CH_2), 3.78 (6 H, s, OCH_3), 6.81 (2 H, d, J = 9 Hz, aromatic ortho to OCH_3), 7.11 (4 H, d, J = 9 Hz, aromatic meta to OCH_3).

No trace of the isomeric 1,1-bis(4-methoxyphenyl)ethane was present in the desulfurized product as judged by the absence of any NMR signals attributable to the Ar_2CHCH_3 protons.

6-Acetoxy-2-(4-acetoxyphenyl)benzo[*b*]thiophene (11). To a solution of 14 (40.0 g, 0.165 mol) in 800 mL of dry pyridine at room temperature was added acetic anhydride (41.6 g, 38.5 mL, 0.407 mol) followed by a catalytic amount (100 mg) of 4-(dimethylamino)pyridine. The mixture was stirred briefly and then was allowed to stand overnight. Most of the pyridine was removed in vacuo at below 40 °C and the residue was slurried with ~3 L of water. The resulting off-white crystals were collected by filtration, washed well with water, and dried in vacuo overnight at 80 °C to give 52.5 g (97%) of 11: mp 208–210 °C; IR ν_{max} 1750 cm^{-1}. Anal. ($C_{18}H_{14}O_4S$) C, H.

6-(Benzoyloxy)-2-[4-(benzoyloxy)phenyl]benzothiophene (12). This compound was prepared by a procedure identical with the preparation of the corresponding diacetate 11 except for the use of benzoyl chloride (51.1 g, 42.0 mL, 0.364 mol) in place of the acetic anhydride. The dibenzoate 12 (73.7 g, 99%) was obtained as white crystals: mp 216–218 °C; IR ν_{max} 1730 cm^{-1}. Anal. ($C_{28}H_{18}O_4S$) C, H.

6-[(Methylsulfonyl)oxy]-2-[4-[(methylsulfonyl)oxy]-phenyl]benzo[*b*]thiophene (13). To a solution of 14 (20.0 g,

(38) Raney nickel was prepared by the standard procedure of R. L. Augustine described in "Catalytic Hydrogenation, Techniques and Applications in Organic Synthesis", Marcel Dekker, New York, 1965.

(39) M. Freund and H. H. Reitz, *Chem. Ber.*, **39**, 2235 (1906).

0.083 mol), 400 mL of anhydrous pyridine, and 50 mg of 4-(dimethylamino)pyridine as catalyst was added 23.4 g (0.204 mol) of methanesulfonyl chloride. The reaction mixture was stirred overnight during which time crystals appeared. The reaction mixture was then poured into 2 L of cold water. Tan crystals that precipitated were filtered, washed well with water, MeOH, and finally Et_2O, and then dried at 60 °C overnight in vacuo to yield 32.5 g (99%) of **13**: mp 195–197 °C. Recrystallization from 4:1 DMF:water yielded an analytical sample of **13**: mp 197–198 °C; NMR (60 MHz, Me_2SO-d_6) δ 3.53 (6 H, s, CH_3SO_2), 7.4–8.3 (8 H, m, aromatic). Anal. ($C_{16}H_{14}O_6S_3$) C, H.

Methyl 4-[2-(1-Pyrrolidinyl)ethoxy]benzoate (22). Method A. A mixture of methyl 4-hydroxybenzoate (100 g, 0.66 mol), 800 mL of anhydrous DMF, and finely powdered anhydrous K_2CO_3 (226 g, 1.64 mol) was heated to 100 °C and 136 g (0.80 mol) of solid *N*-(2-chloroethyl)pyrrolidine hydrochloride was gradually added in portions over about 10 min. The reaction was kept at about 100 °C for 1.5 h, then the solids were filtered off, and the filtrate was evaporated to remove most of the DMF and provide a brown oily residue. The solids from the filtration were dissolved in 1.5 L water and extracted twice with 500 mL of EtOAc. The EtOAc extracts were then used to dissolve the brown oil, and the resulting solution was washed with portions of aqueous NaCl solution (4 × 500 mL). The EtOAc solution was dried ($MgSO_4$) and evaporated to give a brown oil, which showed essentially one spot on TLC analysis (SiO_2:MeOH). This material was carried on without further purification.

Methyl esters **23** and **27** were prepared similarly and hydrolyzed without further purification.

Method B. Methyl 4-[2-(Dimethylamino)ethoxy]benzoate (25). Sodium hydride (28.8 g, 1.2 mol) (washed with two 500-mL portions of Et_2O under a N_2 atmosphere to remove the mineral oil) was suspended in 200 mL of anhydrous DMF. Then methyl 4-hydroxybenzoate (75.0 g, 0.493 mol) in 100 mL of DMF was added rapidly. A solution of 2-(dimethylamino)ethyl chloride hydrochloride (86.43 g, 0.6 mol) in 100 mL of DMF was slowly added at room temperature. After the addition was complete, the reaction was heated to 80 °C for 72 h. After the reaction mixture had been allowed to cool to room temperature, excess NaH was decomposed by the gradual addition of 100 mL of MeOH, and the solvents were evaporated to provide a brown oil. The oil was dissolved in EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, and distilled. The product **25** [bp 130–140 °C (0.2 mm)] was a pale yellow oil which amounted to 68.7 g (63%) and was used in the next step without further purification.

Also prepared by method B were the methyl esters **24** and **26**.

4-[2-(1-Pyrrolidinyl)ethoxy]benzoic Acid Hydrochloride (28). The crude product **22** was hydrolyzed by dissolving the oil in 600 mL of MeOH, adding 200 mL of 5 N NaOH, and allowing the reaction mixture to stir under a N_2 atmosphere for 48 h. The mixture was then evaporated to remove most of the MeOH and the residue diluted with water to make a total volume of 1 L. The resulting solution was cooled to 5 °C and acidified by the gradual addition of 6 N HCl while the temperature was maintained below 10 °C. The white crystals that precipitated were collected and washed with cold MeOH. The product was then recrystallized from 2.5 L of MeOH to provide 122.5 g (67% based on **21**) of white crystalline **28**: mp 235–237 °C; NMR (270 MHz, Me_2SO-d_6) δ 1.88 [4 H, m, $N(CH_2CH_2)_2$], 3.24 [4 H, m, $N(CH_2CH_2)_2$], 3.50 (2 H, t, OCH_2CH_2), 4.53 (2 H, t, OCH_2CH_2N), 7.08 (2 H, d, J = 9 Hz, aromatic ortho to O), 7.94 (2 H, d, J = 9 Hz, aromatic ortho to C=O). Anal. ($C_{13}H_{18}ClNO_3$) C, H, N.

The same hydrolysis procedure was used for preparing compounds **29–33** (see Table I).

[6-Acetoxy-2-(4-acetoxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone Hydrochloride (35). A 25-g (0.092 mol) portion of **28** was converted to its acid chloride by dissolving it in 200 mL of 1,2-dichloroethane and adding one drop of DMF and 36.5 g (0.31 mol) of $SOCl_2$. The mixture was stirred at reflux under a N_2 atmosphere for 2 h and was then evaporated in vacuo to obtain the tannish white crystalline acid chloride.

The acid chloride was dissolved in 1 L of 1,2-dichloroethane, and 20 g (0.061 mol) of **11** were added followed by the addition of 73.4 g (0.55 mol) of $AlCl_3$ in three portions over a period of 3 min with vigorous stirring. The mixture was stirred for 1 h and was then poured into 1 L of ice–water. The layers were separated, and the aqueous layer was extracted three times with 200 mL of warm $CHCl_3$. The organic layers were combined, dried ($MgSO_4$), and evaporated under vacuum to obtain **35** as a yellow oil, which was hydrolyzed without further purification.

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone (38). The yellow oil **35** obtained above was dissolved in 700 mL of MeOH, and 100 mL of 5 N NaOH solution was added. The mixture was stirred for 2 h at ambient temperature, and then the solvent was removed under vacuum. The residue was dissolved in 500 mL of water and was washed with two 500-mL portions of Et_2O. While the temperature was maintained below 20 °C by the addition of ice, the water layer was acidified to pH 2 with methanesulfonic acid. The aqueous phase was then diluted to about 3 L, washed again with two 1-L portions of Et_2O, and made basic by cautious addition of $NaHCO_3$. A pale yellow precipitate appeared, which was collected by filtration, washed with water, and vacuum dried at 70 °C to obtain 13 g of slightly impure product. The material was dissolved in 500 mL of hot acetone, filtered, and evaporated down to a volume of approximately 100 mL. The solution was cooled to obtain 11.3 g of the desired product **38** (40% based on **11**): mp 146–147 °C; NMR (100 MHz, Me_2SO-d_6) δ 1.72 [4 H, m, $N(CH_2CH_2)_2$], 2.68 [4 H, m, $N(CH_2CH_2)_2$], 2.94 (2 H, t, J = 6 Hz, OCH_2CH_2), 4.15 (2 H, t, J = 6 Hz, OCH_2), 6.68 (2 H, d, J = 9 Hz, aromatic ortho to OH), 6.85 (1 H, q, J_{H4-H5} = 9Hz), J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 6.93 (2 H, d, J = 9 Hz, aromatic ortho to OCH_2), 7.18 (2 H, d, J = 9 Hz, aromatic meta to OH), 7.25 (1 H, d, J = 9 Hz, H4 of benzothiophene ring), 7.67 (2 H, d, J = 9 Hz, aromatic ortho to CO), 9.75 (2 H, br s, OH); UV (EtOH) λ_{max} 290 nm (ϵ 32 500); IR (KBr) 1607 cm^{-1}. Anal. ($C_{27}H_{25}NO_4S$) C, H, N.

[6-(Benzoyloxy)-2-[4-(benzoyloxy)phenyl]benzo[*b*]thien-3-yl][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone Hydrochloride (36). An acid chloride was formed from 18.1 g (0.067 mol) of **28** as described in the preparation of **35**. The acid chloride was used to acylate 20 g (0.044 mol) of **12** as described above, using 53.2 g (0.40 mol) of $AlCl_3$. After a reaction time of 1.5 h, the reaction was worked up in the same manner as in the preparation of **35**. Evaporation of the dried $CHCl_3$ extracts gave a tan foam. The bulk of the product was used without further purification in the subsequent hydrolysis step. A small sample of the tan material was recrystallized from denatured EtOH to provide an analytical sample of the desired **36**: mp 218–222 °C; NMR (90 MHz, $CDCl_3$) δ 2.10 [4 H, m, $N(CH_2CH_2)_2$], 2.8–4.0 [4 H, m, $N(CH_2CH_2)_2$], 3.45 (2 H, m, OCH_2CH_2), 4.52 (2 H, m, OCH_2), 6.6–7.9 (15 H, m, aromatic), 8.0–8.3 (6 H, m, aromatic ortho to C=O). Anal. ($C_{41}H_{34}ClNO_6S$) C, H, N.

Hydrolysis of Crude Product 36 with Acid To Provide [6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone (38). To the crude product **36** were added 400 mL of EtOH, 400 mL of water, and 55 mL of methanesulfonic acid. The mixture was heated on a steam bath for 72 h and then concentrated under vacuum. The residue was dissolved in about 4 L with water and washed with 2 L of Et_2O. The resulting aqueous layer was degassed under vacuum and cooled to about 20 °C by adding ice. The pH was then adjusted to 8.4 by the addition of 7.5 M aqueous ammonia. A yellow solid precipitated, which was collected by filtration, washed with cold water, and dried under vacuum at 60 °C. Recrystallization from acetone yielded 16.3 g (81% based on **12**) of purified **38**, which was positively identified by NMR, IR, and UV spectra as identical with the product obtained by the hydrolysis of compound **35** described above.

Hydrolysis of Mesylate 37 To Provide [6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]methanone (38). A mixture of 23.8 g (0.037 mol) of **37**, 600 mL of THF, 240 mL of MeOH, and 40 mL of 5 N NaOH was stirred at ambient temperature for 60 h and then evaporated under vacuum. The residue was diluted to 400 mL with water, and the solution was continuously extracted with Et_2O for 8 h. The aqueous phase was then filtered, cooled to below 10 °C, and acidified to pH 2 with methanesulfonic acid. It was then diluted to about 7 L with water and was extracted with Et_2O. The aqueous layer was degassed under vacuum and made basic with

$NaHCO_3$. The solids that precipitated were collected, vacuum dried, and purified by column chromatography (silica gel, using as eluant a gradient composed of 1% MeOH in $CHCl_3$ phasing to 25% MeOH in $CHCl_3$) to give 13.5 g (79%) of **38** after crystallization from acetone. This product was identical with the product prepared earlier as judged from its melting point as well as its NMR, IR, and UV spectra.

[6-[(Methylsulfonyl)oxy]-2-[4-[(methylsulfonyl)oxy]phenyl]benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone Hydrochloride (39). Method 1 Using $AlCl_3$. The acid chloride was prepared in the usual manner from 19.7 g (0.069 m) of **29** in 200 mL of toluene, with one drop of DMF, and 44.9 g of $SOCl_2$. The acid chloride was dissolved in 600 mL of 1,2-dichloroethane and 20 g (0.05 mol) of **13** was added. Then 59.6 g (0.45 mol) of $AlCl_3$ was added portionwise over a period of 30 min, and the reaction mixture was then stirred for 16 h. It was poured over 2 L of ice–water, and the product was extracted from the aqueous layer with two 200-mL portions of warm $CHCl_3$. The organics were combined, dried, and evaporated to obtain an oil, which was crystallized from 350 mL of MeOH to obtain 28 g (84%) of **39**, mp 133–135 °C. This product was essentially identical with that prepared by method 2 below by its IR, UV, and NMR spectra.

The aroylation procedure described in method 1 was used for preparing **37**, **40–43** (see Table II).

Method 2 Using Trifluoromethanesulfonic Acid. The acid chloride was formed from 2.0 g (7.0 mmol) of **29** as described above and was combined with 2 g (5.0 mmol) of **13** in 50 mL of dichloromethane. A 2.4-g portion of trifluoromethanesulfonic acid was added and the mixture was stirred overnight under reflux. The reaction mixture was then poured over a cold $NaHCO_3$ solution. The organic layer was separated, dried ($MgSO_4$), and evaporated under vacuum to a yellow foam, which was treated with excess 3% HCl in anhydrous MeOH. The mixture was evaporated to dryness under vacuum to obtain a white foam, which was dissolved in 18 mL of boiling MeOH. The solution was cooled to obtain 3.1 g (93%) of the desired **39**: mp 128–130 °C; NMR (90 MHz, Me_2SO-d_6) δ 1.50–2.00 [6 H, m, $CH_2(CH_2)_3CH_2$], 2.57–3.75 (6 H, m, NCH_2), 3.36 (3 H, s, CH_3SO_2), 3.46 (3 H, s, CH_3SO_2), 4.45 (2 H, br t, J = 6 Hz, OCH_2), 6.97 (2 H, d, J = 9 Hz, aromatic ortho to OCH_2), 7.25–7.80 (8 H, m, aromatic), 8.25 (1 H, d, J = 2 Hz, aromatic, ortho to O and S), 10.70–11.00 (1 H, br s, NH). Anal. ($C_{30}H_{32}ClNO_8S_3$) C, H, N.

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (44). A mixture of 4.0 g (6.0 mmol) of **39**, 100 mL of denatured EtOH, and 10 mL of 5 N NaOH was stirred under reflux for 1.5 h and then evaporated to dryness under vacuum. The residue was dissolved in 200 mL of water and washed with 300 mL of Et_2O. The water layer was acidified with 1 N HCl and then made slightly basic with $NaHCO_3$ to precipitate 2.4 g of a yellow solid. The crude product was purified on a silica gel column, eluting first with 5% MeOH in $CHCl_3$, followed by 10% MeOH in $CHCl_3$, to obtain 1.78 g of yellow oil. Crystallization of the oil from 6 mL of acetone gave 1.2 g (42%) of purified **44**: mp 143–147 °C; NMR (100 MHz, Me_2SO-d_6) δ 1.20–1.65 [6 H, m, $(CH_2CH_2)_2CH_2$], 2.30–2.45 [4 H, m, $N(CH_2CH_2)_2$], 2.60 (2 H, t, J = 6 Hz, OCH_2CH_2), 4.06 (2 H, t, J = 6 Hz, OCH_2), 6.68 (2 H, d, J = 9 Hz, aromatic ortho to OH), 6.85 (1 H, q, J_{H4-H5} = 9 Hz, J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 6.90 (2 H, d, J = 9 Hz, aromatic ortho to OCH_2CH_2N), 7.18 (2 H, d, J = 9 Hz, aromatic meta to OH), 7.25 (1 H, d, J = 9 Hz, H4 of benzothiophene ring), 7.66 (2 H, d, J = 9 Hz, aromatic ortho to CO), 9.72 (2 H, br s, OH); UV (EtOH) λ_{max} 290 nm (ϵ 34 000) ($C_{28}H_{27}NO_4S$ requires 473). Anal. ($C_{28}H_{27}NO_4S$) C, H, N.

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-hexahydroazepinyl)ethoxy]phenyl]methanone (45). The method used in the hydrolysis of compound **39** was used to hydrolyze 9.0 g (13.2 mmol) of **40** to yield 5.2 g of a yellow solid after workup. Purification on a silica gel column (eluted with a gradient of 5% to 10% MeOH in $CHCl_3$) yielded 2.45 g (38%) of **45** as a yellow foam: NMR (100 MHz, Me_2SO-d_6) δ 1.53 [8 H, s, $N(CH_2CH_2CH_2)_2$], 2.65 [4 H, m, $N(CH_2CH_2CH_2)_2$], 2.81 (2 H, t, J = 6 Hz, NCH_2CH_2O), 4.04 (2 H, t, J = 6 Hz, CH_2O), 6.68 (2 H, d, J = 9 Hz, aromatic ortho to OH), 6.85 (1 H, q, J_{H4-H5} = 9 Hz, J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 6.90 (2 H, d, J = 9 Hz, aromatic ortho to OCH_2), 7.18 (2 H, d, J = 9 Hz, aromatic meta to OH), 7.26 (1 H, d, J = 9 Hz, H4 of benzothiophene ring), 7.34 (1 H, d, J = 2 Hz, H7 of benzothiophene ring), 7.66 (2 H, d, J = 9 Hz, aromatic ortho to CO), 9.71 (2 H, br s, OH); high-resolution mass spectrum, calcd/found ($C_{29}H_{29}NO_4S$) 487.182/487.181; UV (EtOH) λ_{max} 290 nm (ϵ 32500); IR (KBr) ν 1608 cm^{-1}.

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(dimethylamino)ethoxy]phenyl]methanone (46). The hydrolysis of 2.0 g (3.19 mmol) of **41** in 100 mL of denatured EtOH and 5 mL of 5 N NaOH as described for the reaction of **39** yielded 1.21 g of crude **46**. Column chromatography (silica gel, 1:9 MeOH:$CHCl_3$ eluant) and crystallization from acetone gave 0.64 g (46%) of the desired **46**: mp 141–144 °C; NMR (100 MHz, Me_2SO-d_6) δ 2.17 (6 H, s, NCH_3), 2.57 (2 H, t, J = 6 Hz, NCH_2), 4.05 (2 H, t, J = 6 Hz, OCH_2), 6.66 (2 H, d, J = 9 Hz, aromatic ortho to OH), 6.85 (1 H, q, J_{H4-H5} = 9 Hz, J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 6.90 (2 H, d, J = 9 Hz, aromatic ortho to OCH_2), 7.18 (2 H, d, J = 9 Hz, aromatic meta to OH), 7.26 (1 H, d, J = 9 Hz, H4 of benzothiophene ring), 7.34 (1 H, d, J = 2 Hz, H7 of benzothiophene ring), 7.65 (2 H, d, J = 9 Hz, aromatic ortho to CO), 9.73 (2 H, br s, OH). Anal. ($C_{25}H_{23}NO_4S$) C, H, N.

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(diethylamino)ethoxy]phenyl]methanone (47). Following the method used in the hydrolysis of **37**, 4 g (6.12 mmol) of **42**, 100 mL of THF, 40 mL of MeOH, and 10 mL of 5 N NaOH were stirred at ambient temperature for 24 h. Workup and subsequent chromatography (silica gel, 1:9 MeOH:$CHCl_3$ eluant) gave 2.0 g (71%) of **47** as a yellow foam that could not be induced to crystallize: NMR (100 MHz, Me_2SO-d_6) δ 0.93 (6 H, t, J = 7 Hz, CH_2CH_3), 2.50 (4 H, q, J = 7 Hz, CH_2CH_3), 2.72 (2 H, t, J = 6 Hz, NCH_2), 4.01 (2 H, t, J = 6 Hz, OCH_2), 6.67 (2 H, d, J = 9 Hz, aromatic ortho to OH), 6.85 (1 H, q, J_{H4-H5} = 9 Hz, J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 6.88 (2 H, d, J = 9 Hz, aromatic ortho to OCH_2), 7.18 (2 H, d, J = 9 Hz, aromatic meta to OH), 7.27 (1 H, d, J = 9 Hz, H4 of benzothiophene ring), 7.34 (1 H, d, J = 2 Hz, H7 of benzothiophene ring), 7.66 (2 H, d, J = 9 Hz, aromatic ortho to CO), 9.72 (2 H, br s, OH); high-resolution mass spectrum, calcd/found ($C_{27}H_{27}NO_4S$) 461.166/461.166.

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]methanone Hydrochloride (48). A 5-g (7.3 mmol) portion of the crude product **43** was hydrolyzed as described above in the hydrolysis of compound **37** to give 3.2 g of crude product **48**. Chromatography of the crude product (silica gel, 2% to 20% MeOH in $CHCl_3$ gradient eluant) gave 2.5 g (70%) of purified **48**, which would not crystallize: NMR (100 MHz, Me_2SO-d_6) δ 0.96 [12 H, d, J = 7 Hz, $[CH(CH_3)_2]_2$], 2.72 (2 H, t, J = 6 Hz, NCH_2), 2.96 [2 H, m, J = 7 Hz, $[(CH(CH_3)_2]_2$], 3.88 (2 H, t, J = 6 Hz, OCH_2), 6.65 (2 H, d, J = 9 Hz, aromatic ortho to OH), 6.83 (1 H, q, J_{H4-H5} = 9 Hz, J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 6.87 (2 H, d, J = 9 Hz, aromatic ortho to OCH_2), 7.15 (2 H, d, J = 9 Hz, aromatic meta to OH), 7.26 (1 H, d, J = 9 Hz, H4 of benzothiophene ring), 7.32 (1 H, d, J = 2 Hz, H7 of benzothiophene ring), 7.64 (2 H, d, J = 9 Hz, aromatic ortho to C=O), 9.70 (2 H, s, OH); high-resolution mass spectrum, calcd/found ($C_{29}H_{31}NO_4S$) 489.199/489.199. Anal. ($C_{29}H_{31}NO_4S$) C, H, N.

[6-Methoxy-2-(4-methoxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone Hydrochloride (49). Under N_2, a mixture of 9.0 g (31.5 mmol) of **29**, 100 mL of chlorobenzene, 15 mL of $SOCl_2$, and 5 drops of DMF were stirred at 75–79 °C for 2 h to prepare the corresponding acid chloride. Excess $SOCl_2$ and chlorobenzene were removed by vacuum distillation. Then 50 mL of fresh chlorobenzene was added and the distillation was repeated to remove residual $SOCl_2$. The residue was dissolved in 150 mL of CH_2Cl_2, and to it were added 8.1 g (30.0 mmol) of **8** and 30.0 g (225 mmol) of $AlCl_3$. The mixture was stirred at 27–29 °C for 1.5 h. The reaction was quenched at <25 °C by the addition of 108 mL of THF, followed by 30 mL of 20% HCl and 108 mL of water. The aqueous phase was removed and was extracted with 50 mL of CH_2Cl_2. The organic layers were combined, extracted with 90 mL of water, dried (Na_2SO_4), and evaporated to a solid under vacuum. The solid was slurried in 200 mL of hot chlorobenzene. The slurry was cooled to 5 °C, filtered, washed with 30 mL of chlorobenzene, and dried under vacuum to yield 10.6 g (65.5%) of **49**: mp 216 °C dec; NMR (90 MHz, $CDCl_3$) δ 1.6 [2 H, m, $(CH_2CH_2)_2CH_2$], 2.0 [4 H, m, $N(CH_2CH_2)_2$], 3.1 [4 H, m, $N(CH_2CH_2)_2$], 3.3 [2 H, m,

$CH_2N(CH_2)_5$], 3.7 and 3.9 (3 H, s, OCH_3), 4.5 (2 H, m, OCH_2), 6.7–7.8 (11 H, m, aromatic); UV (MeOH) λ_{max} 286 nm (ϵ 34000). Anal. ($C_{30}H_{32}NO_4SCl$) C, H, N, O, S, Cl.

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone Hydrochloride (50). Via Demethylation of Compound 49. To a solution of 1.78 g (3.3 mmol) of **49** in 20 mL of CH_2Cl_2 was added 2.6 g (19.5 mmol) of $AlCl_3$ followed by 1.22 mL (16.5 mmol) of EtSH. The mixture was stirred at room temperature for 0.5 h. The reaction was quenched by the addition of 12 mL of THF, 3 mL of 20% HCl, and 12 mL of water. The desired **50** crystallized from the two-phase system and was collected by filtration, washed with 40 mL of water and 40 mL of ether, and dried under vacuum to yield 1.31 g (77.5%): mp 204 °C dec; NMR, TLC (SiO_2; $CHCl_3$:MeOH:Et_3N, 8:1:1) identical with that of authentic **50** prepared as described below.

Compound 50 via One-Pot Acylation–Demethylation of Compound 8. Following the procedure described in the preparation of **49**, 1.50 g (5.25 mmol) of **29** was converted to the corresponding acid chloride. The acid chloride was cooled, and 30 mL of CH_2Cl_2, 1.35 g (5.0 mmol) of **8**, and 5.0 g (37.5 mmol) of $AlCl_3$ were added. The mixture was stirred at 27–29 °C for 1.5 h. Then 1.6 mL (22.0 mmol) of EtSH was added and the reaction mixture was stirred at 32–34 °C for 0.5 h. While the temperature was maintained below 30 °C, the reaction was diluted with 18 mL of THF followed by 5 mL of 20% HCl and 18 mL of water. The resulting solid was collected by filtration, washed with water and Et_2O, and dried under vacuum to yield 2.60 g of crude **50** solvated with THF, mp 217 °C dec. Recrystallization of 5.0 g of crude **50** from MeOH/water gave 2.95 g of pure **50**: mp 258 °C dec; NMR (270 MHz, Me_2SO-d_6) δ 1.36, 1.70 [2 H, m, $(CH_2CH_2)_2CH_2$], 1.77 [4 H, m, $N(CH_2CH_2)_2$], 2.96 (2 H, m, OCH_2CH_2N), 3.43 [4 H, m, $N(CH_2CH_2)_2CH_2$], 4.44 (2 H, m, OCH_2), 6.70 (2 H, d, J = 9 Hz, aromatic ortho to OH), 6.87 (1 H, m, J_{H4-H5} = 9 Hz, J_{H5-H7} = 2 Hz, H5 of benzothiophene ring), 6.97 (2 H, d, J = 9 Hz, aromatic ortho to OCH_2), 7.17 (2 H, d, J = 9 Hz, aromatic meta to OH), 7.26 (1 H, d, J = 9 Hz, H4 of benzothiophene ring), 7.37 (1 H, d, J = 2 Hz, H7 of benzothiophene ring), 7.69 (2 H, d, J = 9 Hz, aromatic ortho to CO), 9.87 (1 H, s, OH), 9.87 (1 H, s, OH), 10.50 (1 H, br s, N^+-H); IR (KBr) ν 1642 cm^{-1}; UV (EtOH) λ_{max} 286 nm (ϵ 32800). Anal. ($C_{28}H_{28}NO_4SCl$) C, H, N, O, S, Cl.

To generate the free base **44**, a suspension of 10.0 g (19.6 mol) of **50** in 50 mL of water was treated with 1 N NaOH (about 60 mL) until a solution was obtained. Titration with 1 N HCl to pH 8.5, followed by filtration and drying under vacuum, yielded 8.85 g (95%) of **44** as an amorphous solid. Crystallization of the amorphous material from acetone yielded **44**, which exhibited the same physical and spectral data as that prepared earlier by hydrolysis of dimesylate **39**.

Biological Assays

Rat Uterotropic/Antiuterotropic Bioassay. The estrogenic and antiestrogenic properties of the compounds were determined in an immature rat uterotropic assay (4 day) that has been described previously.[29a] Immature (19–20 day, 40–45 g) Holtzman rats were tested in groups of six. Animals were treated daily for 3 days and sacrificed on the fourth day. Tissues and wet weight were determined to the nearest 0.1 mg. For compounds **38**, **44–48**, and tamoxifen, results of dose–response determinations over a dosage range of 1–1000 μg per animal per day are given in Table III.

Specific Binding to Estrogen Receptors. Binding affinities of the lead compound **38** and the compound showing greatest antiuterotropic activity in the series (**44**) for rat uterine cytoplasmic estrogen receptors were determined at 4, 15, and 30 °C by a competitive assay procedure described previously[29b] and expressed as relative binding affinity (estradiol-17β = 1.0). Figure 1 presents these data graphically.

Inhibition of Growth of DMBA-Induced Tumors by the Hydrochloride Salt of Compound 44. The effect of compound **50**, the HCl salt of **44**, on the growth of mammary tumors in rats was determined as follows. Female Sprague–Dawley rats were obtained from Harlan Industries (Indianapolis, IN). At about 55 days of age they received a single oral feeding of 20 mg of 7,12-dimethylbenzanthracene (DMBA) dissolved in corn oil. The mammary glands were palpated at weekly intervals for the appearance of mammary tumors, starting 6 weeks after DMBA treatment. After the appearance of measurable mammary tumors, the rats were placed into one of three groups. Group 1 (control) received the drug vehicle [PEG-400:water (1:1)], group 2 received vehicle containing 1 mg/kg of **50**, and group 3 received vehicle containing 10 mg/kg of drug. All rats were treated orally, twice a day. Mammary tumors were measured with a metric caliper at the start and at weekly intervals during the tests. The largest and the smallest diameters of the tumors were recorded, and the area of each tumor was determined by multiplying the two diameters. In a separate experiment, the antitumor effect of 10 mg/kg of **50** was compared to that of an equal amount of orally administered tamoxifen. Results are shown in Tables IV and V.

At the end of the study the rats were decapitated and blood was collected for prolactin and LH radioimmunoassay. Serum prolactin was expressed as nanograms of NIAMDD–rat prolactin–RP1 per milliliter, and serum LH was expressed as nanograms of NIAMDD–rat LH per milliliter. Radioimmunoassay kits were purchased from Dr. Albert Parlow, Harbor General Hospital (Torrence, CA), and the assays were performed according to the instructions supplied by the National Institutes of Arthritis Metabolic and Digestive Diseases (NIAMDD) to investigators using their radioimmunoassay materials.

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