Articles

Structure−Activity Relationships of Selective Estrogen Receptor Modulators: Modifications to the 2-Arylbenzothiophene Core of Raloxifene

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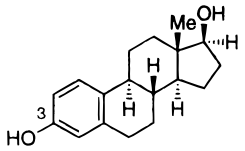
The 2-arylbenzothiophene raloxifene, **1**, is a selective estrogen receptor modulator which is currently under clinical evaluation for the prevention and treatment of postmenopausal osteoporosis. A series of raloxifene analogs which contain modifications to the 2-arylbenzothiophene core have been prepared and evaluated for the ability to bind to the estrogen receptor and inhibit MCF-7 breast cancer cell proliferation *in vitro*. Their ability to function as tissue-selective estrogen agonists *in vivo* has been assayed in a short-term, ovariectomized (OVX) rat model with end points of serum cholesterol lowering, uterine weight gain, and uterine eosinophil peroxidase activity. These studies have demonstrated that (1) the 6-hydroxy and, to a lesser extent, the 4′-hydroxy substituents of raloxifene are important for receptor binding and *in vitro* activity, (2) small, highly electronegative 4′-substituents such as hydroxy, fluoro, and chloro are preferred both *in vitro* and *in vivo*, (3) increased steric bulk at the 4′-position leads to increased uterine stimulation *in vivo*, and (4) additional substitution of the 2-aryl moiety is tolerated while additional substitution at the 4-, 5-, or 7-position of the benzothiophene results in reduced biological activity. In addition, compounds in which the 2-aryl group is replaced by alkyl, cycloalkyl, and naphthyl substituents maintain a profile of *in vitro* and *in vivo* biological activity qualitatively similar to that of raloxifene. Several novel structural variants including 2-cyclohexyl, 2-naphthyl, and 6-carbomethoxy analogs also demonstrated efficacy in preventing bone loss in a chronic OVX rat model of postmenopausal osteopenia, at doses of 0.1−10 mg/kg.

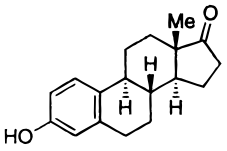
Introduction

The central role of endogenous estrogens, such as 17β-estradiol and estrone, in the development and maintenance of the female reproductive organs, mammary glands, and other sexual characteristics has long been appreciated. More recently estrogens' involvement in the growth and/or function of a number of other tissues, such as the skeleton, the cardiovascular system, and the central nervous system, in both males and females has also been recognized.[1,2] The decreased production of ovarian steroids which occurs after the climacteric has been linked to a number of postmenopausal pathologies, particularly osteoporosis and coronary artery disease.[3,4] Estrogen replacement therapy is effective in reducing the risks associated with these pathologies; however, concerns relating to the increased risk of endometrial cancer have necessitated the development of therapeutic regimens in which the uterine effects of estrogen are opposed by progestin treatment.[5] Side effects of progestin treatment, such as resumption of menses, central nervous system disturbances, and the possibility of attenuated cardiovascular benefits, have significantly reduced patient compliance.[6] Furthermore, recent studies which confirm the increased risk of breast cancer associated with estrogen replacement therapy have stimulated the search for treatment alternatives.[7]

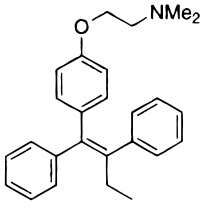
Over the years a variety of steroidal and nonsteroidal



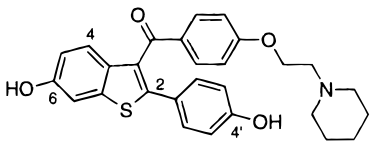
17β-estradiol



estrone



tamoxifen



raloxifene, **1**

compounds which interact with the estrogen receptor (ER) have been developed as contraceptives and for the treatment of breast cancer, uterine dysfunction, and other disorders of the female reproductive system.[8] Tamoxifen, originally developed as an anti-estrogen and widely utilized for the treatment of breast cancer, has paradoxically been found to act as a partial estrogen agonist in the uterus and to display estrogen agonist effects in bone and the cardiovascular system.[9] Recently, several groups have described molecules which fully antagonize the effects of estrogen on uterine and mammary tissue, while mimicking the effects of estro-

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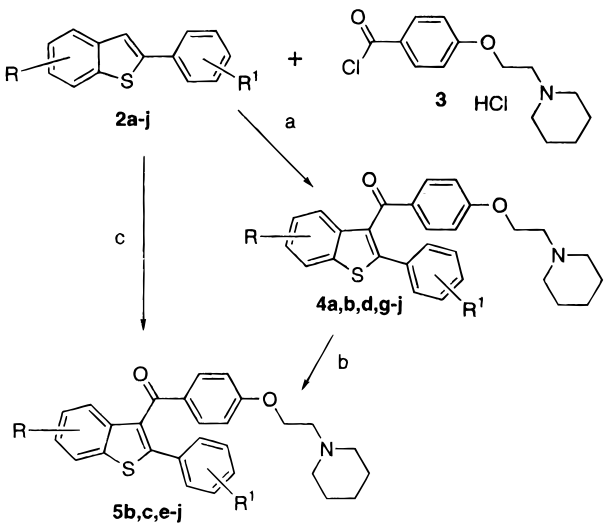
Scheme 1[a]



a R = H, R^1 = H
b R = 6-OH[b], R^1 = 4'-OMe
b' R = 6-OMe, R^1 = 4'-OH[b]
c R = H, R^1 = 4'-OH[b]
d R = H, R^1 = 4'-Cl
e R = 6-OH[b], R^1 = 4'-Cl
f R = 6-Cl, R^1 = 4'-OH[b]
g R = 6-OH[b], R^1 = 4'-Me
h R = 6-Me, R^1 = 4'-OH[b]
i R = 6-OH[c], R^1 = 4'-F
j R = 7-OH[d], R^1 = 4'-OH[d]

[a] Reagents: (a) $AlCl_3$, CH_2Cl_2, 27−84%; (b) $AlCl_3$, EtSH, CH_2Cl_2, 36−83%, or NaOH, 84%; (c) **3**, $AlCl_3$, EtSH, CH_2Cl_2, 12−50%. [b]Protected as methyl ether in compounds **2** and **4**. [c]Protected as mesylate in compounds **2** and **4**. [d]Protected as 4-fluorobenzoate in compounds **2** and **4**.

gen on bone and the cardiovascular system.[10] The term selective estrogen receptor modulator (SERM)[10b] has been coined to describe these agents, and one such compound, raloxifene (LY139481 HCl; **1**), is in advanced clinical trials for the prevention and treatment of osteoporosis.[11,12] As part of a program to further explore structure−activity relationships in the raloxifene series, we have examined a series of analogs in which the 2-arylbenzothiophene substructure has been modified. Herein, we describe the synthesis of these analogs, their *in vitro* effects in receptor binding and cell proliferation assays, and their effects on bone, uterus, and serum lipids in an ovariectomized (OVX) rat model.[13]

Chemistry

Several methods for the synthesis of 2-aryl-3-aroylbenzothiophenes have previously been described.[11,14] The Friedel−Crafts acylation of a 2-arylbenzothiophene **2** with 4-[2-(1-piperidino)ethoxy]benzoyl chloride, **3**, has been utilized for the preparation of a variety of raloxifene analogs **4** and **5** as outlined in Scheme 1. In this sequence, phenolic protecting groups (usually methyl ethers) may be removed in a separate reaction or *in situ* as part of the acylation protocol. Optimal yields are obtained for substrates in which the 3-position of the benzothiophene is further activated by electron-donating substituents on the 2-aryl moiety.

During the course of these investigations, it rapidly became clear that a more general method for the synthesis of 2-aryl-3-aroylbenzothiophenes was required. Difficulties in the preparation of more highly substituted 2-arylbenzothiophenes and inconsistent regioselectivity in the acylation step were problematic. Our desire to prepare analogs which would define a more diverse structure−activity relationship led us to explore an alternative route involving the addition of a Grignard reagent to a 2-amino-3-aroylbenzothiophene. This strategy had previously been reported to result in exclusive 1,4-addition to the enone, even in the presence of excess Grignard reagent.[15]

As described in Scheme 2, we have prepared a variety of substituted 2-aminobenzothiophenes **6** following the general method of Hopkinson and Lee-Ruff.[16] Condensation of **6** with the substituted benzoyl chloride **3** then provided the requisite 2-amino-3-aroylbenzothiophenes **7** in acceptable yields.[15,17] Treatment of **7** with 4-anisylmagnesium bromide gave a series of raloxifene analogs **8** which exhibit alternative substitution patterns on the benzothiophene ring. These could then be demethylated ($AlCl_3$/EtSH or BX_3)[18] to provide their phenolic counterparts **9** if so desired. Alternatively, we have treated **7a** with a variety of substituted phenyl Grignard reagents (Scheme 3) or alkyl, naphthyl, and heteroaryl Grignard reagents (Scheme 4) to provide additional raloxifene analogs **10** and **12** in which the 2-substituent has been altered. Once again, demethylation generally provided the phenolic analogs **11** and **13**. In a few cases (e.g., **8f**, **10k**/**11l**, **10t**), however, standard demethylation protocols were ineffective or led to products with additional modifications.

In order to incorporate functionality in the 2-substituent which was incompatible with the Grignard reaction, an *umpolung* of the reaction partners was desired. Toward that end, **7a** was treated with trimethylstannyllithium[19] to provide, after rapid aqueous workup, the modestly stable 2-stannyl-3-aroylbenzothiophene **14** (Scheme 5). Stille coupling with a variety of aryl bromides followed by demethylation then provided the raloxifene analogs **15** and **16**, respectively.[20]

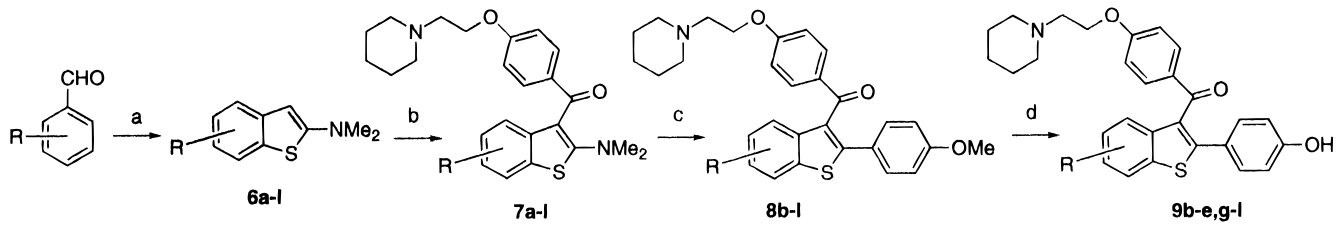
A more efficient synthesis of selectively 6- or 4′-functionalized raloxifene analogs was accomplished via the preparation and separation of the raloxifene silyl ethers **17**−**19** (Scheme 6). After conversion to the aryl triflates **20** and **21**, the triflate moieties were readily transformed into a variety of functional groups via palladium-catalyzed reactions.[21] Methyl esters **22a** and **23a** were further transformed into the carboxylic acid-containing analogs via hydrolysis or the amide-containing analogs via the Weinreb protocol (Scheme 6).[22] In all cases, the silyl ether was readily removed with acid or fluoride to provide the functionalized raloxifene analogs **22** and **23**.

Biological Testing

In Vitro. ER binding affinities were determined by displacement of bound [^{3}H]-17β-estradiol from MCF-7 cell lysate for compounds **4**, **5**, **8**−**13**, **15**, **16**, **22**, and **23** and are reported in Table 1.[23] Antagonism of estrogen action in a mammary tumor cell line was assayed via inhibition of MCF-7 cell proliferation stimulated by 10^{-11} M 17β-estradiol, and IC_{50} values are also included in Table 1.[24]

In Vivo. Tissue-specific estrogen agonist effects were examined in OVX rats,[25] utilizing uterine weight, uterine eosinophil peroxidase (EPO) activity,[26] and serum cholesterol levels as end points (Tables 2 and 3). Specifically, 75-day old OVX Sprague−Dawley rats were dosed daily by oral gavage, for 4 consecutive days, commencing 2 weeks after ovariectomy. A vehicle (20%

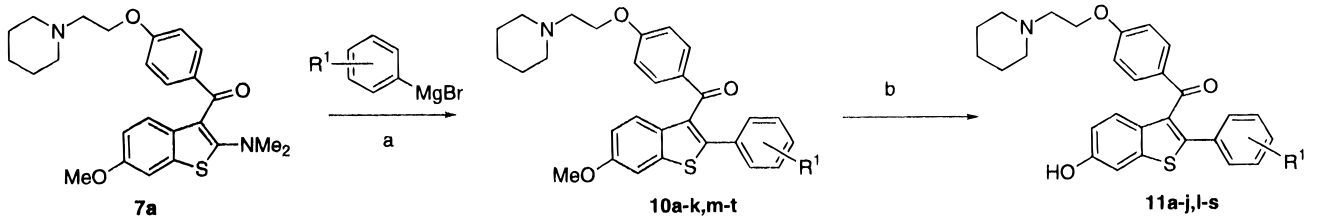
Scheme 2[a]



a R = 6-OMe
b R = 4-OH[b]
c R = 5-OH[b]
d R = 4,6-di(OH)[b]
e R = 5,6-di(OH)[c]
f R = 5,6,7-tri(OMe)
g R = 6-NMe_2
h R = 5-F,6-OH[b]
i R = 5-Me,6-OH[b]
j R = 5,7-di(Me),6-OH[b]
k R = 4,7-di(Me),6-OH[b]
l R = 4,5-benzo,6-OH[b]

[a] Reagents: (a) i. $CH(S)NMe_2$, LDA, −78 °C, 28−62%, ii. MsOH, CH_2Cl_2, 9−99%; (b) **3**, PhCl, 38−77%; (c) 4-anisylMgBr, THF, 15−77%; (d) $AlCl_3$, EtSH, CH_2Cl_2, or BX_3, dichloroethane, 31−97%. [b]Protected as methyl ether in compounds **6**−**8**. [c]Protected as 5-methyl ether, 6-benzyl ether in compounds **6** and **7**. Grignard reaction was carried out using 4-TBSO-phenylMgBr, and the benzyl and silyl protecting groups were removed via TBAF and catalytic transfer hydrogenation following Grignard addition; therefore, in **8e** the 6- and 4′-substituents are hydroxy.

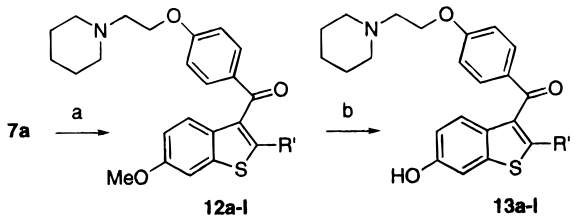
Scheme 3[a]



a R^1 = H
b R^1 = 2′-OH[b]
c R^1 = 3′-OH[c]
d R^1 = 2′-Me
e R^1 = 3′-F
f R^1 = 4′-Et
g R^1 = 4′-*i*-Pr
h R^1 = 4′-*n*-Bu
i R^1 = 4′-Ph
j R^1 = 4′-SMe
k R^1 = 4′-CH_2OH[c]
l R^1 = 4′-CH_2SEt
m R^1 = 4′-CF_3
n R^1 = 2′-Me,4′-OH[b]
o R^1 = 2′-OMe,4′-OH[b]
p R^1 = 3′-Me,4′-OH[b]
q R^1 = 3′-Cl,4′-OH[b]
r R^1 = 3′-F,4′-OH[c]
s R^1 = 3′,5′-diMe,4′-OH[b]
t R^1 = 3′,4′-OCH_2O-

[a] Reagents: (a) THF, 34−90%; (b) $AlCl_3$, EtSH, CH_2Cl_2, or BX_3, dichloroethane, 15−95%. [b]Protected as methyl ether in compound **10**. [c]Protected as TBS ether during Grignard reaction. In some cases, the TBS group was removed during workup.

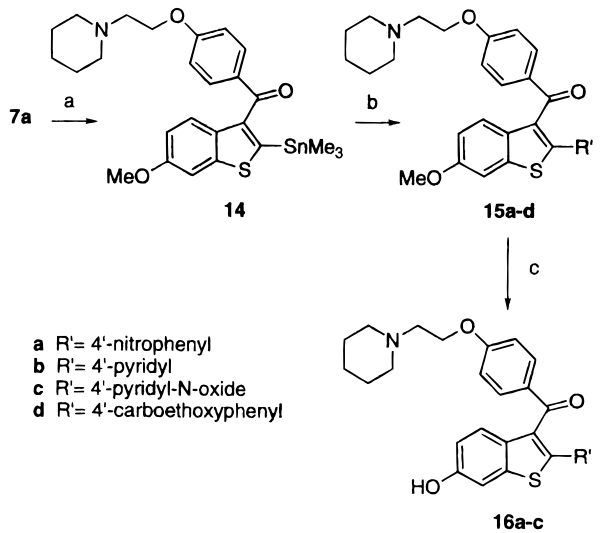
Scheme 4[a]



a R'= 1′-naphthyl
b R'= 2′-naphthyl
c R'= 4′-hydroxy-1′-naphthyl[b]
d R'= 2′-thienyl
e R'= 3′-thienyl
f R'= methyl
g R'= ethyl
h R'= isopropyl
i R'= cyclopentyl
j R'= cyclohexyl
k R'= *trans*-4′-hydroxycyclohexyl[c]
l R'= 4′-hydroxybenzyl[b]

[a] Reagents: (a) R′MgBr, THF, 29−81%; (b) $AlCl_3$, EtSH, CH_2Cl_2, or BX_3, dichloroethane, 68−86%. [b]Protected as methyl ether in compound **12**. [c]Protected as TBS ether in compound **12**.

Scheme 5[a]



a R'= 4′-nitrophenyl
b R'= 4′-pyridyl
c R'= 4′-pyridyl-N-oxide
d R'= 4′-carboethoxyphenyl

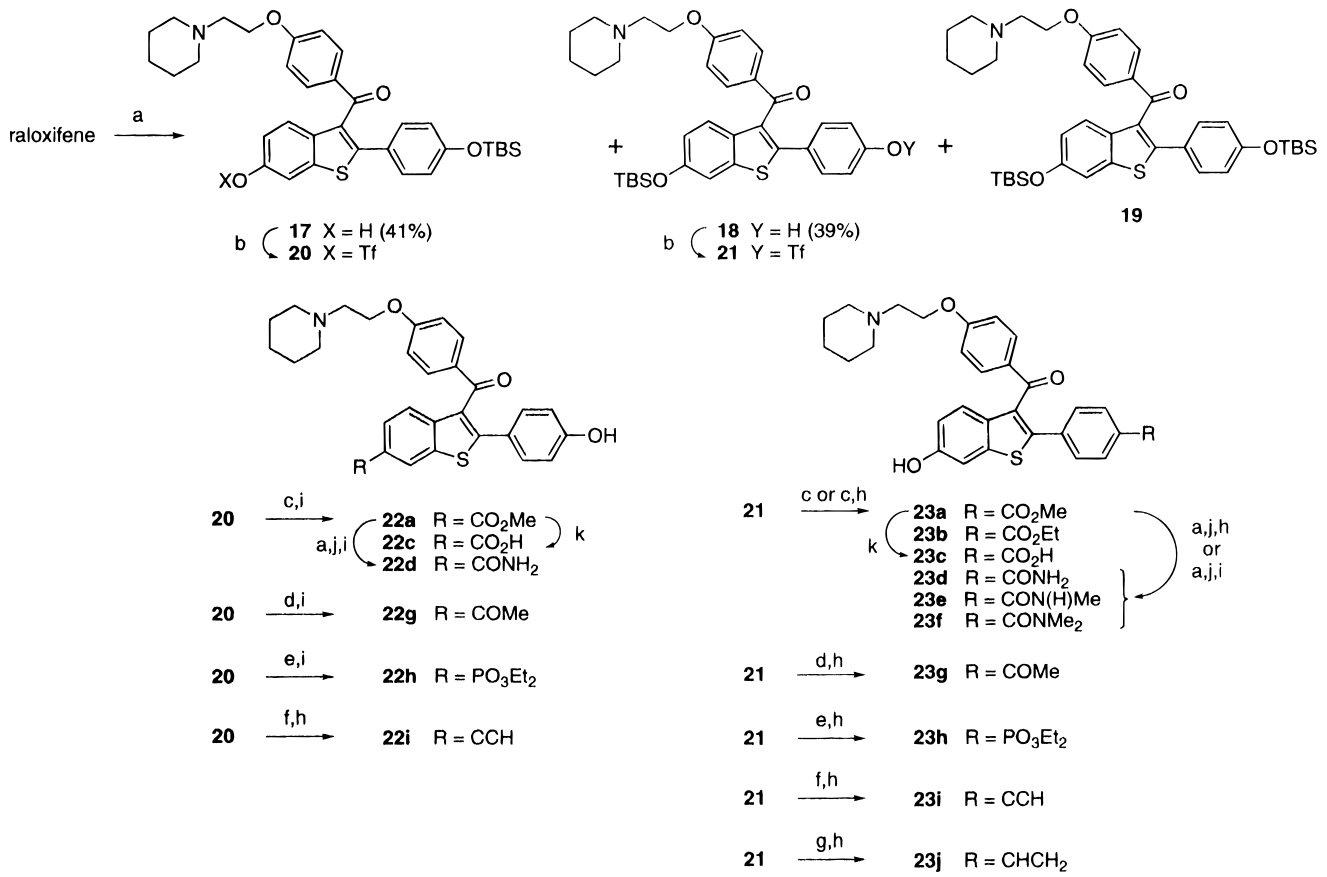
[a] Reagents: (a) Me_3SnLi, THF, 99%; (b) R′Br, $Pd(PPh_3)_4$, DMF, 32−87%; (c) $AlCl_3$, EtSH, CH_2Cl_2, or BX_3, dichloroethane, 56−97%.

β-hydroxycyclodextrin)-treated OVX control group was included in each experiment, as well as OVX rats given either ethynylestradiol (0.1 mg/kg) or raloxifene (0.1 mg/kg) as internal standards. Each new compound was tested at a minimum of three doses. All control groups and experimental groups included five animals at each dose. Selected compounds were further evaluated in a 5-week, OVX rat model in which effects on bone mineral density (BMD) were also examined.[27] In this model, daily oral dosing of Sprague−Dawley rats was initiated 4 days postovariectomy. Bone mineral density was assessed at the distal metaphysis of the femur by X-ray image analysis and is reported as percent protection relative to sham-operated and OVX controls (Table 4).

Results

In Vitro. The *in vitro* results in Table 1 clearly indicate the relative importance of the 6- and 4′-hydroxy groups of raloxifene with respect to receptor binding and

Scheme 6[a]



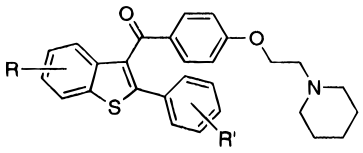
[a] Reagents: (a) TBSCl, Et_3N, THF; (b) $PhN(Tf)_2$, Et_3N, THF, 75−85%; (c) R′OH, CO, $Pd(OAc)_2$, dppp, Et_3N, DMF, 70−80 °C; (d) butyl vinyl ether, $Pd(OAc)_2$, dppp, Et_3N, DMF, 75 °C; (e) $HP(O)(OEt)_2$, $Pd(PPh_3)_4$, Et_3N, CH_3CN, 75 °C; (f) HC≡C−TMS, $PdCl_2(PPh_3)_2$ (or $Pd(OAc)_2$, dppp), Et_3N, DMF, 90 °C; (g) vinyl acetate, $Pd(OAc)_2$, dppp, Et_3N, DMF, 100 °C; (h) TBAF, THF; (i) aq HCl (THF); (j) $R_1R_2NH_2Cl$, $AlMe_3$, toluene, 50 °C; (k) aq NaOH or LiOH, THF, reflux.

cell proliferation activity. Comparison of the binding activities of **11a**, **5c**, and **4a** with that of raloxifene reveals 5-, 100-, and >100-fold decreases in relative binding affinity (RBA) when the 4′-, 6-, or both hydroxy groups, respectively, are replaced with a proton. Activity in the MCF-7 proliferation assay parallels binding activity in this series. A similar trend exists for the mono- and dimethoxy derivatives **5b**,**b′** and **4b**. It has previously been demonstrated that the 3-hydroxy of 17β-estradiol has a greater influence on receptor binding than does the 17-hydroxy.[28] Our results, therefore, imply that the 6-hydroxy group of raloxifene may be imitating the phenolic 3-hydroxy of 17β-estradiol. Similar observations have been made in a series of hydroxylated diarylindenes.[29] The increased importance of the 6-hydroxy moiety relative to the 4′-hydroxy is further evidenced by the relative activities of analogs bearing additional 5- or 7-substituents (i.e., **9e**,**h**−**j**) in comparison to those bearing analogous 3′-substituents (i.e., **11p**−**s**). Steric effects on binding have similarly been reported for 2-substituted estradiols.[30] Alternate placement of the hydroxy at the 5-position (**9c**) resulted in a 3-fold reduction in binding but a 500-fold reduction in MCF-7 growth inhibition. Placement at the 7-position (**5j**) or 4-position (**9b**) produced even more dramatic reductions. Notably, no 6-substituent included within this study functioned as an effective replacement for hydroxy with respect to ER binding or MCF-7 growth inhibition.

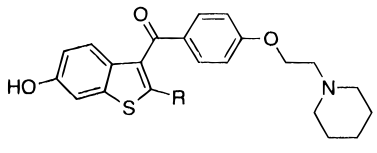
Conversely, a number of effective alternatives to the 4′-hydroxyl substituent in terms of receptor binding or inhibition of MCF-7 proliferation can be identified from Table 1. A 4′-fluoro substituent (**5i**) reduced ER binding affinity by 2-fold or less relative to raloxifene. Furthermore, the 4′-chloro analog **5e** inhibited MCF-7 proliferation with an IC_{50} of 1 nM, approximately 1000-fold greater potency than the corresponding 6-chloro analog **5f**. Movement of the 4′-hydroxyl to the 3′- and 2′-positions (**11b**,**c**) reduced binding affinity by 2- and 6-fold and MCF-7 growth inhibition by factors of 15 and 50, respectively. Surprisingly, significant binding activity was observed for a number of derivatives in which the entire 2-phenyl ring had been replaced. Naphthyl (**13a**,**c**), thienyl (**13d**,**e**), alkyl (**13f**−**h**), benzyl (**13l**), and, to a lesser extent, cycloalkyl (**13i**−**k**) all function as effective replacements for the 2-phenyl ring with respect to receptor binding. With the exception of 1-naphthyl, however, these substitutions all reduced MCF-7 growth inhibition by at least 10-fold. The only substitution which was found to enhance ER binding affinity relative to raloxifene was the incorporation of a 2′-alkyl substituent (**11d**,**n**). A similar, although more pronounced, effect has been observed in the 2,3-diarylindene series, and a torsional effect about the double bond between the pendant aryl rings has been implicated.[31] Presumably, the imposition of the carbonyl group reduces this effect in the raloxifene series.

In Vivo. The *in vivo* data from the 4-day OVX rat assay (Tables 2 and 3) provide a number of additional insights into the effects of subtle structural modifica-

Table 1. ER Binding and Inhibition of MCF-7 Cell Proliferation by Raloxifene Analogs



4,5,8-11,16a,22,23



13,16b,c

no.	R	R′	ER RBA[a,b]	MCF-7 inhibtn IC_{50} (nM)[c]	no.	R	R′	ER RBA[a,b]	MCF-7 inhibtn IC_{50} (nM)[c]
estradiol			1.00	NA[d]	**11m**	6-OH	4′-CF_3	0.008	1000
4-OH-tam[e]			0.36	0.5	**11n**	6-OH	2′-Me, 4′-OH	0.41	2
raloxifene			0.34	0.2	**11o**	6-OH	2′-OMe, 4′-OH	0.16	2
4a[f]	none	none	<0.002	300	**11p**	6-OH	3′-Me, 4′-OH	0.13	1
4b[f]	6-OMe	4′-OMe	<0.002	300	**11q**	6-OH	3′-Cl, 4′-OH	0.12	2.3
5b	6-OH	4′-OMe	0.073	1000	**11r**	6-OH	3′-F, 4′-OH	0.20	0.3
5b′	6-OMe	4′-OH	0.008	250	**11s**	6-OH	3′,5′-di(Me), 4′-OH	0.12	100
4c[g]	none	4′-OMe	0.006	100	**10t**	6-OMe	3′,4′-OCH_2O–	<0.01	500
5c[f]	none	4′-OH	0.003	35	**16a**	6-OH	4′-NO_2	0.05	500
4d[f]	none	4′-Cl	<0.002	NA[d]	**22a**[f]	6-CO_2Me	4′-OH	<0.01	30
5e[f]	6-OH	4′-Cl	0.046	1	**22c**	6-CO_2H	4′-OH	NA[d]	NA[d]
5f[f]	6-Cl	4′-OH	0.006	1000	**22d**	6-$CONH_2$	4′-OH	<0.01	1000
5g[f]	6-OH	4′-Me	0.07	50	**22g**	6-COMe	4′-OH	0.008	60
5h[f]	6-Me	4′-OH	NA[d]	300	**22h**	6-PO_3Et_2	4′-OH	<0.01	200
5i[f]	6-OH	4′-F	0.19	2.3	**22i**	6-C≡CH	4′-OH	0.029	20
5j	7-OH	4′-OH	0.02	300	**23a**	6-OH	4′-CO_2Me	0.07	50
9b	4-OH	4′-OH	<0.002	190	**23b**	6-OH	4′-CO_2Et	0.06	50
9c	5-OH	4′-OH	0.10	100	**23c**	6-OH	4′-CO_2H	0.012	325
9d	4,6-di(OH)	4′-OH	0.05	350	**23d**	6-OH	4′-$CONH_2$	0.039	200
9e	5,6-di(OH)	4′-OH	<0.01	400	**23e**[i]	6-OH	4′-CON(H)Me	0.016	40
8f[f]	5,6,7-tri(OMe)	4′-OMe	0.05	350	**23f**	6-OH	4′-$CONMe_2$	0.040	20
9g	6-NMe_2	4′-OH	0.004	ND[h]	**23g**	6-OH	4′-COMe	0.075	32
9h	5-F, 6-OH	4′-OH	0.098	3	**23h**	6-OH	4′-PO_3Et_2	0.010	210
9i	5-Me, 6-OH	4′-OH	0.07	ND[h]	**23i**	6-OH	4′-C≡CH	0.12	0.8
9j	5,7-di(Me), 6-OH	4′-OH	0.005	500	**23j**	6-OH	4′-CH=CH_2	0.10	7
9k	4,7-di(Me), 6-OH	4′-OH	0.002	100	**13a**	6-OH	1′-naphthyl	0.20	0.8
9l	4,5-benzo, 6-OH	4′-OH	0.009	500	**13b**	6-OH	2′-naphthyl	0.067	80
10a	6-OMe	none	<0.002	>1000	**13c**	6-OH	4′-OH-1′-naphthyl	0.16	2
11a[f]	6-OH	none	0.062	2.5	**13d**	6-OH	2′-thienyl	0.30	20
11b	6-OH	2′-OH	0.057	10	**13e**	6-OH	3′-thienyl	0.20	10
11c	6-OH	3′-OH	0.16	3.2	**13f**	6-OH	methyl	0.15	35
11d	6-OH	2′-Me	0.40	0.7	**13g**	6-OH	ethyl	0.13	20
11e	6-OH	3′-F	0.29	2.5	**13h**	6-OH	isopropyl	0.15	3
11f	6-OH	4′-Et	0.012	5	**13i**	6-OH	cyclopentyl	0.08	5
11g	6-OH	4′-*i*-Pr	0.03	30	**13j**	6-OH	cyclohexyl	0.09	2.5
11h	6-OH	4′-*n*-Bu	0.01	10	**13k**	6-OH	*trans*-4′-OH-cyclohexyl	0.09	2
11i	6-OH	4′-Ph	0.011	100	**13l**	6-OH	4′-hydroxybenzyl	0.19	5
11j	6-OH	4′-SMe	0.04	ND[h]	**16b**	6-OH	4′-pyridyl	0.056	100
10k	6-OMe	4′-CH_2OH	<0.01	600	**16c**	6-OH	4′-pyridyl *N*-oxide	0.005	100
11l	6-OH	4′-CH_2SEt	0.07	100					

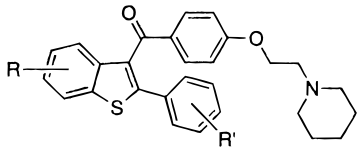
[a] RBA = relative binding affinity by competition with [^{3}H]-17β-estradiol. [b] Average of at least two determinations. Values are ±10%. [c] Dose required to give 50% inhibition of a maximally effective (10^{-11}) dose of 17β-estradiol. Average of at least three determinations. Values are ±10%. [d] NA = not active at the doses tested. [e] 4-Hydroxytamoxifen, the primary biologically active metabolite of tamoxifen. [f] Tested as the hydrochloride salt. [g] Tested as the citrate salt. [h] ND = not determined. [i] Tested as the trifluoroacetate salt.

tions on the complex biological activities of SERMs. The inconsistent correlation between elevation of uterine weight and stimulation of other uterine parameters in this series led to reliance on uterine EPO activity as the primary indicator of estrogenic effects on the uterus.[26,32,33] While both ethynylestradiol and tamoxifen potently reduce serum cholesterol, they also induce significant increases in uterine EPO while raloxifene does not. We have used this parameter, therefore, to discriminate compounds which demonstrate a tamoxifen-like profile from those whose activity parallels that of raloxifene.[32,34]

Compounds in which the 6- and/or 4′-hydroxyls are absent (**4a**, **5c**, **11a**) or are capped as methyl ethers (**4b**, **5b**,**b′**) exhibited potent effects on serum cholesterol reduction and mild to moderate increases in uterine weight without increases in EPO, similar to raloxifene itself. When considered with the receptor binding data for these compounds, these data imply potential metabolic activation either by hydroxylation (as is observed with tamoxifen) or by demethylation. The improved potency and relatively flat dose−response curves obtained for these analogs may be indicative of improved bioavailability. Presence of the hydroxyls at other positions about the 2-arylbenzothiophene (**9b**,**c**, **5j**, **11b**,**c**) impaired their ability to lower serum cholesterol. Only the 6,3′-dihydroxy analog **11c** maintained a significant level of activity, with potency decreased approximately 10-fold from that of raloxifene.

As was observed in the *in vitro* assays, the placement of an additional 4-, 5-, or 7-substituent on the benzothiophene (**9h**,**i**) resulted in reduced *in vivo* activity. Conversely, additional substituents on the pendant phenyl ring had a more modest effect on biological activity. The 2′-methyl (**11n**), 3′-fluoro (**11r**), and 2′-methoxy (**11o**) analogs were particularly potent with

Table 2. Serum Cholesterol-Lowering and Uterine Effects of 2-Aryl Raloxifene Analogs in the OVX Rat



no.	R	R′	uterine weight MED (% incr OVX)[a]	uterine EPO MED (V_{max})[b]	serum cholesterol (% decr OVX)[c] 0.001 mg/kg	0.01 mg/kg	0.1 mg/kg	ED_{50}[d] (mg/kg)
	17α-ethinyl estradiol		0.01 (41.5 ± 13.7)	0.1 (281.7 ± 6)	32.0* ± 10.4	57.1* ± 4.9	84.5* ± 1.7	0.005
					0.1 mg/kg	1.0 mg/kg	10.0 mg/kg	
	tamoxifen		0.1 (62.4 ± 3.0)	0.1 (57.1 ± 3.3)	39.2* ± 4.5	71.1* ± 4.3	67.0* ± 2.2	0.2
	raloxifene		0.1 (23.5 ± 10.0)	>10	44.9* ± 8.0	66.7* ± 4.1	74.0* ± 2.1	0.2
4a[e]	none	none	0.1 (59.2 ± 9.2)	>10	59.4* ± 2.0	72.6* ± 6.1	45.6* ± 5.8	<0.1
4b[e]	6-OMe	4′-OMe	0.1 (57.3 ± 9.5)	>10	62.2* ± 4.2	78.0* ± 3.4	68.5* ± 2.6	<0.1
5b	6-OH	4′-OMe	>10	>10	65.2* ± 7.2	75.6* ± 2.8	72.6* ± 4.0	<0.1
5b′	6-OMe	4′-OH	1.0 (33.5 ± 10.1)	>10	54.8* ± 3.5	64.5* ± 5.3	50.0* ± 9.9	<0.1
5c[e]	none	4′-OH	0.1 (39.2 ± 15.7)	>10	70.7* ± 5.6	69.9* ± 5.5	67.4* ± 4.2	<0.1
11a[e]	6-OH	none	0.1 (38.7 ± 3.9)	>10	55.6* ± 4.5	53.4* ± 12.5	66.0* ± 4.1	<0.1
9b	4-OH	4′-OH	>10	>10	29.6* ± 6.7	18.0* ± 5.2	31.8* ± 6.3	>10
9c[e]	5-OH	4′-OH	>10	>10	10.4 ± 7.7	3.7 ± 13.6	22.6 ± 3.9	
5j	7-OH	4′-OH	10 (43.5 ± 18.2)	>10	−6.1 ± 18.6	−11.7 ± 16.7	−3.4 ± 12.0	
11b	6-OH	2′-OH	>10	>10	7.8 ± 10.3	19.5 ± 5.7	33.2* ± 11.8	>10
11c	6-OH	3′-OH	>10	>10	24.3 ± 4.9	52.3* ± 5.5	49.1* ± 6.3	0.8
9h	5-F, 6-OH	4′-OH	>10	>10	4.6 ± 5.0	4.1 ± 5.6	31.6* ± 6.4	>10
9i	5-Me, 6-OH	4′-OH	10 (25.2 ± 10.8)	>10	−4.3	42.2*	43.7*	5.4
11d	6-OH	2′-Me	>10	>10	31.7 ± 8.5	38.6* ± 3.2	29.3 ± 14.5	>10
11e	6-OH	3′-F	0.1 (53.2 ± 3.2)	>10	18.6 ± 18.9	62.0* ± 9.3	67.3* ± 4.8	1.0
11n	6-OH	2′-Me, 4′-OH	0.1 (54.5 ± 8.2)	>10	39.2* ± 18.5	62.6* ± 2.6	68.5* ± 3.9	0.4
11o	6-OH	2′-OMe, 4′-OH	0.1 (64.1± 17.8)	1.0 (34.2 ± 1.0)	58.8* ± 12.6	79.0* ± 6.0	71.6* ± 9.6	<0.1
11p	6-OH	3′-Me, 4′-OH	>10	>10	28.4 ± 10.8	73.9* ± 3.9	49.7* ± 9.6	1.0
11q	6-OH	3′-Cl, 4′-OH	10 (30.3 ± 9.3)	>10	18.6 ± 12.5	52.7* ± 6.2	71.5* ± 2.8	1.2
11r	6-OH	3′-F, 4′-OH	0.1 (34.3 ± 7.5)	>10	45.9* ± 6.9	59.2* ± 5.3	55.3* ± 6.0	0.4
11s	6-OH	3′,5′-Me, 4′-OH	1.0 (33.8 ± 8.4)	1.0 (40.8 ± 20.7)	23.1 ± 11.2	40.2* ± 11.3	69.1* ± 3.6	1.8
5f[e]	6-Cl	4′-OH	10 (49.6 ± 11.1)	>10	−5.1 ± 18.7	−6.8 ± 13.8	37.6* ± 7.0	>10
5h[e]	6-Me	4′-OH	1.0 (23.9 ± 7.2)	>10	16.9 ± 11.6	33.9* ± 6.0	21.6 ± 10.8	>10
22a[e]	6-CO_2Me	4′-OH	0.1 (37.5 ± 3.2)	>10	13.8 ± 11.3	42.8* ± 7.5	61.0* ± 4.6	2.8
22c	6-CO_2H	4′-OH	1.0 (40.8 ± 8.8)	>10	−16.4 ± 12.5	12.5 ± 8.7	53.3* ± 3.2	9.0
22d	6-$CONH_2$	4′-OH	10 (30.7 ± 11.5)	>10	−33.9 ± 17.4	−14.9 ± 18.9	10.5 ± 6.3	
22i	6-C≡CH	4′-OH	1.0 (27.8 ± 7.7)	>10	39.4* ± 7.9	58.7* ± 3.3	65.8* ± 2.4	0.5
5e[e]	6-OH	4′-Cl	0.1 (56.5 ± 12.2)	>10	32.3* ± 9.5	69.9* ± 6.9	65.0* ± 7.7	0.3
5g[e]	6-OH	4′-Me	1.0 (34.6 ± 5.8)	>10	12.2 ± 5.5	26.5* ± 15.8	69.1* ± 6.0	2.9
5i[e]	6-OH	4′-F	1.0 (50.2 ± 5.2)	>10	20.6 ± 23.5	46.0* ± 3.2	71.9* ± 6.7	1.4
11f	6-OH	4′-Et	10 (29.7 ± 15.6)	1.0 (39.9 ± 15.3)	3.3 ± 18.8	37.2* ± 11.8	57.4* ± 8.3	4.3
11g	6-OH	4′-*i*-Pr	0.1 (24.9 ± 7.4)	1.0 (33.3 ± 0.9)	−24.1 ± 10.2	47.1* ± 10.9	48.5* ± 11.3	3.6
11h	6-OH	4′-*n*-Bu	>10	10 (20.8 ± 3.8)	21.3 ± 5.8	14.5 ± 12.3	72.0* ± 6.2	2.3
11i	6-OH	4′-Ph	0.1 (50.3 ± 10.1)	1.0 (25.4 ± 0.9)	12.9 ± 9.4	37.0* ± 9.1	68.5* ± 10.6	2.4
11j	6-OH	4′-SMe	1.0 (50.2 ± 7.2)	1.0 (37.5 ± 0.9)	27.7 ± 9.7	51.5* ± 10.1	75.3* ± 5.7	0.9
11l	6-OH	4′-CH_2SMe	1.0 (30.5 ± 6.5)	1.0 (36.9 ± 0.9)	21.7 ± 8.8	40.1* ± 8.4	63.0* ± 4.9	2.5
11m	6-OH	4′-CF_3	5.0 (37.4 ± 5.8)	5.0 (16.4 ± 2.1)	45.5* ± 7.8	47.9* ±10.4	71.5* ± 5.6[f]	0.4
23a	6-OH	4′-CO_2Me	1.0 (37.2 ± 6.4)	10 (13.2 ± 1.2)	23.8 ± 11.7	42.1* ± 5.1	56.1* ± 2.2	3.8
23c[g]	6-OH	4′-CO_2H	>10	>10	3.1 ± 7.1	−8.8 ± 9.5	24.6 ± 3.1	
23d	6-OH	4′-$CONH_2$	>10	>10	−3.2 ± 9.3	−21.3* ± 8.6	10.0 ± 3.5	
23i	6-OH	4′-C≡CH	>10	>10	9.1 ± 25.4	32.7* ± 12.4	35.8* ± 11.5	>10
23j	6-OH	4′-CH═CH_2	0.1 (26.9 ± 2.3)	1.0 (48.0 ± 0.0)	−7.0 ± 12.1	41.5* ± 7.5	49.7* ± 9.6	10

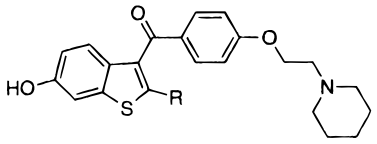
[a] MED = minimally effective dose (mg/kg of body weight) at which a statistically significant ($p \leq 0.05$) increase in uterine weight/body weight was observed. Activity at the MED is expressed as percent increase relative to OVX controls ± standard error. [b] MED at which a significant (>5-fold increase relative to OVX control and value of $V_{max} \geq 10$) increase in EPO activity was observed. Activity at the MED is expressed as V_{max} ± standard error. [c] Percent decrease in serum cholesterol relative to OVX controls ± standard error. Statistically significant ($p \leq 0.05$) differences are denoted with an asterisk. [d] Dose required to reduce serum cholesterol by 50% relative to OVX controls. [e] Tested as the hydrochloride salt. [f] Maximum dose tested = 5.0 mg/kg. [g] Tested as the trifluoroacetate salt.

respect to cholesterol reduction, although the latter compound showed some evidence of uterine stimulation.

In general, replacement of the 6-hydroxy substituent with various functional groups (**5f**,**h**, **22a**−**i**) led to a dramatic reduction in *in vivo* activity. Notable exceptions include the 6-carbomethoxy and 6-alkynyl analogs **22a**,**i** which effectively lowered serum cholesterol without stimulation of uterine EPO. In **22i**, the acetylenic hydrogen may serve to mimic the hydrogen bond-donating capability of the phenolic hydroxy. The *in vivo* activity of **22a** is surprising, in light of its low binding affinity. Metabolic conversion to the corresponding acid **22c** may occur; however, **22c** is less potent *in vivo* and also shows very low receptor affinity. Furthermore, **22c** is inactive in the MCF-7 proliferation assay, while **22a** has an IC_{50} of approximately 30 nM. The corresponding amide **22d** is also essentially inactive.

In contrast, replacement of the 4′-hydroxy moiety with small electronegative groups (**5e**,**i**) led to analogs which demonstrate an *in vivo* profile similar to that of raloxifene, albeit with slightly lower potency. Larger substituents at this position (**11f**−**m**, **23a**,**j**) tended to provoke increased uterine stimulation. Of particular interest is the trifluoromethyl analog **11m** which had

Table 3. Serum Cholesterol-Lowering and Uterine Effects of 2-Alkyl, 2-Naphthyl, and 2-Heteroaryl Raloxifene Analogs in the OVX Rat



no.	R	uterine weight MED (% incr OVX)[a]	uterine EPO MED (V_{max})[b]	serum cholesterol (% decr OVX)[c] 0.001 mg/kg	0.01 mg/kg	0.1 mg/kg	ED_{50}[d] (mg/kg)
	17α-ethynylestradiol	0.01 (41.5 ± 13.7)	0.1 (281.7 ± 6)	32.0* ± 10.4	57.1* ± 4.9	84.5* ± 1.7	0.005
				0.1 mg/kg	1.0 mg/kg	10.0 mg/kg	
	tamoxifen	0.1 (62.4 ± 3.0)	0.1 (57.1 ± 3.3)	39.2* ± 4.5	71.1* ± 4.3	67.0* ± 2.2	0.2
	raloxifene	0.1 (23.5 ± 10.0)	>10	44.9* ± 8.0	66.7* ± 4.1	74.0* ± 2.1	0.2
13a	1-naphthyl	>10	>10	40.1* ± 14.9	53.9* ± 5.1	67.8* ± 4.1	0.5
13b	2-naphthyl	0.1 (72.7 ± 5.3)	0.1 (12.3 ± 0.3)	48.1* ± 6.8	54.5* ± 6.9	63.6* ± 3.6	0.2
13c	4-hydroxy-1-naphthyl	0.1 (59.6 ± 19.7)	0.1 (29.4 ± 0.6)	31.6* ± 15.2	54.7* ± 7.4	59.9* ± 4.8	1.2
13d	2-thienyl	1.0 (32.4 ± 18.3)	>10	−18.6 ± 12.4	−0.9 ± 8.0	51.4* ± 10.8	11
13e	3-thienyl	10 (54.3 ± 10.8)	>10	0.6 ± 18.9	29.8* ± 6.0	31.8* ± 5.9	>10
16b	4-pyridyl	1.0 (33.3 ± 10.2)	>10	7.2 ± 6.6	24.0 ± 4.4	47.6* ± 9.9	14.6
16c	4-pyridyl *N*-oxide	>10	>10	−16.6 ± 11.8	1.8 ± 10.1	42.6* ± 6.2	>10
13f	Me	>10	>10	8.3 ± 13.3	53.8* ± 9.5	62.9* ± 7.3	1.8
13g	Et	10 (55.03 ± 12.2)	>10	4.4 ± 17.3	26.5 ± 26.4	31.1 ± 6.9	
13h	*i*-Pr	>10	>10	12.4 ± 9.9	30.5* ± 6.5	35.0* ± 16.1	>10
13i	cyclopentyl	>10	>10	18.4 ± 16.0	55.6* ± 5.0	69.6* ± 7.1	1.2
13j	cyclohexyl	1.0 (30.2 ± 5.9)	>10	−0.1 ± 9.2	52.9* ± 9.9	61.7* ± 2.3	2.1
13k	*trans*-4-hydroxycyclohexyl	0.1 (46.7 ± 4.9)	>10	48.7* ± 4.0	41.1* ± 4.6	60.4* ± 3.1	1.0
13l	4-hydroxybenzyl	5.0 (36.9 ± 5.6)	>10	−17.6 ± 12.8	41.7* ± 8.8	54.0* ± 5.5[e]	4.0

[a] MED = minimally effective dose (mg/kg of body weight) at which a statistically significant ($p \leq 0.05$) increase in uterine weight/body weight was observed. Activity at the MED is expressed as percent increase relative to OVX controls ± standard error. [b] MED at which a significant (>5-fold increase relative to OVX control and value of $V_{max} \geq 10$) increase in EPO activity was observed. Activity at the MED is expressed as V_{max} ± standard error. [c] Percent decrease in serum cholesterol relative to OVX controls ± standard error. Statistically significant ($p \leq 0.05$) differences are denoted with an asterisk. [d] Dose required to reduce serum cholesterol by 50% relative to OVX controls. [e] Maximum dose tested = 5.0 mg/kg.

potent *in vivo* activity but was nearly inactive in the *in vitro* assays. Although the carbomethoxy replacement (**23a**) is similar in activity to the 6-carbomethoxy analog **22a**, the corresponding acetylenic compound **23i** is substantially less potent than its 6-substituted counterpart **22i**. Conversely, replacement of the 6-hydroxy with chloro (**5f**) resulted in a substantial reduction of *in vivo* activity, while the 4′-substituted analog **5e** maintained activity similar to that of raloxifene. Clearly the structural requirements associated with the two phenol moieties differ, and changes at these positions affect *in vivo* biological activity in different ways. These differences are not surprising since the natures of the hydroxy substituents in the natural ligand are dissimilar, one being phenolic and the other an alkyl hydroxy. Indeed, a similar divergence of biological activity for 3- and 17-modified estradiol analogs has been observed.[35]

A number of the analogs in which the 2-phenyl ring was replaced by alkyl, cycloalkyl, naphthyl, heteroaryl, or benzyl substituents also demonstrated potent *in vivo* biological activity (Table 3). In particular, naphthyl (**13a**−**c**), methyl (**13f**), and cycloalkyl (**13i**−**k**) analogs potently reduced serum cholesterol with minimal uterine stimulation. The surprising finding that substituents as small as methyl and as large as naphthyl give relatively similar biological profiles is intriguing. It may indicate that the positive interactions afforded by the 2-phenyl substituent are of relatively minor importance with respect to their influence on biological activity. The undesirable interactions introduced by larger substituents, particularly at the 4′-position, appear to play a greater role in determining the biological profile of these compounds.

Table 4. Bone Protective Effects of Raloxifene Analogs in the OVX Rat

no.	bone mineral density, distal femur (% protection vs OVX)[a] 0.01 mg/kg/day	0.1 mg/kg/day	1.0 mg/kg/day	10.0 mg/kg/day
17α-ethynyl-estradiol[b]		69.2* ± 7.7		
raloxifene[b]	9.6 ± 5.8	50.0* ± 5.8	57.7* ± 5.8	53.8* ± 5.8
5c[c,d]	−1.3 ± 12.7	−4.0 ± 9.6	41.8* ± 19.0	26.7* ± 14.7
11c		−30.9 ± 20.7[e]	79.7* ± 17.1[e]	44.2* ± 22.9[e]
11r	34.5 ± 36.5	34.1 ± 17.2	68.0* ± 15.1	69.8* ± 20.5
13c	35.9* ± 14.0	42.3* ± 13.7	82.5* ± 14.0	
13k		17.0 ± 8.4	61.3* ± 30.0	67.4* ± 15.0
22a		−10.0 ± 8.4	17.0 ± 8.3	43.9* ± 23.1

[a] Measured by X-ray image analysis. Values are given as percent protection relative to OVX controls ± standard error, with sham control values defined as 100% and OVX controls defined as 0. [b] Values taken from ref 25. [c] Tested as the hydrochloride salt. [d] Tested in 75-day old rats. [e] BMD determined by quantitative computed tomography at the proximal tibia.

Some of the analogs in this study were further evaluated in an OVX rat model of estrogen deficiency-induced osteopenia, and Table 4 contains a representative sampling of these results. All of the analogs tested prevented bone loss to some degree; however, due to the nature and variability of the assay, quantitative comparisons are somewhat speculative. Nevertheless, a number of the compounds showed efficacy similar to that observed for raloxifene and estrogen.

Discussion

In this study, we have employed a battery of assays which reflects by design the unique pattern of tissue-selective estrogen agonist/antagonist activities that have been previously described for the SERM raloxifene.[23−25]

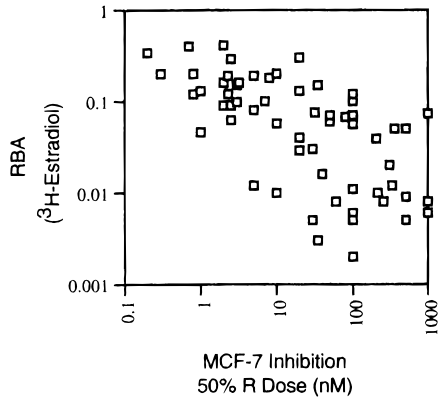


Figure 1. Correlation of ER binding with inhibition of MCF-7 proliferation ($r = -0.586$).

Thus, ER binding activity is requisite for SERM activity.[36] Inhibition of MCF-7 cell proliferation and the lack of *in vivo* increases in uterine weight and uterine EPO are predictive of estrogen antagonist or neutral activities in sexually dimorphic tissues. Finally, reduction in serum cholesterol and preservation of bone mineral density in the OVX rat are indicative of the desirable estrogen agonist effects demonstrated by SERMs.

The overall correlation of inhibition of MCF-7 proliferation with receptor binding for this series was relatively poor (Figure 1, $r = -0.586$). In several cases, compounds with similar RBA's exhibited up to 100-fold differences in MCF-7 activity (i.e., **13d** vs raloxifene). For some analogs, this discrepancy may arise from partial agonist activity, or it may reflect the complex nature of the interactions which determine biological activity. Clearly, receptor binding is only the first step in the pathway which leads to inhibition of tumor cell proliferation.

The correlation of *in vivo* biological activity (as measured by ED_{50} for cholesterol lowering) with binding (RBA) or inhibition of MCF-7 proliferation (IC_{50}) is disappointing ($r = 0.057$ and 0.096, respectively), even when the importance of hydroxy substituents for *in vitro* activity (*vide supra*) is accounted for by limiting the set to those compounds which contain at least one hydroxy moiety. Reasons for this anomoly presumably include differences in absorption, metabolism, and distribution. Indeed, a strong correlation ($r = 0.93$) between cholesterol lowering and ER binding has recently been demonstrated for a smaller set of analogs, in which the position of hydroxylation and substitution pattern of the 2-arylbenzothiophene was less variable.[37] The flat dose−reponse and substantial reduction in maximum efficacy observed with some analogs (e.g., **9b**, **11d**, **5h**) may imply that alternative mechanisms of action which do not involve the ER, such as those recently proposed to explain some of the biological activities of tamoxifen, are operable in these cases.[38] Nevertheless, additional factors associated with the mechanisms by which the ER controls gene transcription may also be involved. It has recently been proposed that the conformation of the ER−ligand complex is dependent upon the nature of the interacting ligand and that the distinct conformation induced by a particular ligand differentially affects which genes are transcriptionally activated.[39,40] Furthermore, it has been demonstrated that the conformation of the ER−raloxifene complex is distinct from those of the ER complexed with 17β-estradiol, tamoxifen, or the pure anti-estrogen ICI-164384, a feature which may be reflected by raloxifene's unique profile of estrogen agonist/antagonist effects.[39a,41] To the extent that structural modification of the raloxifene core disrupts or alters this receptor−ligand conformation, different sets of estrogen responsive genes may be influenced positively or negatively, resulting in an altered biological profile. For that reason, a compound which potently inhibits MCF-7 proliferation may not effectively induce the genes responsible for the reduction of serum cholesterol or for the maintenance of bone density.[42] The recent identification of a novel ER expressed in prostate and ovary adds a further layer of complexity.[43] Clearly, the agonist/antagonist profile for any ER modulator must be determined for each target tissue in question. As additional target tissues are explored and new estrogen-regulated genes are discovered, we anticipate the further development of SERMs with unique selectivity profiles.

In conclusion, we have explored a number of the structural features associated with the 2-arylbenzothiophene core of raloxifene and have demonstrated that some of those features are critical for maintenance of the raloxifene profile while others are more flexible. In particular, the 6-hydroxy and, to a lesser extent, the 4′-hydroxy substituents are important for receptor binding and *in vitro* activity and appear to mimic the corresponding 3- and 17β-hydroxy substituents of estradiol. Modified or additional substitution of the benzothiophene generally results in reduced biological activity; however, some variance in the substitution pattern of the 2-aryl ring is tolerated. Indeed, the entire 2-aryl ring can be replaced by alkyl, cycloalkyl, or naphthyl substituents without disrupting the SERM profile of *in vitro* and *in vivo* biological activity, although increased steric bulk at the 4′-position leads to increased uterine stimulation. Several novel structural variants including 2-cyclohexyl, 2-naphthyl, and 6-carbomethoxy analogs maintain activity similar to that of raloxifene. Nevertheless, the 6-hydroxy-2-(4′-hydroxyphenyl) substitution pattern of raloxifene appears to be nearly optimal for both *in vitro* and *in vivo* activity, especially with respect to serum cholesterol reduction and protection against ovariectomy-induced bone loss without significant stimulation of the uterus.[33] Studies associated with modification of other portions of the raloxifene structure will be reported in due course.

Experimental Section

Chemistry. All reactions were carried out under a nitrogen atmosphere. All solvents and reagents were used as obtained from commercial sources unless otherwise indicated. Flash chromatography was carried out on E. Merck Kieselgel 60 (230−400 mesh). Radial chromatography was carried out on a Harrison Research Chromatotron, using Analtech precoated rotors (1−6 mm) under an atmosphere of nitrogen or ammonia. Preparative HPLC was carried out on Waters PrepPak silica gel cartridges using a Waters Prep LC 2000 or Prep 500 system. Benzothiophenes **2a**−**h** were prepared by literature methods.[11,14] Preparations of benzothiophenes **2i**,**j** are included in the Supporting Information. Aminobenzothiophenes **6a**−**l** were prepared in two steps from the corresponding benzaldehydes and the lithium anion of dimethylthioformamide by the method of Hopkinson and Lee-Ruff.[16] The preparation of compounds **3** and **4b** has been previously described.[11] Grignard reagents were obtained from commercial sources or were prepared from the alkyl or aryl halides by literature methods.[44] Silylated bromo alcohols and bro-

mophenols, utilized for the synthesis of Grignard reagents, were prepared by the method of Corey.[45] The abbreviations THF, DMF, DCE, DMSO, TBS, TBAF, and DMAP refer to tetrahydrofuran, dimethylformamide, 1,2-dichloroethane, dimethyl sulfoxide, *tert*-butyldimethylsilyl, tetra-*N*-butylammonium fluoride, and (*N*,*N*-dimethylamino)pyridine, respectively. Fast atom bombardment mass spectra (FAB) were obtained on a VG ZAB-3 instrument; field desorption mass specta (FD) were obtained on a VG 70SE instrument; high-resolution mass specta (HRMS) were obtained on a VG Analytical ZAB2-SE instrument. NMR spectra were recorded on a GE QE300 specrometer at 300 MHz for proton and 75 MHz for carbon-13. All spectra were recorded in deuteriochloroform unless otherwise indicated. Elemental analyses were carried out by the Physical Chemistry Department of Lilly Research Laboratories and are within ±0.4% of theory unless otherwise noted.

[2-(4-Chlorophenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (4d). A solution of **2d** (1.0 g, 4.1 mmol) and **3** (3.0 g, 9.8 mmol) in DCE was treated with $AlCl_3$ (1.5 g, 11.2 mmol) and heated at reflux for 2 days. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was suspended in 1:1 ethanol:1 M NaOH and heated for 1 h to hydrolyze residual acid chloride. The resulting mixture was filtered hot and concentrated *in vacuo* to a dark, aqueous solution. This mixture was extracted with $CHCl_3$ (3 × 300 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated to provide, after flash chromatography (acetone), the title compound as a yellow oil. This material was treated with concentrated HCl (1 mL) in acetone (25 mL) to give 1.1 g (52%) of the corresponding HCl salt as a yellow solid, mp 95−98 °C: ^{1}H NMR δ 1.3−1.6 (m, 1H), 1.8−2.1 (m, 5H), 2.79 (dd, J = 9.0, 7.0 Hz, 2H), 3.40 (m, 2H), 3.53 (d, J = 12 Hz, 2H), 4.81 (m, 2H), 6.80 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 7.3−7.5 (m, 4H), 7.66 (d, J = 6.0 Hz, 1H), 7.77 (d, J = 9.0 Hz, 2H), 7.90 (d, J = 6 Hz, 1H); MS (FD) *m/e* 475 (M^+). Anal. ($C_{28}H_{26}ClNO_2S\cdot HCl\cdot H_2O$) C,H,N.

(2-Phenylbenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (4a). The title compound was prepared in 36% yield from **2a** and **3** by a method similar to that described for **4d**; analyzed as the corresponding HCl salt: ^{1}H NMR (DMSO-d_6) δ 1.34 (m, 1H), 1.63 (m, 1H), 1.74 (m, 4H), 2.91 (m, 2H), 3.41 (m, 4H), 4.42 (m, 2H), 6.96 (d, J = 8.5 Hz, 2H), 7.38 (m, 8H), 7.70 (d, J = 8.5 Hz, 2H), 8.06 (m, 1H); MS (EI) *m/e* 440 $(M - H)^+$. Anal. ($C_{28}H_{27}NO_2S\cdot HCl$) C,H,N.

[2-(4-Methylphenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (4g). The title compound was prepared from **2g** and **3** by a method similar to that described for **4d**. The free base was converted to the HCl salt using acetone/concentrated HCl to afford 62% of a beige solid, mp 185 °C: ^{1}H NMR (free base) δ 1.4−1.6 (m, 2H), 1.6−1.8 (m, 4H), 2.35 (s, 3H), 2.5−2.8 (m, 4H), 3.90 (m, 2H), 3.95 (s, 3H), 4.1−4.3 (m, 2H), 6.80 (d, J = 8 Hz, 2H), 7.00 (d, J = 10 Hz, 1H), 7.10 (d, J = 8 Hz, 2H), 7.3−7.4 (m, 3H), 7.55 (d, J = 10 Hz, 1H), 7.80 (d, J = 8 Hz, 2H); MS (FD) *m/e* 485 (M^+). Anal. ($C_{30}H_{31}NO_3S\cdot HCl\cdot H_2O$) C,H,N.

[2-(4-Methoxyphenyl)-6-methylbenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (4h). The title compound was prepared from **2h** and **3** by a method similar to that described for **4d**. The free base was converted to the HCl salt using acetone/concentrated HCl to afford 89% of a beige solid, mp 225−228 °C: ^{1}H NMR (DMSO-d_6) δ 1.3−1.5 (m, 1H), 1.7−2.0 (m, 5H), 2.55 (s, 3H), 2.9−3.2 (m, 2H), 3.4−3.6 (m, 4H), 3.80 (s, 3H), 4.5−4.6 (m, 2H), 7.00 (d, J = 10 Hz, 2H), 7.10 (d, J = 10 Hz, 2H), 7.30 (d, J = 8 Hz, 1H), 7.3−7.5 (m, 3H), 7.80 (d, J = 10 Hz, 2H), 7.95 (s, 1H); MS (FD) *m/e* 485 (M^+). Anal. ($C_{30}H_{31}NO_3S\cdot HCl$) C,H,N.

[2-(4-Fluorophenyl)-6-[(methylsulfonyl)oxy]benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (4i). The title compound was prepared in 64% yield from **2i** and **3** by a method similar to that described for **4d**: ^{1}H NMR (270 MHz) δ 1.44 (m, 2H), 1.59 (m, 4H), 2.48 (m, 4H), 2.73 (t, J = 6 Hz, 2H), 3.21 (s, 3H), 4.19 (t, J = 6 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 6.99 (t, J = 9 Hz, 2H), 7.37 (m, 1H), 7.46 (m, 2H), 7.71 (m, 3H), 7.86 (d, J = 2 Hz, 1H); MS (EI) *m/e* 553 (M^+).

[2-[4-[(4-Fluorobenzoyl)oxy]phenyl]-7-[(4-fluorobenzoyl)oxy]benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone (4j). The title compound was prepared in 84% yield from **2j** and **3** by a method similar to that described for **4d**: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.50 (br s, 4H), 2.73 (m, 2H), 4.13 (m, 2H), 6.83 (m, 2H), 7.1−7.6 (m, 11H), 7.78 (m, 2H), 8.18 (m, 2H), 8.33 (m, 2H); MS (FD) *m/e* 717 (M^+). Anal. ($C_{42}H_{33}F_2NO_6S$) C,H,N.

[2-(4-Methoxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5b) and [2-(4-Hydroxyphenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5b′). A solution of **4b** (32.3 g, 60 mmol) in CH_2Cl_2 (360 mL) was treated with $AlCl_3$ (48.0 g, 360 mmol), stirred until dissolution was complete, and treated with *n*-propanethiol (4.57 g, 5.43 mL, 60 mmol). The mixture was heated at 33−35 °C for 1.5 h, cooled to 0 °C, and treated with THF (180 mL), 2.5 M HCl (60 mL), and water (180 mL). The mixture was diluted with CH_2Cl_2 (200 mL) and water (200 mL), the layers were separated, and the aqueous layer was brought to pH 10 with aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2 (200 mL), and the organic layer was concentrated to give 28.7 g of a yellow solid. The residue was partitioned between ether (200 mL) and water (200 mL) at reflux (3×), and the aqueous layer was acidified with 2.5 M HCl and washed with CH_2Cl_2 (200 mL). The organic layer was neutralized with saturated $NaHCO_3$ and concentrated to provide 7.7 g (26%) of a mixture of monomethyl ethers **5b**,**b′**. The mixture was combined with samples from other runs and purified via gravity chromatography (silica gel, 10:1 $CHCl_3$:MeOH). **5b** was obtained as a yellow foam:[46,47] ^{1}H NMR (DMSO-d_6) δ 1.3−1.4 (m, 2H), 1.4−1.6 (m, 4H), 2.38 (m, 4H), 2.61 (t, J = 5.8 Hz, 2H), 3.71 (s, 3H), 4.08 (t, J = 5.8 Hz, 2H), 6.8−7.0 (m, 5H), 7.2−7.4 (m, 4H), 7.67 (d, J = 8.8 Hz, 2H) 9.83 (s, 1H). Anal. ($C_{29}H_{29}NO_4S$) C,H,N.

5b′ was further purified by recrystallization from Et_2O:MeOH, to give a yellow powder: ^{1}H NMR (DMSO-d_6) δ 1.3−1.4 (m, 2H), 1.4−1.6 (m, 4H), 2.39 (m, 4H), 2.62 (t, J = 5.8 Hz, 2H), 3.84 (s, 3H), 4.08 (t, J = 5.8 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.99 (dd, J = 8.8, 2.3 Hz, 1H), 7.22 (m, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.65 (m, 4H), 9.76 (s, 1H). Anal. ($C_{29}H_{29}NO_4S$) C,H,N.

[2-(4-Hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5c). A slurry of **2c** (3.8 g, 16 mmol) and **3** (5.5 g, 18 mmol) in DCE (250 mL) was cooled to 0 °C and treated with $AlCl_3$ (6.4 g, 48 mmol). After 1.5 h, ethanethiol (5.0 g, 6.0 mL, 80 mmol) was added followed by additional $AlCl_3$ (4.0 g, 30 mmol) and the mixture stirred at 0 °C for 1 h. The reaction was quenched with THF (50 mL) followed by concentrated HCl (100 mL), and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified via flash chromatography (CH_2Cl_2, 0−10% MeOH) to provide 2.45 g (29%) of a yellow foam which crystallized upon trituration with MeOH: ^{1}H NMR (270 MHz, DMF-d_7) δ 1.4−1.6 (m, 1H), 1.7−1.9 (m, 3H), 1.9−2.2 (m, 2H), 3.0−3.2 (m, 2H), 3.5−3.7 (m, 4H), 4.65 (t, J = 4.3 Hz, 2H), 6.86 (d, J = 7.9 Hz, 2H), 7.03 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 7.45 (m, 2H), 7.59 (m, 1H), 7.79 (d, J = 7.9 Hz, 2H), 8.13 (m, 1H), 10.22 (s, 1H), 11.98 (br s, 1H). Anal. ($C_{28}H_{27}NO_3S\cdot HCl$) C,H,N.

[2-(4-Chlorophenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5e). The title compound was prepared in 12% yield from **2e** and **3** by a method similar to that described for **5c**; analyzed as the corresponding HCl salt: ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.38 (m, 1H), 1.75 (m, 5H), 2.97 (m, 2H), 3.45 (m, 4H), 4.46 (m, 2H), 6.92 (dd, J = 9, 2.5 Hz, 1H), 7.02 (d, J = 9 Hz, 2H), 7.29 (d, J = 9 Hz, 1H), 7.41 (m, 5H), 7.73 (d, J = 9 Hz, 2H), 10.02 (s, 1H), 10.58 (br s, 1H); MS (FD) *m/e* 492 (M^+). Anal. ($C_{28}H_{26}ClNO_3S\cdot HCl$) C,H,N.

[2-(4-Hydroxyphenyl)-6-chlorobenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5f). The title compound was prepared in 15% yield from **2f** and **3** by a method similar to that described for **5c**; analyzed as the corresponding HCl salt: ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.38 (m, 1H), 1.75 (m, 5H), 2.95 (m, 2H), 3.44 (m, 4H), 4.45 (m, 2H), 6.75 (d, J = 9 Hz, 2H), 6.99 (d, J = 9 Hz, 2H), 7.25 (d, J

= 9 Hz, 2H), 7.46 (m, 2H), 7.72 (d, J = 9 Hz, 2H), 8.26 (d, J = 2.5 Hz, 1H), 10.02 (s, 1H), 10.52 (br s, 1H); MS (EI) *m/e* 491 (M^+). Anal. ($C_{28}H_{26}ClNO_3S$·HCl) C,H,N.

[2-(4-Methylphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5g). A suspension of **4g** (6.0 g, 11.4 mmol, ca. 50% purity) and ethanethiol (9.45 g, 7.0 mL, 153 mmol) in DCE (300 mL) was cooled to 5 °C and treated with $AlCl_3$ (10.0 g, 11.3 mmol). The resultant mixture was allowed to stir at 5 °C for 3 h and warmed to room temperature for an additional 2 h, and the reaction was quenched by the addition of THF (100 mL). The solvents were removed *in vacuo*, and the residue was partitioned between EtOAc (300 mL) and 10% aqueous $NaHCO_3$ (300 mL). The aqueous layer was extracted with EtOAc (2 × 300 mL) and CH_2Cl_2 (2 × 300 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford a dark oil. Purification via flash chromatography (acetone) and conversion to the HCl salt using acetone/concentrated HCl afforded 1.6 g (54%) of the title compound as a tan solid, mp 100−105 °C: ^{1}H NMR (free base) δ 1.4−1.6 (m, 2H), 1.6−1.8 (m, 4H), 2.30 (s, 3H), 2.5−2.8 (m, 4H), 2.8−3.0 (m, 2H), 4.1−4.3 (m, 2H), 6.75 (d, J = 10 Hz, 2H), 6.95 (d, J = 10 Hz, 2H), 7.05 (d, J = 8 Hz, 1H), 7.30 (s, 1H), 7.45 (d, J = 10 Hz, 1H), 7.85 (d, J = 10 Hz, 2H), 8.00 (d, J = 10 Hz, 2H); MS (FD) *m/e* 471 (M^+). Anal. ($C_{29}H_{29}NO_3S$·HCl·2H_2O) C,H,N.

[2-(4-Hydroxyphenyl)-6-methylbenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5h). The title compound was prepared in 62% yield from **4h** by a method similar to that described for **5g**; analyzed as the corresponding HCl salt, a tan solid, mp 220−223 °C: ^{1}H NMR (DMSO-d_6) δ 1.3−1.5 (m, 1H), 1.7−2.0 (m, 5H), 2.55 (s, 3H), 3.0 (m, 2H), 3.4−3.6 (m, 4H), 4.4−4.6 (m, 2H), 6.80 (d, J = 10 Hz, 2H), 7.05 (d, J = 10 Hz, 2H), 7.2−7.4 (m, 3H), 7.40 (d, J = 8 Hz, 1H), 7.75 (d, J = 10 Hz, 2H), 7.90 (s, 1H), 10.00 (s, 1H); MS (FD) *m/e* 471 (M^+). Anal. ($C_{29}H_{29}NO_3S$·HCl·H_2O) C,H,N.

[2-(4-Fluorophenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5i). A solution of **4i** (2.5 g, 4.5 mmol) in THF:MeOH (2:1, 120 mL) at room temperature was treated with 5 N NaOH (10.0 mL, 50 mmol) for 18 h. After acidification to pH 8 with 1 N HCl, the mixture was extracted with EtOAc (3 × 200 mL) and the combined organic extracts were washed sequentially with water (200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated. The residue was purified via chromatography ($CHCl_3$, 3% MeOH), and the resulting solid was dissolved in ether, treated with excess HCl gas, and concentrated. The crude residue was recrystallized from ethanol to give 0.73 g (35%) of the title compound as the corresponding HCl salt: ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.38 (m, 2H), 1.78 (m, 4H), 2.98 (m, 2H), 3.45 (m, 4H), 4.45 (m, 2H), 6.93 (dd, J = 9, 3 Hz, 1H), 7.01 (d, J = 7.5 Hz, 2H), 7.19 (m, 2H), 7.31 (d, J = 9 Hz, 1H), 7.42 (m, 3H), 7.74 (d, J = 7.5 Hz, 2H). Anal. ($C_{28}H_{26}FNO_3S$·HCl) C,H,N.

[2-(4-Hydroxyphenyl)-7-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (5j). Aqueous 5 N NaOH (0.6 mL, 3 mmol) was added to **4j** (0.42 g, 0.6 mmol) in EtOH:THF (5:1, 30 mL) and the mixture stirred for 30 min at room temeperature. The reaction mixture was poured into saturated $NaHCO_3$/ice (200 mL), stirred 15 min, and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4), concentrated, and triturated with petroleum ether to give 0.23 g (84%) of the title product as a yellow solid, mp 135−145 °C: ^{1}H NMR (DMSO-d_6) δ 1.3−1.5 (m, 6H), 2.48 (m, 4H), 2.6−2.7 (m, 2H), 4.10 (m, 2H), 6.7−6.8 (m, 4H), 6.91 (m, 4H), 7.18 (m, 1H), 7.28 (m, 1H), 7.67 (m, 1H), 9.81 (br s, 1H), 10.55 (br s, 1H); MS (FD) *m/e* 474 (M^+) Anal. ($C_{28}H_{27}NO_4S$) C,H,N.

[2-(Dimethylamino)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7a). A solution of **6a** (10.3 g, 49.8 mmol) in chlorobenzene (100 mL) was treated with **3** (15.9 g, 52.3 mmol) and warmed to 100−105 °C for 9 h. The mixture was then allowed to cool to room temperature resulting in complete solidification. The solid was broken up and treated with saturated Na_2CO_3 (60 mL), water (30 mL), CH_2Cl_2 (200 mL), and 50% aqueous NaOH (10 mL). After stirring for a short period, the mixture was diluted with CH_2Cl_2 (300 mL) and water (100 mL), the layers were separated, and the organic layer was washed with 50% saturated Na_2CO_3 (40 mL). The organic layer was dried over solid sodium chloride, decanted, and concentrated under reduced pressure to yield a thick dark oil. Purification via chromatography (CH_2Cl_2, 0−5% MeOH) provided 19.8 g (64%, corrected for trapped CH_2Cl_2) of the title compound as a thick dark oil: ^{1}H NMR δ 1.3−1.4 (m, 2H), 1.5−1.6 (m, 4H), 3.43 (m, 4H), 2.70 (t, J = 5.9 Hz, 2H), 2.76 (s, 6H), 3.70 (s, 3H), 4.07 (t, J = 5.9 Hz, 2H), 6.73 (dd, J = 8.9, 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 190.8, 162.1, 160.8, 155.3, 133.2, 132.0, 131.5, 131.4, 121.8, 113.9, 113.1, 111.2, 104.9, 65.8, 57.4, 55.2, 54.7, 44.6, 25.5, 23.8. Anal. ($C_{25}H_{30}N_2O_3S$) C,H,N.

[2-(Dimethylamino)-4-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7b). The title compound was prepared in 44% yield from **6b** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.51 (m, 4H), 2.79 (m, 2H), 2.88 (s, 6H), 3.41 (s, 3H), 4.14 (m, 2H), 6.62 (d, J = 8 Hz, 1H), 6.89 (m, 2H), 7.09 (m, 1H), 7.26 (d, J = 8 Hz, 1H), 7.84 (m, 2H).

[2-(Dimethylamino)-5-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7c). The title compound was prepared in 44% yield from **6c** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.51 (m, 4H), 2.83 (m, 2H), 2.88 (s, 6H), 3.71 (s, 3H), 4.14 (m, 2H), 6.62 (d, J = 8 Hz, 1H), 6.88 (m, 2H), 7.09 (m, 1H), 7.26 (d, J = 8 Hz, 1H), 7.84 (m, 2H).

[2-(Dimethylamino)-4,6-dimethoxybenzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7d). The title compound was prepared in 47% yield from **6d** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.50 (m, 4H), 2.77 (m, 2H), 2.81 (s, 6H), 3.41 (s, 3H), 3.82 (s, 3H), 4.14 (m, 2H), 6.27 (m, 1H), 6.78 (s, 1H), 6.88 (m, 2H), 7.81 (m, 2H); MS (FD) *m/e* 468 (M^+).

[2-(Dimethylamino)-5-methoxy-6-(benzyloxy)benzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7e). The title compound was prepared in 38% yield from **6e** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.50 (m, 4H), 2.83 (m, 8H), 3.80 (s, 3H), 4.18 (m, 2H), 5.18 (s, 2H), 6.91 (m, 2H), 7.10 (s, 1H), 7.21 (s, 1H), 7.3−7.5 (m, 5H), 7.84 (m, 2H); MS (FD) *m/e* 544 (M^+).

[2-(Dimethylamino)-5,6,7-trimethoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7f). The title compound was prepared in 51% yield from **6f** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.51 (m, 4H), 2.80 (m, 2H), 2.88 (s, 6H), 3.75 (s, 3H), 3.89 (s, 3H), 4.05 (s, 3H), 4.18 (m, 2H), 6.9−7.0 (m, 3H), 7.84 (d, J = 8 Hz, 2H).

[2,6-Bis(dimethylamino)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7g). The title compound was prepared in 6% yield from **6g** and **3** by a method similar to that described for **7a**. This material was carried forward without complete purification: MS (FD) *m/e* 451 (M^+).

[2-(Dimethylamino)-5-fluoro-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7h). The title compound was prepared in 24% yield from **6h** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.21 (m, 2H), 1.55 (m, 4H), 2.50 (m, 4H), 2.82 (t, J = 5.4 Hz, 2H), 2.88 (s, 3H), 3.89 (s, 6H), 4.16 (t, J = 5.4 Hz, 2H), 6.92 (m, 3H), 7.15 (m, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H); MS (FD) *m/e* 456 (M^+).

[2-(Dimethylamino)-5-methyl-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7i). The title compound was prepared in 30% yield from **6i** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.48 (m, 2H), 1.60 (m, 4H), 2.18 (s, 3H), 2.52 (m, 4H), 2.80 (t, J = 6.0 Hz, 2H), 2.84 (s, 6H), 3.85 (s, 3H), 4.18 (t, J = 6.0 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.05 (s, 1H), 7.30 (s, 1H), 7.85 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 452 (M^+).

[2-(Dimethylamino)-5,7-dimethyl-6-methoxybenzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7j). The title compound was prepared in 88% yield from **6j** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.45 (m, 2H), 1.63 (m, 4H), 2.26 (s, 3H), 2.42 (s, 3H), 2.58

(m, 4H), 2.81 (t, J = 5.9 Hz, 2H), 2.87 (s, 6H), 3.74 (s, 3H), 4.18 (t, J = 5.9 Hz, 2H), 6.92 (d, J = 7.6 Hz, 2H), 7.18 (s, 1H), 7.85 (d, J = 7.0 Hz, 2H); MS (FD) *m/e* 466 (M^+). Anal. ($C_{27}H_{34}N_2O_3S$) C,H,N.

[2-(Dimethylamino)-4,7-dimethyl-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7k). The title compound was prepared in 29% yield from **6k** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.45 (m, 2H), 1.62 (m, 4H), 2.15 (s, 3H), 2.38 (s, 3H), 2.65 (m, 4H), 2.75 (s, 6H), 2.80 (t, J = 5.9 Hz, 2H), 3.83 (s, 3H), 4.17 (t, J = 6.0 Hz, 2H), 6.68 (s, 1H), 6.90 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H); MS (FD) *m/e* 466 (M^+). Anal. ($C_{27}H_{34}N_2O_3S$) C,H,N.

[2-(Dimethylamino)-7-methoxynaphtho[1,2-*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (7l). The title compound was prepared in 20% yield from **6l** and **3** by a method similar to that described for **7a**: ^{1}H NMR δ 1.50 (m, 2H), 1.59 (m, 4H), 2.49 (m, 4H), 2.77 (m, 8H), 4.06 (s, 3H), 4.12 (t, J = 6.0 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 7.15 (s, 1H), 7.29 (m, 2H), 7.80 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H), 8.28 (d, J = 8.8 Hz, 1H).

[2-(4-Methoxyphenyl)-4-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8b). A solution of **7b** (1.5 g, 3.4 mmol) in THF (20 mL) at 0 °C was treated with a 1 M THF solution of 4-methoxyphenylmagnesium bromide (prepared from magnesium turnings and 4-bromoanisole) (25 mL, 25 mmol) portionwise. After warming to room temperature, the reaction mixture was stirred for 1.5 h and then recooled and the reaction quenched with ice water. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), concentrated, and purified by preparative HPLC (CH_2Cl_2/0−10% EtOH gradient) to give 1.0 g (60%) of the title compound as a foam: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.50 (m, 4H), 2.77 (m, 2H), 3.60 (s, 3H), 3.80 (s, 3H), 4.12 (m, 2H), 6.70 (d, J = 8 Hz, 1H), 6.83 (m, 4H), 7.29 (m, 2H), 7.46 (m, 2H), 7.77 (m, 2H); MS (FD) *m/e* 501 (M^+).

[2-(4-Methoxyphenyl)-5-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8c). The title compound was prepared in 44% yield from **7c** by a method similar to that described for **8b**: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.50 (m, 4H), 2.77 (m, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 4.13 (m, 2H), 6.7−6.8 (m, 4H), 7.03 (m, 1H), 7.18 (m, 1H), 7.38 (m, 2H), 7.7−7.8 (m, 3H); MS (FD) *m/e* 501 (M^+).

[2-(4-Methoxyphenyl)-4,6-dimethoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8d). The title compound was prepared in 88% yield from **7d** by a method similar to that described for **8b**. The product was obtained as a white solid, mp 108−110 °C: ^{1}H NMR δ 1.4−1.7 (m, 6H), 2.49 (m, 4H), 2.75 (m, 2H), 3.52 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 4.10 (m, 2H), 6.33 (s, 1H), 6.7−6.9 (m, 4H), 6.91 (s, 1H), 7.2 (m, 2H), 7.77 (m, 2H); MS (FD) *m/e* 531 (M^+). Anal. ($C_{31}H_{33}NO_5S$) C,H,N.

[2-(4-Hydroxyphenyl)-5-methoxy-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8e). By the method described for the preparation of **8b**, **7e** (8 mmol) was condensed with 4-(TBSoxy)phenylmagnesium bromide (55 mmol). The crude product was treated with a 1.0 M solution of TBAF (12 mL, 12 mmol) in THF at 0 °C, and after 1 h the resultant mixture was poured into saturated $NaHCO_3$/ice (200 mL) and extracted with EtOAc (4 × 200 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 4.9 g (100%) of crude material as a brown foam.

A solution of the crude product obtained above (1.1 g, ∼1.8 mmol) and ammonium formate (0.23 g, 3.7 mmol) in EtOH (100 mL) was treated with 10% Pd/C (0.16 g, 0.15 mmol) and the mixture stirred at 60 °C for 1 h. Additional ammonium formate (0.75 g, 12 mmol) and 10% Pd/C (0.1 g, 0.1 mmol) were then added, and the reaction mixture was stirred at 60 °C until the starting material was consumed. After cooling to room temperature, the mixture was filtered and concentrated, and the residue was dissolved in EtOAc (200 mL), washed with brine (200 mL), dried (Na_2SO_4), and concentrated. Purification by radial chromatography (CH_2Cl_2/0−20% EtOH gradient) and trituration of the product with CH_2Cl_2/Et_2O provided 0.5 g (55%) of the title product as a yellow solid, mp 153−155 °C: ^{1}H NMR δ 1.4−1.8 (m, 6H), 2.65 (m, 4H), 2.85 (m, 2H), 3.88 (s, 3H), 4.14 (m, 2H), 6.5−6.6 (m, 4H), 7.10 (m, 2H), 7.36 (m, 2H), 7.63 (m, 2H); MS (FD) *m/e* 503 (M^+). Anal. ($C_{29}H_{29}NO_5S$) C,H,N.

[2-(4-Methoxyphenyl)-5,6,7-trimethoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8f). The title compound was prepared in 71% yield from **7f** by a method similar to that described for **8b**. The product was analyzed as the corresponding HCl salt, obtained by treatment with HCl/MeOH, concentration, and trituration with Et_2O, mp 188−190 °C: ^{1}H NMR (DMSO-d_6) δ 1.4−1.7 (m, 6H), 2.51 (m, 4H), 2.78 (m, 2H), 3.78 (s, 3H), 3.85 (s, 3H), 3.94 (s, 3H), 4.08 (m, 2H), 4.15 (s, 3H), 6.74 (m, 4H), 6.98 (s, 1H), 7.33 (m, 2H), 7.77 (m, 2H); MS (FD) *m/e* 561 (M^+). Anal. ($C_{32}H_{35}NO_6S$·HCl) C,H,N.

[2-(4-Methoxyphenyl)-6-(dimethylamino)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8g). The title compound was prepared in 21% yield from **7g** by a method similar to that described for **8b**: ^{1}H NMR δ 1.45 (m, 2H), 1.60 (m, 4H), 2.45 (m, 4H), 2.75 (t, J = 6.0 Hz, 2H), 3.03 (s, 6H), 3.76 (s, 3H), 4.09 (t, J = 6.0 Hz, 2H), 6.76 (m, 4H), 6.86 (dd, J = 9.0, 2.1 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.9 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 515 (M^+).

[2-(4-Methoxyphenyl)-5-fluoro-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8h). The title compound was prepared in 24% yield from **7h** by a method similar to that described for **8b**: ^{1}H NMR δ 1.48 (m, 2H), 1.58 (m, 4H), 2.48 (m, 4H), 2.74 (t, J = 6.0 Hz, 2H), 3.77 (s, 3H), 3.98 (s, 3H), 4.10 (t, J = 6.0 Hz, 2H), 6.76 (d, J = 7.8 Hz, 4H), 7.34 (m, 4H), 7.74 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 519 (M^+). Anal. ($C_{30}H_{30}FNO_4S$) C,H,N.

[2-(4-Methoxyphenyl)-5-methyl-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8i). The title compound was prepared in 43% yield from **7i** by a method similar to that described for **8b**: ^{1}H NMR δ 1.46 (m, 2H), 1.60 (m, 4H), 2.25 (s, 3H), 2.50 (m, 4H), 2.77 (t, J = 5.9 Hz, 2H), 3.76 (s, 3H), 3.92 (s, 3H), 4.10 (t, J = 6.0 Hz, 2H), 6.76 (d, J = 8.9 Hz, 4H), 7.25 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.41 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 515 (M^+).

[2-(4-Methoxyphenyl)-5,7-dimethyl-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8j). The title compound was prepared in 37% yield from **7j** by a method similar to that described for **8b**: ^{1}H NMR δ 1.45 (m, 2H), 1.63 (m, 4H), 2.34 (s, 3H), 2.50 (m, 4H), 2.54 (s, 3H), 2.74 (t, J = 5.9 Hz, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 4.09 (t, J = 5.9 Hz, 2H), 6.76 (d, J = 8.5 Hz, 4H), 7.33 (s, 1H), 7.36 (d, J = 6.7 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 529 (M^+). Anal. ($C_{32}H_{35}NO_4S$·2.0H_2O) C,H,N.

[2-(4-Methoxyphenyl)-4,7-dimethyl-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8k). The title compound was prepared in 35% yield from **7k** by a method similar to that described for **8b**: ^{1}H NMR δ 1.44 (m, 2H), 1.58 (m, 4H), 2.24 (s, 3H), 2.44 (s, 3H), 2.48 (m, 4H), 2.74 (t, J = 6.0 Hz, 2H), 3.76 (s, 3H), 3.89 (s, 3H), 4.10 (t, J = 6.0 Hz, 2H), 6.76 (m, 5H), 7.40 (d, J = 6.9 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H); MS (FD) *m/e* 529 (M^+). Anal. ($C_{32}H_{35}NO_4S$) C,H,N.

[2-(4-Methoxyphenyl)-7-methoxynaphtho[1,2-*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (8l). The title compound was prepared in 15% yield from **7l** by a method similar to that described for **8b**: ^{1}H NMR δ 1.44 (m, 2H), 1.56 (m, 4H), 2.46 (m, 4H), 2.72 (t, J = 6.0 Hz, 2H), 3.76 (s, 3H), 4.02 (t, J = 5.9 Hz, 2H), 4.08 (s, 3H), 6.79 (m, 4H), 7.24 (s, 1H), 7.36 (m, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.3 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H); MS (FD) *m/e* 551 (M^+). Anal. ($C_{34}H_{33}NO_4S$) C,H,N.

[2-(4-Hydroxyphenyl)-4-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9b). The title compound was prepared in 77% yield from **8b** by a method similar to that described for **5g**. The product was obtained as a yellow solid, mp 205−210 °C: ^{1}H NMR δ 1.1−1.4 (m, 6H), 2.22 (m, 4H), 2.48 (m, 2H), 3.84 (m, 2H), 6.4−6.6 (m, 5H), 6.8−

7.1 (m, 4H), 7.47 (d, J = 8 Hz, 2H), 8.90 (br s, 2H); MS (FD) *m/e* 473 (M^+). Anal. ($C_{28}H_{27}NO_4S$) C,H,N.

[2-(4-Hydroxyphenyl)-5-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9c). The title compound was prepared in 97% yield from **8c** by a method similar to that described for **5g**. The product was obtained as a yellow solid, mp 125 °C dec: ^{1}H NMR (DMSO-d_6) δ 1.2−1.7 (m, 6H), 2.36 (m, 4H), 2.59 (m, 2H), 4.06 (m, 2H), 6.6−7.0 (m, 6H), 7.18 (m, 2H), 7.65 (m, 2H), 7.79 (m, 1H), 9.47 (br s, 1H), 9.77 (br s, 2H). Anal. ($C_{28}H_{27}NO_4S$) C,H,N.

[2-(4-Hydroxyphenyl)-4,6-dihydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9d). A solution of **8d** (4.8 g, 9.0 mmol) in MeOH (20 mL) at 0 °C was treated with saturated HCl/MeOH (10 mL). After 15 min, the mixture was concentrated, slurried with Et_2O, and concentrated to give the hydrochloride salt as a foam. This residue was diluted with DCE (50 mL), cooled to 0 °C, treated with 5.5 M BCl_3 in DCE (7 mL, 38 mmol), and allowed to warm to room temperature over 20 h. The reaction was quenched at 0 °C with MeOH (10 mL), and the mixture was poured into saturated aqueous $NaHCO_3$/ice (200 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4), concentrated, and purified by preparative HPLC (CH_2Cl_2/0−30% EtOH gradient). Trituration with EtOH/Et_2O provided 2.9 g (63%) of the title compound as the dihydrate, mp 151−155 °C: ^{1}H NMR δ 1.3−1.6 (m, 6H), 2.21 (m, 4H), 2.58 (m, 2H), 3.30 (br s, 4H, H_2O), 4.08 (m, 2H), 6.20 (s, 1H), 6.6−6.8 (m, 3H), 6.91 (m, 2H), 7.18 (m, 2H), 7.58 (m, 2H), 9.55 (br s, 1H), 9.70 (br s, 2H); MS (FD) *m/e* 489 (M^+). Anal. ($C_{28}H_{27}NO_5S\cdot 2.25H_2O$) C,H,N.

[2-(4-Hydroxyphenyl)-5,6-dihydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9e). The title compound was prepared in 59% yield from **8e** by a method similar to that described for **9d**. The product was obtained as the monohydrate, mp 190−200 °C: ^{1}H NMR (DMSO-d_6) δ 1.3−1.5 (m, 6H), 2.35 (m, 4H), 2.42 (m, 2H), 4.08 (m, 2H), 6.63 (s, 2H), 6.78 (s, 1H), 6.93 (m, 2H), 7.14 (m, 2H), 7.30 (s, 1H), 7.63 (m, 2H), 9.25 (br s, 1H), 9.35 (br s, 1H), 9.70 (br s, 2H); MS (FD) *m/e* 490 $(MH)^+$. Anal. ($C_{28}H_{27}NO_5S\cdot H_2O$) C; H: calcd, 5.76; found, 5.28. N: calcd, 2.76; found, 2.25.

[2-(4-Hydroxyphenyl)-6-(dimethylamino)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9g). The title compound was prepared in 41% yield from **8g** by a method similar to that described for **5g**. The product was obtained as a yellow solid: ^{1}H NMR δ 1.48 (m, 2H), 1.62 (m, 4H), 2.54 (m, 4H), 2.76 (t, J = 6.0 Hz, 2H), 3.03 (s, 6H), 4.10 (t, J = 4.1 Hz, 2H), 6.60 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.9 Hz, 1H), 7.10 (s, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.9 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H); MS (FD) *m/e* 501 (M^+). Anal. ($C_{30}H_{32}N_2O_3S$) C,H,N.

[2-(4-Hydroxyphenyl)-5-fluoro-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9h). The title compound was prepared in 43% yield from **8h** by a method similar to that described for **5g**. The product was obtained as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 2H), 1.48 (m, 4H), 2.39 (m, 4H), 2.65 (t, J = 6.0 Hz, 2H), 4.10 (t, J = 6.0 Hz, 2H), 6.65 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 7.8 Hz, 2H), 7.18 (m, 3H), 7.54 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 9.0 Hz, 2H), 9.98 (br s, 2H); MS (FD) *m/e* 492 (M^+). Anal. ($C_{28}H_{26}FNO_4S$) C,H,N.

[2-(4-Hydroxyphenyl)-5-methyl-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9i). The title compound was prepared in 40% yield from **8i** by a method similar to that described for **5g**. The product was obtained as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.27 (m, 2H), 1.49 (m, 4H), 2.06 (s, 3H), 2.45 (m, 4H), 2.50 (t, J = 5.9 Hz, 2H), 3.90 (t, J = 5.8 Hz, 2H), 6.49 (d, J = 8.5 Hz, 2H), 6.57 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 7.09 (s, 1H), 7.14 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 8.80 (br s, 2H); MS (FD) *m/e* 488 (M^+). Anal. ($C_{29}H_{29}NO_4S$) C,H,N.

[2-(4-Hydroxyphenyl)-5,7-dimethyl-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9j). The title compound was prepared in 69% yield from **8j** by a method similar to that described for **5g**. The product was obtained as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.34 (m, 2H), 1.45 (m, 4H), 2.17 (s, 3H), 2.37 (s, 3H), 2.42 (m, 4H), 2.65 (m, 2H), 4.06 (m, 2H), 6.64 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 7.00 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 8.70 (s, 1H), 9.70 (s, 1H); MS (FD) *m/e* 502 (M^+). Anal. ($C_{30}H_{31}NO_4S\cdot 0.5H_2O$) C,H,N.

[2-(4-Hydroxyphenyl)-4,7-dimethyl-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9k). The title compound was prepared in 49% yield from **8k** by a method similar to that described for **5g**. The product was obtained as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 2H), 1.44 (m, 4H), 1.98 (s, 3H), 2.28 (s, 3H), 2.38 (m, 4H), 2.59 (m, 2H), 4.06 (m, 2H), 6.65 (m, 3H), 6.93 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 9.50 (s, 1H), 9.67 (s, 1H); MS (FD) *m/e* 501 (M^+). Anal. ($C_{30}H_{31}NO_4S\cdot 0.5H_2O$) C,H,N.

[2-(4-Hydroxyphenyl)-6-hydroxynaphtho[1,2-*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (9l). The title compound was prepared in 50% yield from **8l** by a method similar to that described for **5g**. The product was obtained as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.32 (m, 2H), 1.43 (m, 4H), 2.35 (m, 4H), 2.60 (m, 2H), 4.03 (m, 2H), 6.68 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 7.5 Hz, 2H), 7.40 (m, 4H), 7.70 (m, 2H), 8.22 (d, J = 8.3 Hz, 1H), 8.30 (s, 1H), 9.70 (s, 1H); MS (FD) *m/e* 524 (M^+). Anal. ($C_{32}H_{29}NO_4S\cdot 0.75H_2O$) C,H,N.

(2-Phenyl-6-methoxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10a). The title compound was prepared in 87% yield from **7a** and phenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR (90 MHz) δ 1.51 (m, 6H), 2.48 (m, 4H), 2.76 (t, J = 6.4 Hz, 2H), 3.85 (s, 3H), 4.08 (t, J = 6.4 Hz, 2H), 6.75 (d, J = 9 Hz, 2H), 6.90 (dd, J = 9, 2 Hz, 1H), 7.30 (m, 7H), 7.76 (d, J = 9 Hz, 2H); MS (EI) *m/e* 471 (M^+). Anal. ($C_{29}H_{29}NO_3S$) C,H,N.

[2-(2-Methoxyphenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10b). The title compound was prepared in 62% yield from **7a** and 2-methoxyphenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.44 (m, 2H), 1.60 (m, 4H), 2.48 (m, 4H), 2.72 (t, J = 5.9 Hz, 2H), 3.51 (s, 3H), 3.87 (s, 3H), 4.06 (t, J = 5.9 Hz, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.6 Hz, 2H), 6.89 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.9 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.33 (s, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H); MS (FD) *m/e* 501 (M^+).

[2-[3-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-methanone (10c). The title compound was prepared in 73% yield from **7a** and 3-[(*tert*-butyldimethylsilyl)oxy]phenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 0.11 (s, 6H), 0.95 (s, 9H), 1.45 (m, 2H), 1.61 (m, 4H), 2.50 (m, 4H), 2.76 (t, J = 5.9 Hz, 2H), 3.89 (s, 3H), 4.09 (t, J = 5.9 Hz, 2H), 6.69 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 8.5 Hz, 2H), 6.90 (s, 1H), 6.9−7.1 (m, 3H), 7.34 (m, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H); MS (FD) *m/e* 601 (M^+). Anal. ($C_{35}H_{43}NO_4SSi$) C,H,N.

[2-(2-Methylphenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10d). The title compound was prepared in 49% yield from **7a** and 2-methylphenylmagnesium bromide by a method similar to that described for **8b**. The product could not be fully purified at this stage and was carried on to **11d** without complete characterization: ^{1}H NMR δ 1.5 (m, 2H), 1.7 (m, 4H), 2.4 (s, 3H), 2.6 (m, 4H), 2.8 (t, 2H), 4.0 (s, 3H), 4.2 (t, 2H), 6.8 (d, 2H), 7.0 (dd, 1H), 7.1−7.2 (m, 3H), 7.3−7.4 (m, 1H), 7.5 (d, 1H), 7.7 (d, 1H), 7.8 (d, 2H).

[2-(3-Fluorophenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10e). The title compound was prepared in 68% yield from **7a** and 3-fluorophenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.44 (m, 2H), 1.58 (m, 4H), 2.47 (m, 4H), 2.73 (t, J = 6.0 Hz, 2H), 3.89 (s, 3H), 4.08 (t, J = 6.0 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.90 (m, 1H), 6.97 (dd, J = 8.9, 2.3 Hz, 1H), 7.1−7.2 (m, 3H), 7.33 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 489 (M^+). Anal. ($C_{29}H_{28}FNO_3S$) C,H,N.

[2-(4-Ethylphenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10f). The title compound was prepared in 68% yield from **7a** and 4-ethylphenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.18 (t, J = 7.6 Hz, 3H), 1.45 (m, 2H), 1.60 (m, 4H), 2.48 (m, 4H), 2.58 (q, J = 7.6 Hz, 2H), 2.74 (t, J = 5.9 Hz, 2H), 3.89 (s, 3H), 4.09 (t, J = 5.9 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.97 (dd, J = 8.8, 2.2 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 7.35 (m, 3H), 7.52 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 499 (M^+). Anal. ($C_{31}H_{33}NO_3S$) C,H,N.

[2-[4-(2-Propyl)phenyl]-6-methoxybenzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10g). The title compound was prepared in 65% yield from **7a** and 4-(2-propyl)phenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.17 (d, J = 7.0 Hz, 6H), 1.43 (m, 2H), 1.59 (m, 4H), 2.45 (m, 4H), 2.73 (t, J = 6.0 Hz, 2H), 2.82 (m, 1H), 3.88 (s, 3H), 4.07 (t, J = 6.0 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 6.95 (dd, J = 8.8, 2.1 Hz, 1H), 7.07 (d, J = 8.1 Hz, 2H), 7.34 (m, 3H), 7.52 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 513 (M^+). Anal. ($C_{32}H_{35}NO_3S$) C,H,N.

[2-[4-(1-Butyl)phenyl]-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10h). The title compound was prepared in 65% yield from **7a** and 4-(1-butyl)phenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 0.90 (t, J = 7.3 Hz, 3H), 1.2−1.4 (m, 2H), 1.4−1.7 (m, 8H), 2.4−2.6 (m, 6H), 2.75 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 4.09 (t, J = 6.0 Hz, 2H), 6.76 (d, J = 8.9 Hz, 2H), 6.97 (dd, J = 8.9, 2.4 Hz, 1H), 7.03 (d, J = 8.1 Hz, 2H), 7.34 (m, 3H), 7.54 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 527 (M^+). Anal. ($C_{33}H_{37}NO_3S$) C,H,N.

[2-(4-Biphenylyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10i). The title compound was prepared in 49% yield from **7a** and 4-biphenylylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.42 (m, 2H), 1.57 (m, 4H), 2.46 (m, 4H), 2.71 (t, J = 5.9 Hz, 2H), 3.88 (s, 3H), 4.07 (t, J = 5.9 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.97 (dd, J = 8.8, 2.6 Hz, 1H), 7.2−7.6 (m, 11H), 7.80 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 547 (M^+). Anal. ($C_{35}H_{33}NO_3S$) C,H,N.

[2-[4-(Thiomethyl)phenyl]-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10j). The title compound was prepared in 90% yield from **7a** and 4-thioanisylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.46 (m, 2H), 1.62 (m, 4H), 2.43 (s, 3H), 2.51 (m, 4H), 2.77 (t, J = 6.0 Hz, 2H), 3.89 (s, 3H), 4.12 (t, J = 6.0 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.97 (dd, J = 8.9, 2.6 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 7.35 (m, 3H), 7.51 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 517 (M^+). Anal. ($C_{30}H_{31}NO_3S_2 \cdot 0.5H_2O$) C,H,N.

[2-[4-(Hydroxymethyl)phenyl]-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10k). The title compound was prepared from **7a** and 4-[(TBSoxy)-methyl]phenylmagnesium bromide by a method similar to that described for **8b**. After the reaction was complete, the mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (20 mL) and treated with 1.0 M TBAF in THF (5.1 mL, 5.1 mmol). After 1 h, the mixture was partitioned between CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ (100 mL), and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (1:1 hexane:EtOAc, 0−5% MeOH) to provide 0.46 g (20%) of the title compound as an off-white solid: ^{1}H NMR δ 1.46 (m, 2H), 1.63 (m, 4H), 2.54 (m, 4H), 2.75 (t, J = 4.9 Hz, 2H), 3.90 (s, 3H), 4.11 (t, J = 5.4 Hz, 2H), 4.60 (s, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.98 (dd, J = 8.9, 2.4 Hz, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.9 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 24.9, 26.6, 55.9, 56.6, 58.4, 65.3, 67.0, 105.4, 115.2, 115.9, 125.2, 127.9, 130.0, 131.3, 132.3, 133.2, 133.5, 134.8, 141.2, 142.5, 143.4, 158.8, 163.8, 192.9; HRMS (FD) *m/e* calcd for $C_{30}H_{32}NO_4S$ (MH^+) 502.2043, found 502.2052. Anal. ($C_{30}H_{31}NO_4S \cdot 0.5H_2O$) C,H; N: calcd, 2.74; found, 2.24.

[2-[4-(Trifluoromethyl)phenyl]-6-methoxybenzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10m). The title compound was prepared in 81% yield from **7a** and 4-(trifluoromethyl)phenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.45 (m, 2H), 1.63 (m, 4H), 2.54 (m, 4H), 2.79 (t, J = 5.8 Hz, 2H), 3.89 (s, 3H), 4.13 (t, J = 5.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.98 (dd, J = 8.9, 2.3 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 539 (M^+). Anal. ($C_{30}H_{28}F_3NO_3S$) C,H,N.

[2-(2-Methyl-4-methoxyphenyl)-6-methoxybenzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10n). The title compound was prepared in 55% yield from **7a** and 2-methyl-4-methoxyphenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.46 (m, 2H), 1.63 (m, 4H), 2.26 (s, 3H), 2.54 (m, 4H), 2.79 (t, J = 5.8 Hz, 2H), 3.47 (s, 3H), 3.89 (s, 3H), 4.12 (t, J = 5.8 Hz, 2H), 6.60 (m, 2H), 6.74 (d, J = 8.8 Hz, 2H), 6.98 (dd, J = 8.9, 2.4 Hz, 1H), 7.19 (d, J = 9.3 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 515 (M^+). Anal. ($C_{31}H_{33}NO_4S$) C,H,N.

[2-(2,4-Dimethoxyphenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10o). The title compound was prepared in 58% yield from **7a** and 2,4-dimethoxyphenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.44 (m, 2H), 1.60 (m, 4H), 2.49 (m, 4H), 2.74 (t, J = 6.0 Hz, 2H), 3.49 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 4.07 (t, J = 6.0 Hz, 2H), 6.21 (d, J = 2.2 Hz, 1H), 6.42 (dd, J = 8.5, 2.3 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 6.95 (dd, J = 8.9, 2.3 Hz, 1H), 7.32 (m, 2H), 7.63 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 531 (M^+). Anal. ($C_{31}H_{33}NO_5S$) C,H,N.

[2-(3-Methyl-4-methoxyphenyl)-6-methoxybenzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10p). The title compound was prepared in 69% yield from **7a** and 3-methyl-4-methoxyphenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.43 (m, 2H), 1.58 (m, 4H), 2.11 (s, 3H), 2.46 (m, 4H), 2.71 (t, J = 5.8 Hz, 2H), 3.75 (s, 3H), 3.86 (s, 3H), 4.06 (t, J = 5.8 Hz, 2H), 6.64 (d, J = 8.9 Hz, 1H), 6.75 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.9 Hz, 1H), 7.20 (s, 2H), 7.31 (s, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H); MS (FD) *m/e* 515 (M^+). Anal. ($C_{31}H_{33}NO_4S$) C,H,N.

[2-(3-Chloro-4-methoxyphenyl)-6-methoxybenzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10q). The title compound was prepared in 62% yield from **7a** and 3-chloro-4-methoxyphenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.43 (m, 2H), 1.58 (m, 4H), 2.73 (t, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 4.08 (t, J = 5.9 Hz, 2H), 6.74 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 9.2 Hz, 2H), 6.96 (dd, J = 8.9, 2.2 Hz, 1H), 7.26 (dd, J = 8.7, 2.2 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 535 (M^+). Anal. ($C_{30}H_{30}ClNO_4S$) C,H,N.

[2-[3-Fluoro-4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone (10r). The title compound was prepared in 75% yield from **7a** and 3-fluoro-4-(TBSoxy)phenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 0.12 (s, 6H), 0.96 (s, 9H), 1.43 (m, 2H), 1.59 (m, 4H), 2.48 (m, 4H), 2.74 (t, J = 6.0 Hz, 2H), 3.87 (s, 3H), 4.07 (t, J = 6.0 Hz, 2H), 6.7−6.8 (m, 3H), 6.9−7.2 (m, 3H), 7.32 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 619 (M^+). Anal. ($C_{35}H_{42}FNO_4SSi$) C,H,N.

[2-(3,5-Dimethyl-4-methoxyphenyl)-6-methoxybenzo-[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10s). The title compound was prepared in 57% yield from **7a** and 3,5-dimethyl-4-methoxyphenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.45 (m, 2H), 1.60 (m, 4H), 2.17 (s, 6H), 2.49 (m, 4H), 2.75 (t, J = 5.9 Hz, 2H), 3.65 (s, 3H), 3.90 (s, 3H), 4.09 (t, J = 5.9 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 7.16 (m, 2H), 7.25 (s, 2H), 7.33 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.7 Hz, 1H); MS (FD) *m/e* 529 (M^+).

[2-[3,4-(Methylenedioxy)phenyl]-6-methoxybenzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (10t). The title compound was prepared in 65% yield from **7a** and 3,4-(methylenedioxy)phenylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.36 (m, 2H), 1.53 (m, 4H), 2.41 (m, 4H), 2.66 (t, J = 5.8 Hz, 2H),

3.78 (s, 3H), 4.02 (t, J = 5.8 Hz, 2H), 5.82 (s, 2H), 6.60 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 8.8 Hz, 2H), 6.8−7.0 (m, 3H) 7.24 (d, J = 2.2 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 516 (MH^+). Anal. ($C_{30}H_{29}NO_5S$) C,H,N.

(2-Phenyl-6-hydroxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11a). The title compound was prepared in 69% yield from **10a** by a method similar to that described for **5g**. The product was converted to its HCl salt for evaluation: ^{1}H NMR (DMSO-d_6) δ 1.40 (m, 1H), 1.79 (m, 5H), 2.98 (m, 2H), 3.45 (m, 4H), 4.45 (m, 2H), 6.91 (d, J = 9 Hz, 1H), 6.98 (d, J = 9 Hz, 2H), 7.35 (m, 7H), 7.78 (d, J = 9 Hz, 2H), 9.96 (s, 1H), 10.35 (br s, 1H); MS (FD) *m/e* 457 (M^+). Anal. ($C_{28}H_{27}NO_3S\cdot$HCl) C,H,N.

[2-(2-Hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11b). The title compound was prepared in 49% yield from **10b** by a method similar to that described for **5g**: ^{1}H NMR δ 1.47 (m, 2H), 1.62 (m, 4H), 2.54 (m, 4H), 2.75 (t, J = 5.4 Hz, 2H), 4.10 (t, J = 5.4 Hz, 2H), 4.87 (br s, 2H), 6.64 (d, J = 8.1 Hz, 1H), 6.7−6.9 (m, 4H), 7.02 (m, 1H), 7.25 (m, 2H), 7.47 (d, J = 8.9 Hz, 1H), 7.67 (d, J = 8.6 Hz, 2H); MS (FD) *m/e* 473 (M^+). Anal. ($C_{28}H_{27}NO_4S$) C,H,N.

[2-(3-Hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11c). The title compound was prepared in 95% yield from **10c** by a method similar to that described for **5g**: ^{1}H NMR (CD_3OD) δ 1.45 (m, 2H), 1.59 (m, 4H), 2.50 (m, 4H), 2.72 (t, J = 5.5 Hz, 2H), 4.11 (t, J = 5.5 Hz, 2H), 4.88 (br s, 2H), 6.61 (m, 1H), 6.8−6.9 (m, 5H), 7.01 (t, J = 8.1 Hz, 1H), 7.27 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.7 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{28}H_{28}NO_4S$ (MH^+) 474.1739, found 474.1741. Anal. ($C_{28}H_{27}NO_4S\cdot0.75H_2O$) C,H,N.

[2-(2-Methylphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11d). The title compound was prepared in 36% yield from **10d** by a method similar to that described for **5g**: ^{1}H NMR δ 1.48 (m, 2H), 1.66 (m, 4H), 2.23 (s, 3H), 2.58 (m, 4H), 2.80 (t, J = 5.6 Hz, 2H), 4.09 (t, J = 5.6 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 6.82 (dd, J = 8.8, 2.1 Hz, 1H), 7.0−7.1 (m, 3H), 7.1−7.3 (m, 2H), 7.48 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.7 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{29}H_{30}NO_3S$ (MH^+) 472.1946, found 472.1942. Anal. ($C_{29}H_{29}NO_3S\cdot0.5H_2O$) C,H,N.

[2-(3-Fluorophenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11e). The title compound was prepared in 53% yield from **10e** by a method similar to that described for **5g**: ^{1}H NMR δ 1.47 (m, 2H), 1.67 (m, 4H), 2.60 (m, 4H), 2.82 (t, J = 5.4 Hz, 2H), 4.11 (t, J = 5.4 Hz, 2H), 6.56 (d, J = 8.9 Hz, 2H), 6.76 (dd, J = 8.8, 2.1 Hz, 1H), 6.87 (m, 1H), 7.0−7.2 (m, 4H), 7.34 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H); HRMS (FD) *m/e* calcd for $C_{28}H_{27}FNO_3S$ (MH^+) 476.1705, found 476.1696. Anal. ($C_{28}H_{26}FNO_3S$) C,H,N.

[2-(4-Ethylphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11f). The title compound was prepared in 65% yield from **10f** by a method similar to that described for **5g**: ^{1}H NMR δ 1.17 (t, J = 7.5 Hz, 3H), 1.48 (m, 2H), 1.66 (m, 4H), 2.5−2.6 (m, 6H), 2.80 (t, J = 5.7 Hz, 2H), 4.10 (t, J = 5.5 Hz, 2H), 6.63 (d, J = 8.9 Hz, 2H), 6.78 (dd, J = 8.8, 2.2 Hz, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 2.2 Hz, 1H), 7.30 (m, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 15.3, 23.9, 25.2, 28.5, 55.0, 57.7, 65.2, 107.5, 114.1, 115.4, 124.1, 128.1, 128.9, 130.5, 130.8, 131.0, 132.3, 133.3, 140.3, 142.1, 144.6, 154.8, 162.8, 193.7; HRMS (FD) *m/e* calcd for $C_{30}H_{32}NO_3S$ (MH^+) 486.2088, found 486.2103. Anal. ($C_{30}H_{31}NO_3S\cdot1.5H_2O$) C,N; H: calcd, 6.69; found, 6.11.

[2-[4-(2-Propyl)phenyl]-6-hydroxybenzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11g). The title compound was prepared in 33% yield from **10g** by a method similar to that described for **9d**: ^{1}H NMR δ 1.16 (d, J = 6.9 Hz, 6H), 1.47 (m, 2H), 1.65 (m, 4H), 2.58 (m, 4H), 2.79 (m, 3H), 4.07 (t, J = 5.3 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 6.74 (dd, J = 8.8, 2.1 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 2.1 Hz, 1H), 7.2−7.3 (m, 2H), 7.35 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.8, 2H); HRMS (FD) *m/e* calcd for $C_{31}H_{34}NO_3S$ (MH^+) 500.2259, found 500.2269. Anal. ($C_{31}H_{33}NO_3S\cdot0.3H_2O$) C,H,N.

[2-[4-(1-Butyl)phenyl]-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11h). The title compound was prepared in 56% yield from **10h** by a method similar to that described for **5g**: ^{1}H NMR δ 0.89 (t, J = 7.3 Hz, 3H), 1.27 (m, 2H), 1.4−1.6 (m, 4H), 1.67 (m, 4H), 2.5−2.6 (m, 6H), 2.81 (t, J = 5.5 Hz, 2H), 4.09 (t, J = 5.5 Hz, 2H), 6.59 (d, J = 8.7 Hz, 2H), 6.77 (dd, J = 8.7, 2.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.6 Hz, 2H); HRMS (FD) *m/e* calcd for $C_{32}H_{36}NO_3S$ (MH^+) 514.2420, found 514.2416. Anal. ($C_{32}H_{35}NO_3S\cdot1.25H_2O$) C,H,N.

[2-(4-Biphenylyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11i). The title compound was prepared in 56% yield from **10i** by a method similar to that described for **5g**: ^{1}H NMR δ 1.47 (m, 2H), 1.65 (m, 4H), 2.56 (m, 4H), 2.80 (t, J = 5.3 Hz, 2H), 4.10 (t, J = 5.5 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 6.83 (dd, J = 8.8, 2.2 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.2−7.6 (m, 10H), 7.74 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 533 (M^+). Anal. ($C_{34}H_{31}NO_3S$) C,H,N.

[2-[4-(Thiomethyl)phenyl]-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11j). The title compound was prepared in 23% yield from **10j** by a method similar to that described for **5g**: ^{1}H NMR δ 1.49 (m, 2H), 1.68 (m, 4H), 2.42 (s, 3H), 2.62 (m, 4H), 2.83 (t, J = 5.4 Hz, 2H), 4.12 (t, J = 5.4 Hz, 2H), 6.59 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 8.8, 2.1 Hz, 1H), 7.07 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.7 Hz, 1H), 7.68 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 14.4, 22.9, 24.2, 54.1, 56.8, 64.2, 106.6, 113.3, 114.7, 123.2, 125.2, 128.2, 129.2, 129.5, 130.2, 131.4, 132.2, 138.2, 139.3, 140.2, 154.1, 161.9, 192.7; HRMS (FD) *m/e* calcd for $C_{29}H_{30}NO_3S_2$ (MH^+) 504.1647, found 504.1667. Anal. ($C_{29}H_{29}NO_3S_2\cdot1.5H_2O$) C,N; H: calcd, 6.08; found, 5.63.

[2-[4-[(Ethylthio)methyl]phenyl]-6-hydroxybenzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11l). By the method described for **8b**, a solution of **7a** (2.6 g, 6.0 mmol) in THF (23 mL) was treated with a 0.6 M THF solution of 4-[(TBSoxy)methyl]phenylmagnesium bromide as described for **10k**. Chromatography of the intermediate product (1:1 hexane:EtOAc, 0−10% MeOH) provided 2.2 g (60%) of the silylated intermediate as an unstable brown oil. Treatment of this material by the method described for **5g** followed by treatment with TBAF as described for **10k** provided 0.54 g (14% overall) of the title product as a yellow solid: ^{1}H NMR δ 1.14 (t, J = 7.3 Hz, 3H), 1.47 (m, 2H), 1.66 (m, 4H), 2.29 (q, J = 7.3 Hz, 2H), 2.59 (m, 4H), 2.80 (t, J = 5.4 Hz, 2H), 3.60 (s, 2H), 4.10 (t, J = 5.5 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 8.8, 2.2 Hz, 1H), 7.1−7.2 (m, 3H), 7.29 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.7 Hz, 1H), 7.65 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 532 (MH^+). Anal. ($C_{31}H_{33}NO_3S_2$) C,H,N.

[2-[4-(Trifluoromethyl)phenyl]-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11m). A solution of **10m** (480 mg, 0.89 mmol) in anhydrous CH_2Cl_2 (15 mL) was cooled to −78 °C and treated with a 1.0 M CH_2Cl_2 solution of boron tribromide (0.8 mL, 0.8 mmol). The mixture was allowed to warm to room temperature, stirred overnight, and treated with additional boron tribromide (1.75 mL, 1.75 mmol) in two portions. After 72 h, the mixture was diluted with 75 mL of water and extracted with CH_2Cl_2 (2 × 75 mL). The organic layers were washed with 2 N NaOH, and the resultant aqueous layer was acidified and extracted with CH_2Cl_2 (75 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified via radial chromatography (2:1:0.1 hexane:EtOAc:MeOH, under an ammonia atmosphere) to provide 110 mg (24%) of the title product as an amorphous green solid: ^{1}H NMR δ 1.45 (m, 2H), 1.63 (m, 4H), 2.57 (m, 4H), 2.79 (t, J = 4.9 Hz, 2H), 4.08 (t, J = 4.9 Hz, 2H), 6.59 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.7 Hz, 1H), 7.15 (s, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.42 (s, 4H), 7.64 (d, J = 8.6 Hz, 2H), 8.18 (br s, 1H); HRMS (FD) *m/e* calcd for $C_{29}H_{27}F_3NO_3S$ (MH^+) 526.1664, found 526.1669. Anal. ($C_{29}H_{26}F_3NO_3S\cdot H_2O$) C,H,N.

[2-(2-Methyl-4-hydroxyphenyl)-6-hydroxybenzo[*b*]thien-

3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11n). The title compound was prepared in 27% yield from **10n** by a method similar to that described for **5g**: ^{1}H NMR δ 1.47 (m, 2H), 1.61 (m, 4H), 2.13 (s, 3H), 2.55 (m, 4H), 2.77 (t, J = 5.5 Hz, 2H), 4.09 (t, J = 5.5 Hz, 2H), 4.87 (s, 2H), 6.45 (m, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.87 (dd, J = 8.8, 2.2 Hz, 1H), 7.01 (d, J = 9.1 Hz, 1H), 7.23 (d, J = 2.2 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{29}H_{30}NO_4S$ (MH^+) 488.1896, found 488.1911. Anal. ($C_{29}H_{29}NO_4S\cdot0.5H_2O$) C,H,N.

[2-(2-Methoxy-4-hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11o). The title compound was prepared in 15% yield from **10o** by a method similar to that described for **5g**: ^{1}H NMR (1:1 $CDCl_3/CD_3OD$) δ 1.44 (m, 2H), 1.59 (m, 4H), 2.49 (m, 4H), 2.73 (t, J = 5.7 Hz, 2H), 3.43 (s, 3H), 4.07 (t, J = 5.7 Hz, 2H), 6.11 (d, J = 2.1 Hz, 1H), 6.31 (dd, J = 8.5, 2.2 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.84 (dd, J = 8.8, 2.3 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 2.1 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.68 (d, J = 8.7 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{29}H_{30}NO_5S$ (MH^+) 504.1845, found 504.1875. Anal. ($C_{29}H_{29}NO_5S\cdot0.5H_2O$) C,H,N.

[2-(3-Methyl-4-hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11p). The title compound was prepared in 64% yield from **10p** by a method similar to that described for **5g**: ^{1}H NMR (DMSO-d_6) δ 1.34 (m, 2H), 1.44 (m, 4H), 2.37 (m, 4H), 2.60 (t, J = 5.7 Hz, 2H), 4.05 (t, J = 5.7 Hz, 2H), 6.64 (d, J = 8.3 Hz, 1H), 6.82 (dd, J = 8.8, 2.1 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.96 (dd, J = 8.3, 2.1 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 1.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 9.62 (br s, 1H), 9.75 (br s, 1 H); MS (FD) *m/e* 487 (M^+). Anal. ($C_{29}H_{29}NO_4S$) C,H,N.

[2-(3-Chloro-4-hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11q). The title compound was prepared in 59% yield from **10q** by a method similar to that described for **5g**: ^{1}H NMR δ 1.33 (m, 2H), 1.44 (m, 4H), 2.37 (m, 4H), 2.48 (s, 1H), 2.60 (t, J = 5.7 Hz, 2H), 4.06 (t, J = 5.7 Hz, 2H), 6.8−7.0 (m, 4H), 7.12 (dd, J = 8.5, 2.0 Hz, 1H), 7.25 (m, 2H), 7.33 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 8.7 Hz, 2H), 9.82 (br s, 1H); HRMS (FAB) *m/e* calcd for $C_{28}H_{27}ClNO_4S$ (MH^+) 508.1349, found 508.1344. Anal. ($C_{28}H_{27}ClNO_4S$) C,H,N.

[2-(3-Fluoro-4-hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11r). The title compound was prepared in 60% yield from **10r** by a method similar to that described for **5g**: ^{1}H NMR (MeOD-d_4) δ 1.62 (m, 2H), 1.80 (m, 4H), 3.11 (m, 4H), 3.34 (t, J = 6.0 Hz, 2H), 4.32 (t, J = 6.0 Hz, 2H), 4.86 (br s, 2H), 6.75 (t, J = 8.6 Hz, 1H), 6.88 (dd, J = 8.8, 2.2 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.9−7.1 (m, 3H), 7.27 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{28}H_{27}FNO_4S$ (MH^+) 492.1645, found 492.1642. Anal. ($C_{28}H_{26}FNO_4S\cdot0.75H_2O$) C,H,N.

[2-(3,5-Dimethyl-4-hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (11s). The title compound was prepared in 49% yield from **10s** by a method similar to that described for **5g**: ^{1}H NMR δ 1.48 (m, 2H), 1.66 (m, 4H), 2.11 (s, 6H), 2.58 (m, 4H), 2.80 (t, J = 5.4 Hz, 2H), 4.09 (t, J = 5.4 Hz, 2H), 6.60 (d, J = 8.7 Hz, 2H), 6.79 (dd, J = 8.7, 2.0 Hz, 1H), 6.96 (s, 2H), 7.19 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H); HRMS (FAB) *m/e* calcd for $C_{30}H_{32}NO_4S$ (MH^+) 502.2052, found 502.2054. Anal. ($C_{30}H_{31}NO_4S\cdot1.75H_2O$) C,H,N.

[2-(1-Naphthyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12a). The title compound was prepared in 58% yield from **7a** and 1-naphthylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.46 (m, 2H), 1.60 (m, 4H), 2.47 (m, 4H), 2.68 (t, J = 5.9 Hz, 2H), 3.92 (s, 3H), 3.96 (t, J = 5.9 Hz, 2H), 6.47 (d, J = 8.8 Hz, 2H), 7.06 (dd, J = 8.9, 2.3 Hz, 1H), 7.2−7.5 (m, 5H), 7.54 (d, J = 8.8 Hz, 2H), 7.6−7.8 (m, 2H), 7.79 (d, J = 8.9 Hz, 1H), 8.08 (m, 1H); MS (FD) *m/e* 521 (M^+).

[2-(2-Naphthyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12b). The title compound was prepared in 75% yield from **7a** and 2-naphthylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.43 (m, 2H), 1.59 (m, 4H), 2.45 (m, 4H), 2.70 (t, J = 6.0 Hz, 2H), 3.91 (s, 3H), 4.02 (t, J = 6.0 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 7.01 (dd, J = 8.8, 2.1 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.45 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.6−7.8 (m, 4H), 7.82 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 1.6 Hz, 1H); MS (FD) *m/e* 521 (M^+). Anal. ($C_{33}H_{31}NO_3S$) C,H,N.

[2-(4-Methoxy-1-naphthyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12c). The title compound was prepared in 47% yield from **7a** and 4-methoxy-1-naphthylmagnesium bromide (prepared from 4-methoxy-1-bromonaphthalene[48]) by a method similar to that described for **8b**: ^{1}H NMR (acetone-d_6) δ 1.3−1.5 (m, 2H), 1.5−1.7 (m, 4H), 2.41 (m, 4H), 2.59 (t, J = 6.0 Hz, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 4.00 (t, J = 6.0 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.0 Hz, 1H), 7.09 (dd, J = 8.8, 2.2 Hz, 1H), 7.4−7.6 (m, 5H), 7.69 (d, J = 8.8 Hz, 2H), 8.04 (dd, J = 7.9, 1.6 Hz, 1H), 8.17 (dd, J = 7.7, 1.9 Hz, 1H); MS (FD) *m/e* 551 (M^+). Anal. ($C_{34}H_{33}NO_4S$) C,H,N.

[2-(2-Thienyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12d). The title compound was prepared in 72% yield from **7a** and 2-thienylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR (acetone-d_6) δ 1.3−1.4 (m, 2H), 1.4−1.6 (m, 4H), 2.42 (m, 4H), 2.66 (t, J = 5.8 Hz, 2H), 3.88 (s, 3H), 4.12 (t, J = 5.9 Hz, 2H), 6.96 (m, 4H), 7.16 (d, J = 2.5 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.43 (d, J = 5.0 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 477 (M^+). Anal. ($C_{27}H_{27}NO_3S_2$) C,H,N.

[2-(3-Thienyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12e). The title compound was prepared in 81% yield from **7a** and 3-thienylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR (acetone-d_6) δ 1.3−1.4 (m, 2H), 1.4−1.6 (m, 4H), 2.43 (m, 4H), 2.66 (t, J = 5.8 Hz, 2H), 3.88 (s, 3H), 4.12 (t, J = 5.9 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.97 (dd, J = 8.9, 2.3 Hz, 1H), 7.12 (dd, J = 5.1, 1.0 Hz, 1H), 7.40 (m, 2H), 7.53 (m, 2H), 7.75 (d, J = 8.8 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{27}H_{28}NO_3S_2$ (MH^+) 478.1511, found 478.1521.

(2-Methyl-6-methoxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12f). The title compound was prepared in 52% yield from **7a** and methylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.46 (m, 2H), 1.62 (m, 4H), 2.47 (s, 3H), 2.52 (m, 4H), 2.81 (t, J = 6.0 Hz, 2H), 3.87 (s, 3H), 4.18 (t, J = 6.0 Hz, 2H), 6.90 (dd, J = 8.9, 2.3 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 2.3 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 409 (M^+). Anal. ($C_{24}H_{27}NO_3S$) C,H,N.

(2-Ethyl-6-methoxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12g). The title compound was prepared in 58% yield from **7a** and ethylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.27 (t, J = 7.5 Hz, 3H), 1.44 (m, 2H), 1.60 (m, 4H), 2.50 (m, 4H), 2.78 (t, J = 5.9 Hz, 2H), 2.83 (q, J = 7.5 Hz, 2H), 3.83 (s, 3H), 4.16 (t, J = 5.9 Hz, 2H), 6.87 (dd, J = 8.9, 2.2 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.81 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 424 (M^+). Anal. ($C_{25}H_{29}NO_3S$) C,H,N.

[2-(2-Propyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12h). The title compound was prepared in 57% yield from **7a** and 2-propylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.32 (d, J = 6.8 Hz, 6H), 1.52 (m, 2H), 1.75 (m, 4H), 2.72 (m, 4H), 2.97 (m, 2H), 3.35 (m, 1H), 3.87 (s, 3H), 4.32 (m, 2H), 6.88 (dd, J = 8.9, 2.3 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 7.28 (s, 1H), 7.29 (d, J = 2.3 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 437 (M^+).

(2-Cyclopentyl-6-methoxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12i). The title compound was prepared in 60% yield from **7a** and cyclopentylmagnesium bromide by a method similar to that described for **8b**: ^{1}H NMR δ 1.4−1.8 (m, 12H), 2.04 (m, 2H), 2.53 (m, 4H), 2.80 (t, J = 5.9 Hz, 2H), 3.35 (quintet, J = 8.3 Hz, 1H), 3.85 (s, 3H), 4.18 (t, J = 5.9 Hz, 2H), 6.87 (dd, J = 8.8, 2.2 Hz,

1H), 6.93 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 463 (M^+).

(2-Cyclohexyl-6-methoxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12j). The title compound was prepared in 65% yield from **7a** and cyclohexylmagnesium chloride by a method similar to that described for **8b**: ^{1}H NMR δ 1.23 (m, 3H), 1.44 (m, 5H), 1.59 (m, 4H), 1.74 (m, 2H), 1.99 (d, J = 12.3 Hz, 2H), 2.51 (m, 4H), 2.79 (t, J = 6.0 Hz, 2H), 2.99 (m, 1H), 3.83 (s, 3H), 4.17 (t, J = 6.0 Hz, 2H), 6.85 (dd, J = 8.9, 2.3 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.9 Hz, 1H), 7.27 (d, J = 2.3 Hz, 1H), 7.81 (d, J = 8.8 Hz, 2H); MS (FD) 478 (MH^+). Anal. ($C_{29}H_{35}NO_3S$) C,H,N.

[2-*trans*-[4-[(*tert*-Butyldimethylsilyl)oxy]cyclohexyl]-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone (12k). The title compound was prepared in 53% yield from **7a** and *trans*-4-(TBSoxy)cyclohexylmagnesium bromide[13] by a method similar to that described for **8b**: ^{1}H NMR δ 0.54 (s, 6H), 0.88 (s, 9H), 1.2−1.8 (m, 10H), 1.8−2.1 (m, 4H), 2.53 (m, 4H), 2.81 (m, 2H), 2.92 (m, 1H), 3.61 (m, 1H), 3.84 (s, 3H), 4.18 (m, 2H), 6.87 (m, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.2−7.3 (m, 2H), 7.81 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 607 (M^+). Anal. ($C_{35}H_{49}NO_4SSi$) C,H,N.

[2-[(4-Methoxyphenyl)methyl]-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (12l). The title compound was prepared in 29% yield from **7a** and 4-methoxybenzylmagnesium chloride by a method similar to that described for **8b** as a tan crystalline solid, mp 126 °C: ^{1}H NMR (acetone-d_6) δ 1.3−1.5 (m, 2H), 1.5−1.7 (m, 4H), 2.4−2.6 (m, 4H), 2.77 (m, 2H), 3.73 (s, 3H), 3.83 (s, 3H), 4.08 (s, 2H), 4.23 (m, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.90 (dd, J = 8.8, 2.5 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.9 Hz, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.80 (d, J = 8.7 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{31}H_{34}NO_4S$ (MH^+) 516.2208, found 516.2200. Anal. ($C_{31}H_{33}NO_4S\cdot0.5H_2O$) C,H,N.

[2-(1-Naphthyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13a). The title compound was prepared in 53% yield from **12a** by a method similar to that described for **5g**: ^{1}H NMR δ 1.46 (m, 2H), 1.65 (m, 4H), 2.54 (m, 4H), 2.73 (t, J = 5.4 Hz, 2H), 3.96 (t, J = 5.4 Hz, 2H), 6.37 (d, J = 8.7 Hz, 2H), 6.88 (dd, J = 8.8, 1.9 Hz, 1H), 7.2−7.3 (m, 2H), 7.3−7.5 (m, 5H), 7.6−7.7 (m, 3H), 8.04 (m, 1H), 8.28 (br s, 1H); MS (FD) *m/e* 508 (MH^+). Anal. ($C_{32}H_{29}NO_3S$) C,H,N.

[2-(2-Naphthyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13b). The title compound was prepared in 98% yield from **12b** by a method similar to that described for **5g**: ^{1}H NMR δ 1.46 (m, 2H), 1.66 (m, 4H), 2.58 (m, 4H), 2.77 (t, J = 5.5 Hz, 2H), 4.04 (t, J = 5.5 Hz, 2H), 6.54 (d, J = 8.9 Hz, 2H), 6.75 (dd, J = 8.8, 2.2 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.4−7.5 (m, 4H), 7.64 (d, J = 8.6 Hz, 1H), 7.7−7.8 (m, 4H), 7.86 (d, J = 1.5 Hz, 1H); MS (FD) *m/e* 507 (M^+). Anal. ($C_{32}H_{29}NO_3S$) C,H,N.

[2-(4-Hydroxy-1-naphthyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13c). The title compound was prepared in 71% yield from **12c** by a method similar to that described for **5g**: ^{1}H NMR (DMF-d_7) δ 1.3−1.4 (m, 2H), 1.4−1.6 (m, 4H), 2.38 (m, 4H), 2.59 (t, J = 5.8 Hz, 2H), 4.01 (t, J = 5.8 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 7.8 Hz, 1H), 7.04 (dd, J = 8.7, 2.2 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.4−7.6 (m, 4H), 7.66 (d, J = 8.7 Hz, 2H), 8.04 (m, 1H), 8.18 (d, J = 7.9 Hz, 1H), 10.1 (br s, 2H); HRMS (FAB) *m/e* calcd for $C_{32}H_{30}NO_4S$ (MH^+) 524.1896, found 524.1907. Anal. ($C_{32}H_{29}NO_4S\cdot0.5H_2O$) C,H,N.

[2-(2-Thienyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13d). The title compound was prepared in 95% yield from **12d** by a method similar to that described for **5g**: ^{1}H NMR (acetone-d_6) δ 1.3−1.4 (m, 2H), 1.5−1.6 (m, 4H), 2.43 (m, 4H), 2.66 (t, J = 5.9 Hz, 2H), 4.12 (t, J = 5.9 Hz, 2H), 6.9−7.0 (m, 4H), 7.13 (m, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.38 (m, 2H), 7.77 (m, 2H); MS (FD) *m/e* 463 (M^+). Anal. ($C_{26}H_{25}NO_3S_2$) C,H,N.

[2-(3-Thienyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13e). The title compound was prepared from **12e** by a method similar to that described for **5g**. Crystallization from methylene chloride/ethyl acetate provided a 68% yield of the title compound as yellow crystals, mp 121−123 °C: ^{1}H NMR (CD_3OD) δ 1.4−1.5 (m, 2H), 1.5−1.7 (m, 4H), 2.49 (m, 4H), 2.72 (t, J = 5.5 Hz, 2H), 4.10 (t, J = 5.5 Hz, 2H), 6.86 (m, 3H), 7.05 (dd, J = 5.1, 1.1 Hz, 1H), 7.2−7.4 (m, 4H), 7.73 (d, J = 8.8 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{26}H_{26}NO_3S_2$ (MH^+) 464.1354, found 464.1368. Anal. ($C_{26}H_{25}NO_3S_2\cdot0.5H_2O$) C,H,N.

(2-Methyl-6-hydroxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13f). The title compound was prepared in 72% yield from **12f** by a method similar to that described for **5g**: ^{1}H NMR δ 1.54 (m, 2H), 1.77 (m, 4H), 2.42 (s, 3H), 2.50 (s, 1H), 2.77 (m, 4H), 3.00 (t, J = 5.2 Hz, 2H), 3.99 (t, J = 5.2 Hz, 2H), 6.82 (m, 3H), 7.2−7.3 (m, 2H), 7.75 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 396 (MH^+). Anal. ($C_{23}H_{25}NO_3S$) C,H,N.

(2-Ethyl-6-hydroxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13g). The title compound was prepared in 81% yield from **12g** by a method similar to that described for **5g**: ^{1}H NMR δ 1.23 (t, J = 7.5 Hz, 3H), 1.46 (m, 2H), 1.66 (m, 4H), 2.60 (m, 4H), 2.79 (q, J = 7.5 Hz, 2H), 2.84 (t, J = 5.7 Hz, 2H), 4.17 (t, J = 5.7 Hz, 2H), 6.73 (dd, J = 8.8, 2.2 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 2.2 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 410 (MH^+). Anal. ($C_{24}H_{27}NO_3S$) C,H,N.

[2-(2-Propyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13h). The title compound was prepared in 84% yield from **12h** by a method similar to that described for **5g**: ^{1}H NMR δ 1.29 (d, J = 6.8 Hz, 6H), 1.51 (m, 2H), 1.72 (m, 4H), 2.68 (m, 4H), 2.93 (t, J = 5.4 Hz, 2H), 3.32 (septet, J = 6.8 Hz, 1H), 4.24 (t, J = 5.4 Hz, 2H), 6.75 (dd, J = 8.7, 2.2 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 2.2 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 424 (MH^+). Anal. ($C_{25}H_{29}NO_3S$) C,H,N.

(2-Cyclopentyl-6-hydroxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13i). The title compound was prepared in 86% yield from **12i** by a method similar to that described for **5g**: ^{1}H NMR δ 1.4−1.8 (m, 12H), 2.03 (m, 2H), 2.60 (m, 4H), 2.85 (t, J = 5.7 Hz, 2H), 3.30 (quintet, J = 8.2 Hz, 1H), 4.17 (t, J = 5.7 Hz, 2H), 6.70 (dd, J = 8.8, 2.2 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 449 (M^+). Anal. ($C_{27}H_{31}NO_3S$) C,H,N.

(2-Cyclohexyl-6-hydroxybenzo[*b*]thien-3-yl)[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13j). The title compound was prepared in 76% yield from **12j** by a method similar to that described for **5g**: ^{1}H NMR δ 1.22 (m, 4H), 1.47 (m, 4H), 1.68 (m, 7H), 1.96 (m, 2H), 2.63 (m, 4H), 2.88 (t, J = 5.4 Hz, 2H), 2.96 (m, 1H), 4.20 (t, J = 5.4 Hz, 2H), 6.71 (dd, J = 8.7, 1.9 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 1.9 Hz, 1H), 7.74 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 463 (M^+). Anal. ($C_{28}H_{33}NO_3S$) C,H,N.

[2-*trans*-(4-Hydroxycyclohexyl)-6-hydroxybenzo[*b*]-thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13k). The title compound was prepared in 84% yield from **12k** by a method similar to that described for **5g**: ^{1}H NMR (DMSO-d_6) δ 1.0−1.2 (m, 2H), 1.3−1.6 (m, 8H), 1.85 (m, 4H), 2.46 (m, 4H), 2.70 (t, J = 5.7 Hz, 2H), 2.77 (m, 1H), 3.42 (m, 1H), 4.17 (t, J = 5.7 Hz, 2H), 4.57 (d, J = 4.0 Hz, 1H), 6.79 (dd, J = 8.8, 2.2 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 9.68 (br s, 1H); MS (FD) *m/e* 480 (MH^+). Anal. ($C_{28}N_{33}NO_4S$) C,H,N.

[2-[(4-Hydroxyphenyl)methyl]-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (13l). The title compound was prepared in 86% yield from **10g** by a method similar to that described for **9d**. Residual EtOAc was removed via azeotropic distillation with CCl_4: ^{1}H NMR (acetone-d_6) δ 1.3−1.5 (m, 2H), 1.5−1.7 (m, 4H), 2.4−2.6 (m, 4H), 2.73 (t, J = 5.8 Hz, 2H), 4.01 (s, 2H), 4.18 (t, J = 5.8 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 6.84 (dd, J = 8.8, 2.1 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.79 (d, J = 8.7 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 24.8, 26.4, 35.1, 55.5, 58.3, 66.9, 107.9, 115.2, 115.4, 116.0, 116.1, 124.6, 130.5, 131.2, 132.0, 132.6, 132.8, 140.7, 146.2, 155.8, 156.9, 164.0, 192.3; IR ($CHCl_3$) 3599,

3309, 1644, 1599 cm^{-1}; HRMS (FAB) *m/e* calcd for $C_{29}H_{30}NO_4S$ (MH^+) 488.1896, found 488.1857. Anal. ($C_{29}H_{29}NO_4S \cdot 0.5CCl_4$) C,H,N.

[2-(Trimethylstannyl)-6-(methoxyoxy)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (14). Lithium metal (7.1 g, 1.02 mol) was suspended in THF (100 mL) and treated with trimethylstannyl chloride (1.0 M in THF, 103 mL, 103 mmol) dropwise at 0 °C. After warming to room temperature, the mixture was allowed to stir overnight.

An aliquot of the Me_3SnLi solution prepared above (0.507 M in THF, 19.4 mL, 9.85 mmol) was added dropwise to a solution of **7a** (2.4 g, 5.47 mmol) in THF (48 mL) at −78 °C. The mixture was allowed to slowly warm to room temperature over 5 h and the reaction quenched rapidly by pouring into a mixture of ice-cold saturated NH_4Cl (100 mL) and CH_2Cl_2 (100 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (100 mL), dried (Na_2SO_4), and concentrated to provide 3.1 g of the crude title compound as a brown oil: ^{1}H NMR δ 0.34 (s, 9H), 1.4−1.6 (m, 2H), 1.6−1.8 (m, 4H), 2.6−2.8 (m, 4H), 2.86 (m, 2H), 3.86 (s, 3H), 4.27 (m, 2H), 6.84 (dd, J = 8.9, 2.3 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.25 (m, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H).

[2-(4-Nitrophenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (15a). A solution of **14** (2.5 g, 4.5 mmol), 1-bromo-4-nitrobenzene (2.9 g, 15.0 mmol), and $Pd(PPh_3)_4$ (0.41 g, 0.4 mmol) in DMF (20 mL) was heated at 100 °C overnight. After cooling to room temperature, the mixture was concentrated and the residue was purified via flash chromatography (1:1 hexane:EtOAc, 0−1% MeOH) to provide 0.35 g (15%) of the title compound as a bright yellow solid: ^{1}H NMR δ 1.43 (m, 2H), 1.57 (m, 4H), 2.46 (m, 4H), 2.72 (t, J = 6.0 Hz, 2H), 3.89 (s, 3H), 4.08 (t, J = 6.0 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 6.98 (dd, J = 9.0, 2.3 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 8.09 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 516 (M^+). Anal. ($C_{29}H_{28}N_2O_5S$) C,H,N.

[2-(4-Pyridyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (15b). The title compound was prepared in 54% yield from **14** and 4-bromopyridine by a method similar to that described for **15a**: ^{1}H NMR (acetone-d_6) δ 1.3−1.4 (m, 2H), 1.4−1.6 (m, 4H), 2.04 (m, 2H), 2.65 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 4.10 (t, J = 6.0 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.04 (m, 1H), 7.36 (dd, J = 4.5, 1.5 Hz, 2H), 7.4−7.8 (m, 4H), 8.48 (m, 2H); MS (FD) *m/e* 472 (M^+).

[2-(*N*-Oxo-4-pyridyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (15c). The title compound was prepared in 41% yield from **14** and 4-bromopyridine *N*-oxide by a method similar to that described for **15a**: ^{1}H NMR (acetone-d_6) δ 1.3−1.5 (m, 2H), 1.4−1.6 (m, 4H), 2.04 (m, 4H), 2.67 (t, J = 5.9 Hz, 2H), 3.91 (s, 3H), 4.13 (t, J = 5.9 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 7.04 (dd, J = 8.9, 2.2 Hz, 1H), 7.38 (d, J = 7.1 Hz, 2H), 7.48 (d, J = 9.2 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 7.0 Hz, 2H); HRMS (FAB) *m/e* calcd for $C_{28}H_{29}N_2O_4S$ ($MH)^+$ 489.1848, found 489.1849.

[2-(4-Carbethoxyphenyl)-6-methoxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (15d). The title compound was prepared in 87% yield from **14** and ethyl 4-bromobenzoate by a method similar to that described for **15a**: ^{1}H NMR (acetone-d_7) δ 1.34 (t, J = 7.7 Hz, 3H), 1.4−1.6 (m, 2H), 1.6−1.8 (m, 4H), 2.52 (m, 4H), 2.77 (t, J = 5.8 Hz, 2H), 3.88 (s, 3H), 4.11 (t, J = 5.8 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 6.76 (d, J = 9.7 Hz, 2H), 6.99 (dd, J = 9.7, 2.9 Hz, 1H), 7.34 (d, J = 2.9 Hz, 1H), 7.5−7.7 (m, 3H), 7.75 (d, J = 9.7 Hz, 2H), 7.90 (d, J = 9.7 Hz, 2H).

[2-(4-Nitrophenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (16a). The title compound was prepared in 56% yield from **15a** by a method similar to that described for **9d**: ^{1}H NMR δ 1.49 (m, 2H), 1.67 (m, 4H), 2.61 (m, 4H), 2.84 (t, J = 5.4 Hz, 2H), 4.13 (t, J = 5.4 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.80 (dd, J = 8.8, 2.1 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H); HRMS (FD) *m/e* calcd for $C_{28}H_{27}N_2O_5S$ (MH^+) 503.1642, found 503.1641. Anal. ($C_{28}H_{26}N_2O_5S \cdot 0.25H_2O$) C,H,N.

[2-(4-Pyridyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (16b). The title compound was prepared in 92% yield from **15b** by a method similar to that described for **5g**: ^{1}H NMR (acetone-d_7) δ 1.3−1.4 (m, 2H), 1.4−1.6 (m, 4H), 2.45 (m, 4H), 2.68 (t, J = 5.9 Hz, 2H), 4.12 (t, J = 5.9 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.97 (dd, J = 8.8, 2.3 Hz, 1H), 7.35 (m, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.74 (d, J = 8.7 Hz, 2H), 8.47 (dd, J = 4.5, 1.5 Hz, 2H); ^{13}C NMR δ 23.74, 25.18, 54.91, 57.51, 65.39, 107.42, 114.42, 116.18, 122.97, 124.71, 130.09, 132.25, 132.75, 134.19, 136.53, 140.89, 141.54, 149.52, 156.21, 163.22, 192.84; HRMS (FD) *m/e* calcd for $C_{27}H_{27}N_2O_3S$ ($MH)^+$ 459.1742, found 459.1746. Anal. ($C_{27}H_{26}N_2O_3S \cdot 2.25H_2O$) C,N; H: calcd, 6.16; found, 5.39.

[2-(*N*-Oxo-4-pyridyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (16c). The title compound was prepared in 97% yield from **15c** by a method similar to that described for **5g**: ^{1}H NMR (acetone-d_7) δ 1.3−1.4 (m, 2H), 1.4−1.6 (m, 4H), 2.43 (m, 4H), 2.66 (t, J = 6.0 Hz, 2H), 4.12 (t, J = 6.0 Hz, 2H), 6.95 (m, 3H), 7.36 (d, J = 7.1 Hz, 2H), 7.44 (m, 2H), 7.75 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 7.1 Hz, 2H); MS (FD) *m/e* 475 ($MH)^+$. Anal. ($C_{27}H_{26}N_2O_4S$) C,H,N.

[2-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (17) and [2-(4-Hydroxyphenyl)-6-[(*tert*-butyldimethylsilyl)oxy]benzothien-3-yl][4-[2-(1-piperidinyl)-ethoxy]phenyl]methanone (18). A solution of raloxifene (10.0 g, 21.1 mmol) and DMAP (6.0 g, 49.1 mmol) in 6:1 THF:DMF (700 mL) was stirred at room temperature for 1 h. After cooling to 0 °C, TBSCl (2.9 g, 19.3 mmol) was added slowly and the mixture was allowed to warm to room temperature. After 72 h, the mixture was washed with saturated NH_4Cl (500 mL), water (500 mL), and brine (500 mL), and the organic extract was filtered and concentrated. The crude product was triturated with CH_2Cl_2 and the resulting mixture allowed to stand at room temperature for 3 h and then filtered to remove unreacted starting material. To the filtrate was added silica gel (500 g), and the slurry was carefully concentrated. Purification by flash chromatography (silica gel, $CHCl_3$/0−10% MeOH gradient) provided 5.1 g of **17** (41%) and 4.8 g of **18** (38%), both as yellow crystalline solids. **17**: ^{1}H NMR δ 0.12 (s, 6H), 0.92 (s, 9H), 1.46 (m, 2H), 1.67 (m, 4H), 2.56 (m, 5H), 2.79 (t, J = 5.6 Hz, 2H), 4.07 (t, J = 5.7 Hz, 2H), 6.55 (d, J = 8.9 Hz, 2H), 6.66 (d, J = 8.5 Hz, 2H), 6.77 (dd, J = 8.7, 2.2 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 7.20 (d, J = 8.6 Hz, 3H), 7.44 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.9 Hz, 2H); MS (FD) *m/e* 587 (M^+). Anal. ($C_{34}H_{41}NO_4SSi$) C,H,N.

18: ^{1}H NMR δ 0.23 (s, 6H), 1.00 (s, 9H), 1.47 (m, 2H), 1.64 (m, 4H), 2.56 (m, 4H), 2.77 (t, J = 5.6 Hz, 2H), 4.08 (t, J = 5.6 Hz, 2H), 6.58 (d, J = 6.9 Hz, 2H), 6.64 (d, J = 7.0 Hz, 2H), 6.89 (dd, J = 8.7, 2.2 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 2.3 Hz, 1H), 7.42 (s, 1H), 7.60 (d, J = 8.9 Hz, 2H); MS (FD) *m/e* 587 (M^+). Anal. ($C_{34}H_{41}NO_4SSi$) C,H,N.

[2-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-6-[[(trifluoromethyl)sulfonyl]oxy]benzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (20). A solution of **17** (10 g, 17.5 mmol) in DCE (100 mL) was cooled to 5 °C and treated with Et_3N (5 mL, 3.6 g, 35.9 mmol, 2.0 equiv) followed by *N*-phenyltrifluoromethanesulfonimide (7 g, 19.5 mmol, 1.1 equiv). The resultant solution was allowed to warm to room temperature overnight, filtered to remove insolubles, and concentrated. Purification via chromatography (CH_2Cl_2) afforded 11 g (88%) of the title compound as an off-white foam: ^{1}H NMR δ 0.05 (s, 6H), 0.85 (s, 9H), 1.35 (m, 2H), 1.55 (m, 4H), 2.40 (m, 4H), 2.65 (t, J = 7 Hz, 2H), 4.00 (t, J = 7 Hz, 2H), 6.65 (m, 4H), 7.20 (m, 3H), 7.65 (d, J = 10 Hz, 2H), 7.75 (m, 2H); MS (FD) *m/e* 720 (MH^+).

[2-[4-[[(Trifluoromethyl)sulfonyl]oxy]phenyl]-6-[(*tert*-butyldimethylsilyl)oxy]benzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (21). The title compound was prepared in 88% yield from **18** by a method similar to that described for **20**: ^{1}H NMR δ 0.24 (s, 6H), 1.02 (s, 9H), 1.44 (m, 2H), 1.58 (m, 4H), 2.48 (m, 4H), 2.73 (t, J = 6.0 Hz,

2H), 4.08 (t, J = 6.0 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.92 (dd, J = 8.8, 2.2 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H); MS (FD) *m/e* 719 (M^+). Anal. ($C_{35}H_{40}F_3NO_6S_2Si$) C,H,N.

[2-(4-Hydroxyphenyl)-6-(methoxycarbonyl)benzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (22a). A solution of **20** (1 g, 1.4 mmol), Et_3N (5 mL), MeOH (5 mL), and 1,3-bis(diphenylphosphino)propane (58 mg, 0.14 mmol) in anhydrous DMF (15 mL) was purged with electronic grade CO at room temperature for 15 min. Palladium(II) acetate (31 mg, 0.14 mmol) was then added, and the mixture was heated to 75 °C for 6 h under a CO atmosphere. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was dissolved in THF (25 mL), filtered, and reconcentrated. The crude product was then partitioned between EtOAc (100 mL) and 1 N HCl (100 mL) and stirred at room temperature for 2 h. The solution was then brought to pH 4−5 with HOAc/OAc^- buffer, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified via chromatography (CH_2Cl_2, 0−15% MeOH) to provide 555 mg (77%) of the title compound, which was converted to its HCl salt (mp 128 °C) using MeOH/anhydrous HCl: ^{1}H NMR (DMSO-d_6) δ 1.3−1.9 (m, 6H), 2.9−3.1 (m, 4H), 3.45 (m, 2H), 3.95 (s, 3H), 4.35 (m, 2H), 6.80 (d, J = 8 Hz, 2H), 7.05 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H), 7.65 (d, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 2H), 8.00 (d, J = 8 Hz, 1H), 8.80 (s, 1H), 10.00 (s, 1H); MS (FD) *m/e* 515 (M^+). Anal. ($C_{30}H_{29}NO_5S\cdot HCl\cdot 1.5H_2O$) C,H,N.

[2-(4-Hydroxyphenyl)-6-carboxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (22c). A solution of **22a** (2 g, 4.0 mmol) and LiOH (0.2 g, 8.0 mmol) in a mixture of THF (100 mL) and H_2O (10 mL) was heated at reflux for 18 h. After the solution was allowed to cool to room temperature, the solvents were removed *in vacuo*, and the residue was partitioned between EtOAc (300 mL) and 1 N HCl (300 mL). The precipitate was filtered, washed with acetone, and dried to afford 0.7 g (37%) of the HCl salt of the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.3−1.5 (m, 2H), 1.5−1.6 (m, 4H), 2.4−2.6 (m, 4H), 2.7−2.8 (m, 2H), 4.1−4.2 (m, 2H), 6.75 (d, J = 8 Hz, 2H), 6.95 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 2H), 7.95 (d, J = 8 Hz, 1H), 8.65 (s, 1H); MS (FD) *m/e* 501 (M^+). Anal. ($C_{29}H_{27}NO_5S\cdot HCl\cdot 1.5H_2O$) C,H,N.

[2-(4-Hydroxyphenyl)-6-carbamoylbenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (22d). A solution of **22a** (500 mg, 0.97 mmol) and Et_3N (1 mL) in THF (50 mL) was treated with TBSCl (300 mg, 1.99 mmol), and the resultant mixture was stirred overnight at room temperature. The solvents were removed *in vacuo*, and the remnant was suspended in toluene (25 mL) and filtered to remove unreacted TBSCl. The filtrate was concentrated *in vacuo*, and the toluene extraction was repeated twice to afford approximately 700 mg of crude silyl ether which was used without purification.

The crude silyl ether generated above was dissolved in toluene (10 mL), treated with a 0.32 M solution of MeAl(Cl)-NH_2 in toluene (15 mL, 4.8 mmol), and stirred overnight at room temperature.[22] The solvent was removed *in vacuo*, and the residue was suspended in THF:1 N HCl (9:1, 50 mL) and heated at reflux for 5 h. After concentration, the residue was purified via chromatography ($CHCl_3$, 0−15% MeOH) to afford 150 mg (31%) of the title compound as a yellow oil. The hydrochloride salt was subsequently prepared by treatment with THF/concentrated HCl and trituration of the resultant material with Et_2O: ^{1}H NMR (free base, CD_3OD) δ 1.5−1.7 (m, 2H), 1.7−1.8 (m, 4H), 2.80−3.0 (m, 4H), 3.10 (t, J = 5 Hz, 2H), 4.25 (t, J = 5 Hz, 2H), 6.70 (d, J = 8 Hz, 2H), 6.90 (d, J = 10 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.6−7.8 (m, 3H), 7.90 (d, J = 8 Hz, 1H), 8.50 (s, 1H); HRMS (FAB) *m/e* calcd for $C_{29}H_{29}N_2O_4S$ (MH^+) 501.1848, found 501.1855. Anal. ($C_{29}H_{28}N_2O_4S\cdot HCl\cdot 2.25H_2O$) C; H: calcd, 5.85; found, 5.31. N: calcd, 4.85; found, 4.37.

[2-(4-Hydroxyphenyl)-6-acetylbenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (22g). A solution of **20** (1.0 g, 1.4 mmol), butyl vinyl ether (1.1 mL, 7.7 mmol), Et_3N (1 mL), 1,3-bis(diphenylphosphino)propane (58 mg, 0.14 mmol), and $Pd(OAc)_2$ (31 mg, 0.14 mmol) in DMF (15 mL) was heated at 75 °C for 5 h. After cooling to room temperature, 5 N HCl (15 mL) was added and the solution which resulted was stirred overnight. Workup similar to that described for **22a** afforded 430 mg (62%) of the title compound as an orange solid, mp 97−100 °C: ^{1}H NMR (DMSO-d_6) δ 1.40 (m, 2H), 1.80 (m, 4H), 2.70 (s, 3H), 3.35 (m, 4H), 3.45 (m, 2H), 4.40 (m, 2H), 6.75 (d, J = 8 Hz, 2H), 7.00 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 1H), 8.80 (s, 1H), 10.00 (s, 1H); MS (FD) *m/e* 499 (M^+). Anal. ($C_{30}H_{29}NO_4S\cdot H_2O$) C,H,N.

[2-(4-Hydroxyphenyl)-6-(diethylphosphonyl)benzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (22h). A solution of **20** (2.0 g, 2.8 mmol), diethyl phosphite (0.58 g, 0.54 mL, 4.2 mmol), and Et_3N (5 mL) in CH_3CN (15 mL) was degassed via N_2 stream for 15 min, treated with $Pd(PPh_3)_4$, and heated at 75 °C for 36 h. Workup similar to that described for **22a** afforded 800 mg (49%) of the title compound as a yellow solid, mp 75−78 °C: ^{1}H NMR (DMSO-d_6) δ 1.25 (t, J = 7 Hz, 6H), 1.40 (m, 2H), 1.50 (m, 4H), 2.45 (m, 4H), 2.70 (t, J = 5 Hz, 2H), 4.0−4.3 (m, 6H), 6.80 (d, J = 8 Hz, 2H), 7.00 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H), 7.6−7.7 (m, 2H), 7.75 (d, J = 8 Hz, 2H), 8.55 (d, J = 15 Hz, 1H), 10.05 (br s, 1H); MS (FD) *m/e* 594 (MH^+). Anal. ($C_{32}H_{36}NO_6PS\cdot 1.5H_2O$) C,H,N.

[2-(4-Hydroxyphenyl)-6-ethynylbenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (22i). A solution of **20** (2.0 g, 2.8 mmol), (trimethylsilyl)acetylene (0.68 g, 1.0 mL, 6.9 mmol), 1,3-bis(diphenylphosphino)propane (116 mg, 0.28 mmol), and Et_3N (5 mL) in DMF (20 mL) was degassed via N_2 stream for 15 min, treated with $Pd(OAc)_2$ (62 mg, 0.24 mmol), and heated at 75 °C for 10 h. Workup similar to that described for **22a** afforded 1.5 g of a dark yellow foam.

The crude product was then dissolved in THF (100 mL) and treated with TBAF (0.5 g, 2.7 mmol) and the mixture stirred overnight. The reaction mixture was concentrated *in vacuo*, and the residue was purified via chromatography ($CHCl_3$, 0−20% EtOH) to afford 300 mg (22%) of the title compound as a beige solid, mp 97−100 °C: ^{1}H NMR δ 1.60 (m, 2H), 1.80 (m, 4H), 2.80 (m, 4H), 3.00 (t, J = 5 Hz, 2H), 3.25 (s, 1H), 4.25 (t, J = 5 Hz, 2H), 6.7−6.8 (m, 4H), 7.25 (d, J = 8 Hz, 2H), 7.60 (d, J = 10 Hz, 1H), 7.75 (d, J = 10 Hz, 2H), 7.85 (d, J = 10 Hz, 1H), 8.10 (s, 1H); MS (FD) *m/e* 481 (M^+). Anal. ($C_{30}H_{27}NO_3S\cdot H_2O$) C,H,N.

[2-[4-(Methoxycarbonyl)phenyl]-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23a). Carbon monoxide was bubbled through solutions of **21** (10.2 g, 14 mmol) in DMF (45 mL) and of $Pd(OAc)_2$ (0.10 g, 0.46 mmol), 1,3-bis(diphenylphosphino)propane (0.17 g, 0.41 mmol), MeOH (22.5 mL, 560 mmol), and Et_3N (4.1 mL, 29 mmol) in DMF (45 mL) for 15 min. The solutions were then combined and heated to 70 °C under a CO atmosphere for 4.5 h. The mixture was then diluted with saturated $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), concentrated, and purified by chromatography (1:1 hexane:EtOAc, 0−10% MeOH) to give 1.9 g (27%) of the title compound as a bright yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.36 (m, 2H), 1.45 (m, 4H), 2.37 (m, 4H), 2.59 (t, J = 5.8 Hz, 2H), 3.82 (s, 3H), 4.07 (t, J = 5.8 Hz, 2H), 6.92 (m, 3H), 7.34 (d, J = 8.9 Hz, 1H), 7.43 (s, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 7.8 Hz, 2H), 7.87 (d, J = 7.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 23.8, 25.4, 52.1, 54.2, 57.0, 65.9, 107.1, 114.6, 115.7, 124.0, 128.4, 129.0, 129.4, 129.6, 131.8, 132.0, 132.6, 137.5, 137.7, 140.1, 156.2, 163.0, 165.5, 192.0; HRMS (FD) *m/e* calcd for $C_{30}H_{30}NO_5S$ (MH^+) 516.1856, found 516.1845. Anal. ($C_{30}H_{29}NO_5S\cdot 1.5H_2O$) C,H,N.

An additional 4.8 g (54%) of the corresponding TBS ether was also obtained and used in subsequent reactions: ^{1}H NMR δ 0.23 (s, 6H), 1.00 (s, 9H), 1.45 (m, 2H), 1.61 (m, 4H), 2.52 (m, 4H), 2.77 (t, J = 5.6 Hz, 2H), 3.87 (s, 3H), 4.10 (t, J = 5.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 6.89 (dd, J = 8.8, 2.0 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.49 (m, 3H), 7.75 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H); MS (FD) *m/e* 629 (M^+).

[2-[4-(Ethoxycarbonyl)phenyl]-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23b). Carbon monoxide was bubbled through solutions of **21** (6.2 g, 8.7 mmol) in DMF (30 mL) and of $Pd(OAc)_2$ (70 mg, 0.3 mmol), 1,3-bis(diphenylphosphino)propane (120 mg, 0.3 mmol), EtOH (22.8 mL, 390 mmol), and Et_3N (2.9 mL, 20 mmol) in DMF (20 mL) for 10 min. The solutions were then combined and heated to 70 °C under a CO atmosphere for 4.5 h. The mixture was then concentrated to dryness, and the residue was dissolved in CH_2Cl_2 (50 mL) and treated with 1.0 M TBAF (9.5 mL, 9.5 mmol) in THF for 3 h. The reaction mixture was then partitioned between saturated NH_4Cl (200 mL) and EtOAc (200 mL), and the organic layer was washed with saturated NH_4Cl (3 × 200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated. Purification by chromatography (1:1 hexane:EtOAc, 6−10% MeOH) provided 2.1 g (44%) of the title compound as a bright yellow solid: ^{1}H NMR δ 1.35 (t, J = 7.1 Hz, 3H), 1.47 (m, 2H), 1.65 (m, 4H), 2.58 (m, 4H), 2.80 (t, J = 5.5 Hz, 2H), 4.10 (t, J = 5.5 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 8.8, 2.1 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H); MS (FD) *m/e* 530 (MH^+). Anal. ($C_{31}H_{31}NO_5S$) C,H,N.

[2-(4-Carboxyphenyl)-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23c). A solution of **23a** (1.0 g, 1.9 mmol) in THF (100 mL) was treated with 1.0 N NaOH (47.2 mL, 47.2 mmol) and heated to 70 °C for 22 h. The mixture was then diluted with saturated $NaHCO_3$ (200 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), concentrated, and purified by chromatography (1:1 hexane:EtOAc, 10−70% MeOH) to give 0.49 g (51%) of the title product as a bright yellow solid: ^{1}H NMR (CD_3OD) δ 1.4−1.9 (m, 6H), 2.98 (m, 2H), 3.48 (m, 4H), 4.36 (m, 2H), 6.93 (dd, J = 6.4, 2.2 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 9.1 Hz, 2H), 7.86 (d, J = 7.9 Hz, 2H); HRMS (FD) *m/e* calcd for $C_{29}H_{28}NO_5S$ (MH^+) 502.1694, found 502.1688. Anal. ($C_{29}H_{27}NO_5S\cdot1.6H_2O$) C,N; H: calcd, 5.74; found, 5.11.

[2-(4-Carbamoylphenyl)-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23d). The title compound was prepared in 46% yield from the TBS ether of **23a** and MeAl(Cl)NH_2 by a method similar to that described for **22d**: ^{1}H NMR (CD_3OD) δ 1.45 (m, 2H), 1.59 (m, 4H), 2.52 (m, 4H), 2.74 (t, J = 5.4 Hz, 2H), 4.09 (t, J = 5.5 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 8.8, 2.0 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.43 (m, 3H), 7.71 (m, 4H); HRMS (FD) *m/e* calcd for $C_{29}H_{29}N_2O_4S$ (MH^+) 501.1860, found 501.1848. Anal. ($C_{29}H_{28}N_2O_4S\cdot0.75H_2O$) C,H,N.

[2-[4-(*N*-Methylcarbamoyl)phenyl]-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23e). A solution of the TBS ether of **23a** (1.0 g, 1.6 mmol) in toluene (50 mL) was treated with a 0.32 M solution of MeAl(Cl)N(H)Me in toluene (30 mL, 9.6 mmol) and stirred at 50 °C for 21 h.[22] After the reaction was quenched with 0.01 N HCl, the mixture was diluted with saturated $NaHCO_3$ (200 mL) and washed with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), concentrated, and purified via chromatography to provide 0.67 g (67%) of the TBS ether of **23e** as an off-white foam: ^{1}H NMR (CD_3OD) δ 0.24 (s, 6H), 1.01 (s, 9H), 1.45 (m, 2H), 1.58 (m, 4H), 2.50 (m, 4H), 2.72 (t, J = 5.5 Hz, 2H), 2.85 (s, 3H), 4.08 (t, J = 5.5 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.96 (dd, J = 8.8, 2.1 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.46 (m, 3H), 7.68 (m, 4H); MS (FD) *m/e* 628 (M^+).

The silyl ether obtained above was desilylated by a method similar to that described for **23b** to provide 0.46 g (91%) of the title compound as a bright yellow solid: ^{1}H NMR (CD_3OD) δ 1.26 (m, 2H), 1.40 (m, 4H), 2.30 (m, 4H), 2.51 (t, J = 5.4 Hz, 2H), 2.68 (s, 3H), 3.87 (t, J = 5.4 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.70 (dd, J = 8.8, 2.1 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.23 (m, 3H), 7.49 (m, 3H); HRMS (FD) *m/e* calcd for $C_{30}H_{31}N_2O_4S$ (MH^+) 515.2021, found 515.2005. Anal. ($C_{30}H_{30}N_2O_4S\cdot H_2O$) C,H,N.

[2-[4-(*N*,*N*-Dimethylcarbamoyl)phenyl]-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23f). The title compound was prepared in two steps and 72% overall yield from the TBS ether of **23a** by a method similar to that described for **23e**: ^{1}H NMR (CD_3OD) δ 1.29 (m, 2H), 1.44 (m, 4H), 2.34 (m, 4H), 2.56 (t, J = 5.4 Hz, 2H), 2.64 (s, 3H), 2.87 (s, 3H), 3.89 (t, J = 5.4 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.73 (dd, J = 8.8, 2.1 Hz, 1H), 7.08 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 2.1 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.7 Hz, 2H); HRMS (FD) *m/e* calcd for $C_{31}H_{33}N_2O_4S$ (MH^+) 529.2145, found 529.2161. Anal. ($C_{31}H_{32}N_2O_4S\cdot0.5H_2O$) C,H,N.

[2-(4-Acetylphenyl)-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23g). A solution of **21** (0.88 g, 1.2 mmol), butyl vinyl ether (0.9 mL, 6.9 mmol), Et_3N (0.39 mL, 2.8 mmol), 1,3-bis(diphenylphosphino)propane (25 mg, 0.061 mmol), and $Pd(OAc)_2$ (19 mg, 0.086 mmol) in DMF (4 mL) was heated at 80 °C for 19 h. The mixture was then diluted with 0.1 M HCl (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (3 × 50 mL), dried (Na_2SO_4), and concentrated. The residue was desilylated by a method similar to that described for **23b** to provide 0.25 g (41%) of the title compound as a bright yellow solid: ^{1}H NMR δ 1.47 (m, 2H), 1.66 (m, 4H), 2.52 (s, 3H), 2.60 (m, 4H), 2.82 (t, J = 5.4 Hz, 2H), 4.10 (t, J = 5.4 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 8.8, 2.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H); MS (FD) *m/e* 500 (MH^+). Anal. ($C_{30}H_{29}NO_4S$) C,H,N.

[2-[4-(Diethylphosphonyl)phenyl]-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23h). A solution of **21** (1.1 g, 1.5 mmol), 2,6-lutidine (0.5 mL, 4.3 mmol), diethyl phosphite (0.22 mL, 1.7 mmol), and $Pd(PPh_3)_4$ (0.078 g, 0.067 mmol) in CH_3CN (10 mL) was heated at 70 °C for 16 h. The mixture was then diluted with EtOAc (50 mL), washed with 10% citric acid (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was desilylated by a method similar to that described for **23b** to provide 0.77 g (86%) of the title compound as a bright yellow solid: ^{1}H NMR δ 1.28 (t, J = 7.0 Hz, 6H), 1.45 (m, 2H), 1.62 (m, 4H), 2.55 (m, 4H), 2.78 (t, J = 5.6 Hz, 2H), 4.0−4.2 (m, 6H), 6.66 (d, J = 8.8 Hz, 2H), 6.85 (dd, J = 8.8, 2.1 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.47 (m, 2H), 7.6−7.7 (m, 4H); MS (FD) *m/e* 594 (MH^+). Anal. ($C_{32}H_{36}NO_6PS$) C,H,N.

[2-(4-Ethynylphenyl)-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23i). The title compound was prepared in 45% yield by a method similar to that described for **22i**: ^{1}H NMR δ 1.48 (m, 2H), 1.67 (m, 4H), 2.60 (m, 4H), 2.82 (t, J = 5.4 Hz, 2H), 3.09 (s, 1H), 4.10 (t, J = 5.4 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 6.75 (dd, J = 8.8, 2.1 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 7.2−7.4 (m, 5H), 7.64 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 23.9, 25.2, 55.0, 57.7, 60.5, 65.3, 78.5, 83.2, 107.5, 114.2, 115.8, 121.9, 124.4, 128.7, 130.3, 132.0, 132.3, 133.1, 134.0, 140.3, 140.6, 155.3, 163.0, 193.4; HRMS (FAB) *m/e* calcd for $C_{30}H_{28}NO_3S$ (MH^+) 482.1790, found 482.1798. Anal. ($C_{30}H_{27}NO_3S\cdot0.25H_2O$) C,H; N: calcd, 2.88; found, 2.46.

[2-(4-Ethenylphenyl)-6-hydroxybenzothien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (23j). A solution of **21** (10.1 g, 14 mmol), vinyl acetate (12.8 mL, 140 mmol), Et_3N (6.0 mL, 43 mmol), 1,3-bis(diphenylphosphino)propane (0.63 g, 1.5 mmol), and $Pd(OAc)_2$ (0.32 g, 1.4 mmol) in DMF (20 mL) was heated at 100 °C for 4 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (100 mL), washed with 5% HCl (2 × 100 mL) and water (2 × 100 mL), dried (Na_2SO_4), and concentrated. The residue was desilylated by a method similar to that described for **23b** to provide 0.48 g (7%) of the title product as a bright yellow solid: ^{1}H NMR δ 1.48 (m, 2H), 1.67 (m, 4H), 2.60 (m, 4H), 2.81 (t, J = 5.4 Hz, 2H), 4.10 (t, J = 5.4 Hz, 2H), 5.23 (d, J = 10.9 Hz, 1H), 5.70 (d, J = 17.6 Hz, 1H), 6.58 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 10.9 Hz, 1H), 6.75 (dd, J = 8.7, 2.1 Hz, 1H), 7.1−7.4 (m, 6H), 7.68 (d, J = 8.7 Hz, 2H); MS (FD) *m/e* 484 (MH^+). Anal. ($C_{30}H_{29}NO_3S$) C,H,N.

Radioligand Binding Studies. Serial dilutions of test compounds or standards were mixed with 0.5 nM ^{3}H-labeled

17β-estradiol, along with 0.5−1.0 mg/mL total protein content (MCF-7 cell lysate), in a total volume of 0.14 mL. Binding took place for 18 h at 4 °C followed by addition of 0.07 mL of dextran/charcoal and centrifugation to remove nonbound radioligand. Aliquots of supernatant containing bound radioligand were removed, mixed with scintillant, and counted using a microbeta scintillation β-counter (Wallac). Relative binding affinity (RBA) was calculated as (IC_{50}(17β-estradiol)/IC_{50}(test compound)) × 100.

MCF-7 Proliferation Assay. MCF-7 breast adenocarcinoma cells (ATCC HTB 22) were maintained in MEM (minimal essential medium, phenol red-free; Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum (FBS) (v/v), L-glutamine (2 mM), sodium pyruvate (1 mM), HEPES (*N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid; 10 mM), nonessential amino acids, and bovine insulin (1 μg/mL) (maintenance medium). Ten days prior to assay, MCF-7 cells were switched to maintenance medium supplemented with 10% dextran-coated charcoal-stripped fetal bovine serum (DCC-FBS) (assay medium) in place of 10% FBS to deplete internal stores of steroids. Cells were removed from maintenance flasks using cell dissociation medium (Ca^{2+}/Mg^{2+}-free HBSS) (phenol red-free) supplemented with 10 mM HEPES and 2 mM EDTA. Cells were washed twice with assay medium, and 100 μL (8000 cells) was added to flat-bottom microculture wells (Costar 3596) followed by incubation at 37 °C in a 5% CO_2 humidified incubator for 24 h to allow for cell adherence and equilibration after transfer. Serial dilutions of drugs, or DMSO as a diluent control, were prepared in assay medium, and 50 μL was transferred to triplicate microcultures followed by 50 μL of assay medium containing 17β-estradiol (10 pM final concentration). After an additional 48 h at 37 °C in a 5% CO_2 humidified incubator, microcultures were pulsed with tritiated thymidine (1 μCi/well) for 4 h. Cultures were terminated by freezing at −70 °C for 24 h followed by thawing and harvesting of microcultures using a Skatron semiautomatic cell harvester. Samples were counted by liquid scintillation using a Wallac BetaPlate β-counter.

Four-Day Ovariectomized Rat Assays. Virgin, virus-antibody-free, OVX Sprague−Dawley rats (75-days old) were obtained from Charles Rivers Laboratories (Portage, MI) and group housed on a 12 h light:12 h dark cycle (lights on at 0600 h) with room temperature set at 22 °C. The animals had *ad libitum* access to both food and tap water. Animals were randomized into experimental treatment groups, with five to six animals per treatment group. Compound administration was initiated 14 days after ovariectomy, in order to insure clearance of endogenous estrogen and to allow for acclimation to the home cage. For most studies, compounds were dissolved in 20% β-hydroxycyclodextrin (CDX) and given by daily oral gavage in a volume of 1 mL/kg of body weight. In some cases, 1.5% carboxymethylcellulose was used in place of CDX. Animals were dosed for 4 consecutive days and fasted the evening following the final dose. On the following morning the animals were weighed and anesthetized (carbon dioxide), and a blood sample was collected by cardiac puncture. The animals were then euthanized by carbon dioxide asphyxiation, and the uteri were collected and weighed. One horn of the uterus was removed, weighed, and transferred into a Tris buffer for analysis of uterine EPO activity. Ethynylestradiol and tamoxifen were purchased from Sigma Chemical Co. (St. Louis, MO), and β-hydroxycyclodextrin was purchased from SAF Bulk Chemicals (Milwaukee, WI).

Uterine Eosinophil Peroxidase Activity. Uterine EPO activity was determined by a modification of the method of White.[49] After removal of the uterus and recording of whole uterine weight, the uterine horns were bisected. One horn from each animal was weighed and homogenized (Brinkmann Polytron, Brinkmann Instruments Co., Westbury, NY) on ice in 50 mM Tris buffer (pH 8.0, 50 μL/mg of tissue) containing 0.05% (v/v) Triton X-100 (Pierce, Rockford, IL). Samples were centrifuged at 3000 rpm for 10 min at 4 °C in a Beckman GPR centrifuge (Palo Alto, CA). The resulting supernatant was filtered in a 3 mL syringe through a 45 μm filter. Duplicate 50 μL aliquots of the filtered supernatant fraction (equivalent to 1 mg of tissue) were added to a 96-well flat-bottomed microtiter plate. The reaction was initiated with the addition of 200 μL of substrate solution containing 3.5 mM *o*-phenylenediamine·2HCl and 0.0005% H_2O_2 in 50 mM Tris buffer (pH 8.0). The apparent maximal velocity was determined by continuously monitoring the oxidation of *o*-phenylenediamine in the presence of H_2O_2 at 490 nm at room temperature using a computer-controlled microplate reader (EL312 Bio-kinetic microplate reader, Bio-Tek Instruments, Winooski, VT) utilizing the DeltaSoft software program.

Serum Cholesterol Assay. Blood samples were allowed to clot at 4 °C for 2 h and then centrifuged at 2000*g* for 10 min. Serum samples were collected and stored at −70 °C for subsequent analytical procedures. Serum cholesterol was determined using a Boehringer Mannheim Diagnostics high-performance cholesterol colorimetric assay (Indianapolis, IN) as originally described by Weibe and Bernet.[50]

Five-Week Ovariectomized Rat Assay. Following a protocol similar to that described above, 6-month old, virgin, OVX Sprague−Dawley rats (Harlan, IN) were treated daily for 35 days, beginning on day 4 following ovariectomy. At the time of sacrifice, the uteri were removed and dissected free of extraneous tissue, and the fluid contents were expelled before determination of wet weight in order to confirm estrogen deficiency associated with complete ovariectomy. Uterine weight was routinely reduced about 75% in response to ovariectomy.

Methods of tissue collection and data analysis have been previously described.[51,52] Generally, the right femurs were excised and digitized X-rays generated and analyzed at the distal metaphysis.[51] In one case, the proximal aspect of the tibiae from these animals was scanned by quantitative computed tomography.[52] Percent protection was calculated by the following formula: % protection = [($BMD_{\text{test compound}}$ − $BMD_{\text{OVX control}}$)/($BMD_{\text{sham control}}$ − $BMD_{\text{OVX control}}$)] × 100.

For both the 4-day and 5-week OVX rat assays, statistical evaluations were made by one-way analysis of variance (ANOVA). Significance was ascribed at a $p \leq 0.05$.

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Supporting Information Available: Experimental details and spectral data for compounds **2i**,**j** (4 pages). Ordering information is given on any current masthead page.

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