Synthesis and Antiestrogenic Activity of Diaryl Thioether Derivatives

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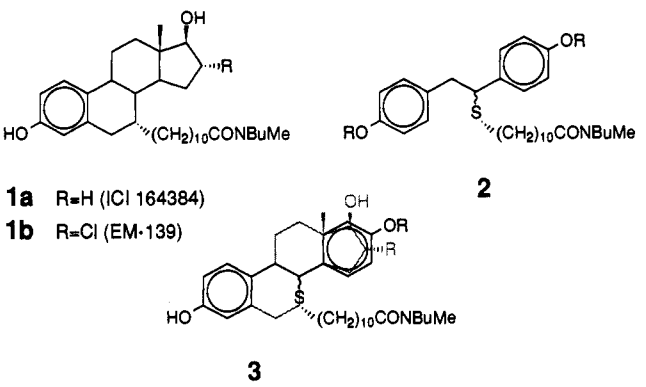
The reaction of 1,2-diarylethanol and mercapto side chain catalyzed by ZnI_2 was used as a key step in the short (three to five steps) and efficient synthesis of 17 diaryl thioether derivatives. Several of these compounds contain a methyl butyl amide chain and an hydroxyaryl moiety, respectively, for antiestrogenic activity and binding affinity on estrogen receptor. No binding affinity for crude cytosolic preparation of the estrogen receptor was observed for compounds without phenolic group, while a low affinity (0.01–0.05%) was measured for mono- or diphenol derivatives. Like the pure steroidal antiestrogen EM-139, these novel nonsteroidal compounds did not exert any stimulatory effect on cell proliferation of (ER^+) ZR-75-1 human breast cancer cells and partially reversed the amplitude of the stimulatory effect induced by estradiol on this (ER^+) cell line. No proliferative or antiproliferative effect on (ER^-) MDA-MB-231 human breast cancer cells was also observed for three of these compounds (**39–41**). Among the newly synthesized nonsteroidal compounds, the thioether derivative **41** (*N*-butyl-*N*-methyl-13,14-bis(4′-hydroxyphenyl)-12-thiatetradecanamide), with a long methylbutylalkanamide side chain and a diphenolic nucleus, was selected as the best antiestrogenic compound. However, this compound was 100-fold less antiestrogenic in (ER^+) ZR-75-1 cells than the steroidal antiestrogen EM-139.

Pure antiestrogens, as opposite to the mixed agonistic/antagonistic activities of Tamoxifen,[1-4] have been described as promising drugs for the endocrine therapy of breast cancer.[4-6] Recently, a new generation of steroidal compounds having pure antiestrogenic activity has been described.[5-14] These compounds represented by ICI 164384,[7] EM-139,[9] or RU 51625[11] contain a long alkanamide side chain at the 7α- or 11β-position of an estradiol nucleus, while ICI 182780[12] contains a long alkanesulfoxide side chain at the 7α-position of estradiol. These new steroidal antiestrogens may achieve their pure antagonistic activity through several different mechanisms, some of which require yet to be further investigated.[15-21] It can thus be postulated that the unique biological activities of these compounds may be explained, at least in part, by the presence of the long alkanamide or alkanesulfoxide side chain.

The several steps and the low overall yields involved in the chemical synthesis of these promising pure antiestrogens is, however, an important disadvantage. For more readily obtained compounds with chemical groups similar to ICI 164384 (**1a**) or EM-139 (**1b**), we developed a series of nonsteroidal derivatives **2** (Chart 1). These compounds contain the important methylbutyl alkanamide side chain added to a diarylethane substrate by a thioether link. We selected the thioether link because it is easily formed by a ZnI_2-catalyzed reaction of 1,2-diarylethanol and mercapto side chain. The side-chain moiety was included for antiestrogenic activity, while the hydroxyaryl moiety (**2**, R = H) appears important for binding affinity for the estrogen receptor. The chemical structure of these new compounds is somewhat analogous to ICI 164384 (see structure **3**), particularly the pseudo-3-hydroxyl group and the alkanamide side chain, two parts of the molecule which appear very important for binding and antiestrogenic activity, respectively.

In this work, we report the short and efficient synthesis of 17 new compounds and their relative binding affinity (RBA) to the crude estrogen receptor preparation as well as their estrogenic and antiestrogenic activity in the estrogen-sensitive (ER^+) human breast cancer cell line ZR-75-1. For three of these compounds (**39–41**), we also report their proliferative and antiproliferative effect in the estrogen-insensitive (ER^-) human breast cancer cell line MDA-MB-231.

Chart 1



Chemistry

1. **Synthesis of Starting Alcohols: 8–11.** The starting racemic alcohols **8–11** were all synthesized from desoxyanisoin (Scheme 1). Dimethoxy alcohol **8** was obtained by sodium borohydride ($NaBH_4$) reduction of desoxyanisoin (**4**). The monomethoxy derivatives **9** and **10** were obtained by the same reduction of the corresponding benzyl (Bn) ketone **5** or tetrahydropyranyl (THP) ketone **6**. The intermediate ketones **5** and **6** were obtained in two steps: (1) carefull monodemethylation of **4** with boron tribromide at −10 °C and (2) successive benzylation (BnCl, K_2CO_3) or tetrahydropyranylation (DHP, *p*-TSA) of the phenolic group. The last starting alcohol **11** was obtained by $NaBH_4$ reduction of di-THP ketone **7** which was also synthesized in two steps by total demethylation of desoxyanisoin with pyr·HCl followed by

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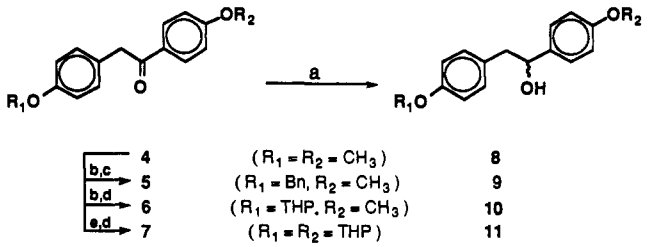
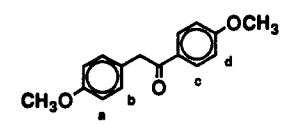
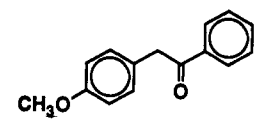
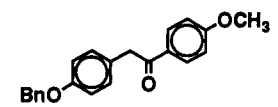
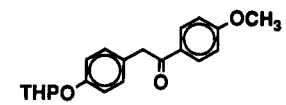
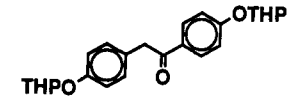
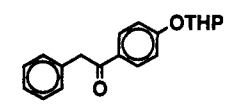
Scheme 1



[a] (a) $NaBH_4$, MeOH; (b) BBr_3, CH_2Cl_2, −10 °C; (c) K_2CO_3, BnCl, DMF; (d) DHP, *p*-TSA, benzene; (e) pyr·HCl, reflux.

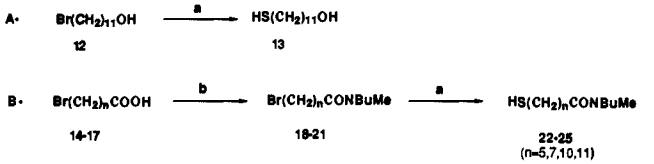
Table 1. NMR and MS Data Supporting the Localization of BBr_3 Monodeprotection of Desoxyanisoin (4)

ketones[a]	^{1}H NMR δ (ppm)[b] a	b	c	d	MS[c] (*m/e*)
4 	6.86	7.18	7.99	6.92	121, 135
4a 	6.87	7.18	8.01		121
5 	6.92	7.18	7.99	6.92	135
6 	7.00	7.17	7.99	6.92	135
7 	6.99	7.16	7.96	7.06	
7a 			7.99	7.08	

[a] For NMR and MS data of 4a, see ref 22 (compound 3f). Compound 7a was obtained from benzyl 4-hydroxyphenyl ketone (Aldrich, Milwaukee, WI) after THP formation. [b] Aromatic protons attribution was done by COSY experiments and literature data (refs 22 and 23). [c] The fragment ion peaks at *m/e* = 121 and 135 are due respectively to CH_2PhOCH_3 and $COPhOCH_3$.

di-THP formation. Boron tribromide was not suitable for performing the total demethylation of desoxyanisoin. In the monodeprotection process (1 equiv of BBr_3 at −10 °C), only the methoxy group nonconjugated to the ketone (4, $R_1 = CH_3$) was cleaved. In fact, the Lewis acid BBr_3 preferably chelates and cleaves the more nucleophilic oxygen atom (located in the nonconjugated methoxy group). Localization of the monophenolic group was confirmed by NMR and MS data (Table 1). Using NMR spectroscopy, the assignment of aromatic protons was done by COSY experiments and literature data.[22,23] Since chemical displacements (δ) of H_b (7.16–7.18 ppm) and H_c (7.96–8.01 ppm) are not influenced by the nature of aromatic *meta* substitution, they are not suitable for NMR

Scheme 2



[a] (a) 1. Thiourea, EtOH, 2. NaOH (10% w/v); (b) 1. $N(Bu)_3$, $ClCOOi$-Bu, CH_2Cl_2, 2. HNBuMe.

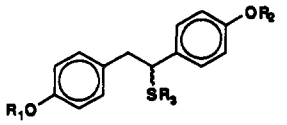
proof of phenol localization. However, δH_a and δH_d are influenced by the chemical nature of the *ortho* subtituent and are consequently more informative. In fact, we observed the same δH_d for compounds **5**, **6**, and desoxyanisoin (**4**) (6.92 ppm), while the δH_a for **5** and **6** (6.92 and 7.00 ppm) were different from the δH_a of **4** and **4a** (6.86 and 6.87 ppm). Consequently, compounds **5** and **6** have no CH_3OPhCH_2 group. On the other hand, the δH_d of compounds **7** and **7a** (7.06 and 7.08 ppm) are characteristic of the THPOPhCO group. However, a similar δ is not observed for the mono-THP derivative **6**. By mass spectrometry, two fragments are particularly interesting. These fragments (*m/e* = 121 and 135) correspond respectively to the CH_3OPhCH_2 and CH_3OPhCO groups. These two fragments are observed for desoxyanisoin (**4**), but only one (*m/e* = 135) is observed for compounds **5** and **6**. The presence of fragment *m/e* = 135 in the mass spectrum of compounds **5** and **6** but not in **4a** and the chemical displacements of H_a and H_d confirm localization of the BBr_3 monodeprotection.

2. Synthesis of Starting Mercapto Side Chains (Thiols): 13 and 22–25. The mercapto side chains used for thioether formation were synthesized from corresponding bromides (Scheme 2) except methyl 3-mercaptopropionate which was commercially available. 11-Mercaptoundecanol (**13**) and *n*-mercaptoalkanamides **22–25** were obtained respectively from 11-bromoundecanol (**12**) and *n*-bromoalkanamides **18–21** by a standard two-step procedure:[24] (1) formation of alkyl isothiourea hydrobromide and (2) hydrolysis of this salt to the corresponding mercapto derivatives. This method was found efficient for thiol formation but needs a longer reaction time than that in the standard described procedures, particularly for the first step. The bromoalkanamides **18–21** have been previously obtained from bromo acids **14–17** by activation of the carboxylic group and treatment with *N*-methylbutylamine.[25]

3. Synthesis of Racemic Thioethers: 26–42. The synthesis of thioethers **26–42** (Table 2) was performed according to the general equation represented in Sheme 3. In this reaction, an activated alcohol like **8–11** reacts with a mercapto group (HSR_3) in the presence of zinc iodide to give a thioether. This reaction, first reported by Guindon et al.,[26] is very simple and efficient. Herein, we used four racemic alcohols (**8–11**) and three kinds of mercapto side chains ($HSCH_2CH_2COOCH_3$; mercapto ester, $HS(CH_2)_nCONBuMe$; mercapto amide, $HS(CH_2)_{11}OH$; mercapto alcohol) as starting material (Table 3). When a THP group was present in the starting alcohol (entries 3 and 4, Scheme 3), we observed the partial hydrolysis of the THP-protective group. In fact, this group was cleaved by zinc iodide to give the suitable phenolic group. The THP ether not cleaved was easily hydrolyzed to a phenolic compound by *p*-TSA in MeOH.[27]

The new compounds resulting from the general coupling reaction were characterized by spectroscopic means. In

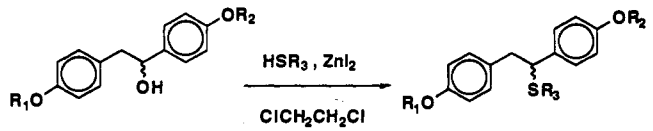
Table 2. Racemic Thioether Derivatives and Their Biological Activities



compound		substituents				ZR-75-1 cells[b]		
series	no.	R_1	R_2	R_3	RBA[a] (%)	basal level (ng of DNA/dish)	E_2-induced level (ng of DNA/dish)	antiestrogenic activity (%)
control (series I–III)						955 ± 18	1591 ± 27	0
EM-139[c] (pure antiestrogen) (series I–III)					1.2	679 ± 28	662 ± 10	103 ± 5
I	43	CH_3	CH_3	$(CH_2)_2CONBuMe$	N	741 ± 12	1014 ± 38	57 ± 7
I	27	CH_3	CH_3	$(CH_2)_7CONBuMe$	N	746 ± 26	1151 ± 49	36 ± 9
I	28	CH_3	CH_3	$(CH_2)_{11}CONBuMe$	N	800 ± 6	1353 ± 4	13 ± 5
II	44	Bn	CH_3	$(CH_2)_2CONBuMe$	N	789 ± 13	1021 ± 15	64 ± 4
II	30	Bn	CH_3	$(CH_2)_7CONBuMe$	N	791 ± 18	1073 ± 22	56 ± 5
II	31	Bn	CH_3	$(CH_2)_{10}CONBuMe$	N	749 ± 26	1115 ± 9	42 ± 5
II	32	Bn	CH_3	$(CH_2)_{11}OH$	N	725 ± 13	1098 ± 2	41 ± 6
III	47	H	CH_3	$(CH_2)_2CONBuMe$	0.01	684 ± 11	902 ± 29	66 ± 5
III	34	H	CH_3	$(CH_2)_7CONBuMe$	0.05	698 ± 17	915 ± 9	66 ± 2
III	35	H	CH_3	$(CH_2)_{10}CONBuMe$	N	733 ± 18	1315 ± 29	8 ± 7
III	36	H	CH_3	$(CH_2)_{11}CONBuMe$	N	807 ± 9	1093 ± 34	55 ± 6
III	37	H	CH_3	$(CH_2)_{11}OH$	0.02	839 ± 21	1279 ± 12	31 ± 5
control (series IV)						1949 ± 33	3132 ± 71	0
EM-139[c] (pure antiestrogen) (series IV)					1.2	1326 ± 34	1403 ± 47	94 ± 5
IV	48	H	H	$(CH_2)_2CONBuMe$	0.01	1888 ± 32	2602 ± 26	40 ± 5
IV	39	H	H	$(CH_2)_5CONBuMe$	0.01	1445 ± 5	2050 ± 4	49 ± 3
IV	40	H	H	$(CH_2)_7CONBuMe$	0.01	1408 ± 21	2067 ± 53	44 ± 6
IV	41	H	H	$(CH_2)_{10}CONBuMe$	0.01	1151 ± 60	1393 ± 52	80 ± 7
IV	42	H	H	$(CH_2)_{11}OH$	0.02	1539 ± 46	2230 ± 40	42 ± 6

[a] RBA: relative binding affinity on estrogen receptor. The RBA of E_2 is taken as 100%. N: no binding observed. [b] ZR-75-1 cell assays were performed in triplicate. Compounds were tested at a dose of 1 μM, and cell stimulation was provided by estradiol (0.1 nM). See the Experimental Section for cell growth conditions and equation used to calculate antiestrogenic activity. [c] EM-139: *N*-butyl-*N*-methyl-11-(16′α-chloro-3′,17′β-dihydroxyestra-1′,3′,5′(10′)-trien-7′α-yl)undecanamide.

Scheme 3



entry		
1	**8** $R_1 = R_2 = CH_3$	**26-28** $R_1 = R_2 = CH_3$
2	**9** $R_1 = Bn$, $R_2 = CH_3$	**29-32** $R_1 = Bn$, $R_2 = CH_3$
3	**10** $R_1 = THP$, $R_2 = CH_3$	**33-37** $R_1 = THP$, $R_2 = CH_3$
4	**11** $R_1 = R_2 = THP$	**38-42** $R_1 = R_2 = THP$

[a] $R_3 = CH_2CH_2COOCH_3$, $(CH_2)_nCONBuMe$ (n = 5, 7, 10, 11), $(CH_2)_{11}OH$.

IR, we observed the disappearance of the starting alcohol for compounds of series I and II and compounds of series III and IV when THP groups were not cleaved. Characteristic bands indicating the presence of the side chain, like ester and amide, were also observed in thioether derivatives, but not the thiol band. In ^1H and ^{13}C NMR, a very characteristic signal displacement from 4.8 and 75 ppm to 3.8–4.0 and 51–52 ppm was attributed to $PhCH_2\mathbf{C}H(OH)Ph$ and $PhCH_2\mathbf{C}H(SR)Ph$ arrangements, respectively. Other signals related to the side chain moiety were also easily observed, particularly the carbons and protons of carbons bonded to the nitrogen atom of the amide group ($CON\mathbf{C}H_3$ and $CON\mathbf{C}H_2$). For compound **27** (as an example), these protons appear as two singlets (2.88 and 2.93 ppm; NCH_3) and two triplets (3.22 and 3.33 ppm; NCH_2) while the carbons appear as two peaks for NCH_3 (35.2 and 33.3 ppm) and also two peaks for NCH_2 (49.7 and 47.4 ppm). The duplication of signal in ^1H and ^{13}C NMR spectroscopy is explained by the two conformations of the amide bond.[28] In electronic ionization mass spectrometry (MS), the molecular peak (M^+) is very weak or not observed. However, all thioethers show a characteristic peak corresponding to $M^+ - (ROPhCH_2)$. High-resolution mass spectra (FAB) were also in agreement with the molecular formula. Other fragments related to the side chain were also characteristic of thioether formation.

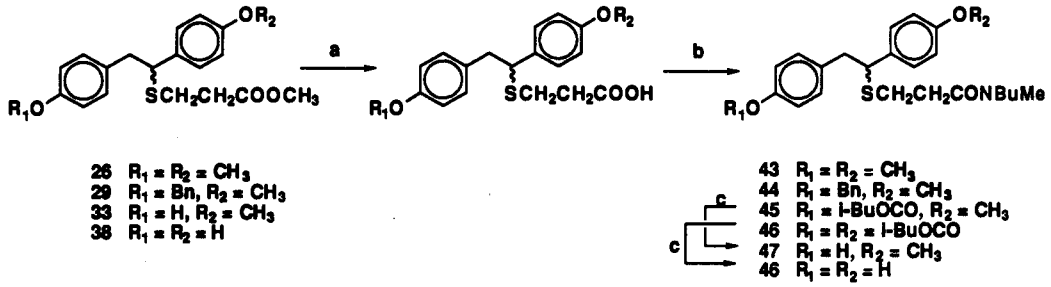
Table 3. Experimental Conditions Used for the Synthesis of Racemic Thioethers **26–42**

alcohol		side chain		ZnI_2	solvent	time	thioether	
no.	mmol	no.	mmol	(mmol)	(mL)	(h)	no.	yield (%)[a]
8	1.94	*b*	2.33	0.96[c]	3	1	**26**	57
8	1.16	**23**	1.39	1.67[d]	10	6	**27**	79
8	0.27	**25**	0.33	0.28[e]	2	3	**28**	74
9	0.90	*b*	1.08	0.90	5	2.5	**29**	90
9	0.60	**23**	0.72	0.60	11	18	**30**	81
9	0.75	**24**	0.90	0.75	5	6	**31**	60
9	0.60	**13**	0.72	0.60	11	1.5	**32**	93
10	0.61	*b*	0.73	0.61	6	14	**33**	80
10	0.30	**23**	0.41	0.30	10	18	**34**	36[f]
10	0.64	**24**	0.77	0.63	8	3	**35**	48[f]
10	0.83	**25**	0.83	0.83	8	4	**36**	45 + 7[g]
10	0.46	**13**	0.55	0.46	10	1.5	**37**	40 + 46[g]
11	1.26	*b*	1.92	0.40	4	1.5	**38**	51[f]
11	0.75	**22**	0.90	1.13	14	19	**39**	46 + 47[g]
11	0.75	**23**	0.90	0.82	14	5.5	**40**	44[f]
11	0.75	24	0.90	1.13	10	22	**41**	28 + 27[g]
11	0.75	**13**	0.90	1.13	10	4	**42**	11 + 52[g]

[a] Yields were not optimized. [b] Methyl 3-mercaptopropionate (Aldrich, Milwaukee, WI). [c] $ZnCl_2$. [d] 0.58 mmol at the beginning, 0.31 mmol after 45 min, and 0.78 mmol after 4 h. [e] 0.14 mmol at the beginning and 0.14 mmol after 3 h. [f] Crude thioether was submitted to hydrolysis of THP group without purification (*p*-TSA, MeOH, room temperature, 1 h). [g] Yields were given respectively for phenolic and THP derivatives.

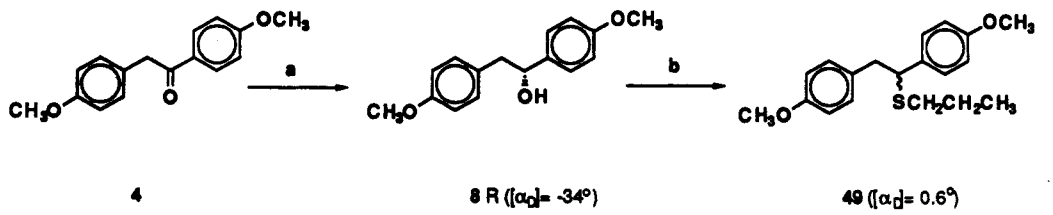
4. Synthesis of Racemic Thioethers with a Short Alkanamide Chain: 43, 44, 47, and 48. The thioethers **43**, **44**, **47**, and **48** (Table 2; Scheme 4) were synthesized from ester derivatives **26**, **29**, **33**, and **38** previously obtained by the general coupling strategy (Scheme 3). The methyl esters were hydrolyzed to the corresponding carboxylic

Scheme 4



[a] (a) KOH, H_2O, MeOH; (b) 1. ClCOO*i*-Bu, $N(Bu)_3$, 2. HNBuMe; (c) K_2CO_3, H_2O, MeOH.

Scheme 5



[a] (a) (+)-Diisocampheylchloroborane,[30] MeOH; (b) $HSCH_2CH_2CH_3$, ZnI_2, $ClCH_2CH_2Cl$.

acids (NaOH, H_2O, MeOH) which, with no further purification, were transformed to the methyl butyl amides **43–46**.[29] When free phenolic groups were present, the isobutyl carbonate derivatives **45** and **46** were obtained. These compounds were formed by reaction of the phenol group and isobutyl chloroformate used for the amide preparation. Compounds **45** and **46** were, however, easily hydrolyzed (K_2CO_3, H_2O, MeOH)[29] to the corresponding phenolic derivatives **47** and **48**.

5. Nature of the Asymmetric Center of Thioether Compounds. The thioether compounds **26–42** were obtained from racemic alcohols **8–11** ($[\alpha]_D = 0.3°$ for **8**) such that the corresponding thioether formed was necessarily racemic ($[\alpha]_D = 0.5°$ for **49**). In order to check, for our compounds, the proposal of Guindon et al.[22] according to a S_N1 process, we synthesized the optically active alcohol **8** (*R*) at 83% yield by reduction of ketone **4** with an asymmetric reagent ((+)-diisocampheylchloroborane[30,31]) in methanol (Scheme 5). The enantiomeric excess of alcohol (97%) was measured by integration of the benzylic methine proton of the corresponding Mosher ester[31,32] (NMR, 300 MHz, $\delta = 6.04$ and 6.11 ppm). For this alcohol, the optical rotation in $CHCl_3$ was −34°. Starting with this chiral alcohol, mercaptopropane, and zinc iodide (1 equiv), we obtained the thioether **49** with an optical rotation of 0.6°. This low optical value (nearly zero) indicates a loss of chirality with racemization. Consequently, a S_N1 mechanism with carbocation formation occurs in this reaction. This result confirms the statement of Guindons group but also indicates the impossibility of obtaining, using this methodology, a chiral thioether from an optically active alcohol.

Biological Results

The relative binding affinity (RBA) of the synthesized compounds (Table 2) for the estrogen receptor was determined *in vitro* using cytosol from the immature rat uterus. Using the IC_{50} values of displacement of the tested compounds and estradiol (E_2), we measured the relative binding affinity, taking arbitrarily the binding of E_2 as 100%. No affinity for the estrogen receptor was detected for compounds of series I and II (with no phenolic group), while very low affinity (0.01–0.05%) was measured for compounds of series III and IV (mono- or diphenol derivatives). A free phenolic group (like phenolic steroid, estradiol) is an important requirement for good binding affinity, so the absence of detectable bindings obtained for compounds of series I and II was predictable. The low affinity measured for compounds of other series (III and IV) was rather deceptive, taking into account that the RBA obtained for similar compounds, like the dihydro derivative of diethylstilbestrol (hexestrol), was good (RBA = 300%).[33,34] Two reasons can explain these low values: firstly, the introduction of a side chain onto the diarylethane nucleus (see Katzenellenbogen's data[35] on side-chain derivatives of hexestrol) and, secondly, the high level of nonspecific binding to cytosol components[36] from crude receptor preparations. In fact, under similar conditions, the pure antiestrogen EM-139, with a long alkanamide side chain, has a low RBA of only 1.2%.[9]

The proliferation of the estrogen-sensitive (ER^+) ZR-75-1 human breast cancer cells permits us to assess the *in vitro* estrogenic or antiestrogenic activity of the new compounds. We thus evaluated the ability of these compounds, at a dose of 1 μM, to stimulate the basal cell proliferation of ZR-75-1 cells and/or to inhibit the E_2-induced proliferation of ZR-75-1 cells. At this concentration, no proliferation suggesting an estrogenic effect was observed for any compound including the series of compounds with a phenolic group (Table 2). Under similar growth conditions, E_2 causes a 1.6-fold increase of the ZR-75-1 cell proliferation. The ability of new compounds to inhibit the E_2 (0.1 nM)-induced stimulation of cell proliferation was also evaluated. In this screening test (Table 2), the compounds inhibit the E_2-induced cell proliferation with values ranging from 8% to 80%. The compound **41**, with two hydroxyaryl moieties, shows the best inhibition (80%), while the pure antiestrogen EM-139 completely abolishes the proliferative effect of E_2. These two compounds have the same alkanamide side chain. However, the length of the alkanamide chain and the nature of aromatic substituents (MeO, BnO, HO) or side chains (amide, alcohol) do not seem to correlate with the inhibition values. Moreover, the inhibitory effects of

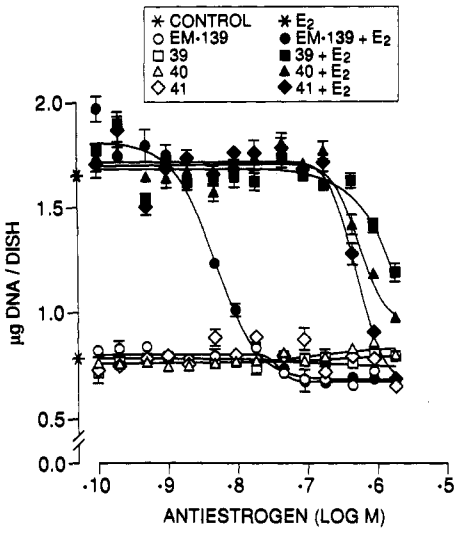


Figure 1. Comparison of the effects of diphenolic compounds **39–41** with those of the pure antiestrogen EM-139 on basal (open symbols) and E_2-induced cell proliferation (closed symbols) in (ER^+) ZR-75-1 human breast cancer cells. The IC_{50} values obtained in the presence of E_2 were 5.4, 590, 650, and 2000 nM, respectively for compounds EM-139, **39**, **40**, and **41**. Data obtained in the absence of the indicated antiestrogen are indicated on the *y* axis. Three days after plating, cells were incubated for 9 days with indicated concentrations of antiestrogens in the presence or absence of 0.1 nM E_2. Media were changed every second day. Results are expressed as means ± SEM of triplicate dishes. When SEM overlaps with the symbol, only the symbol is shown.

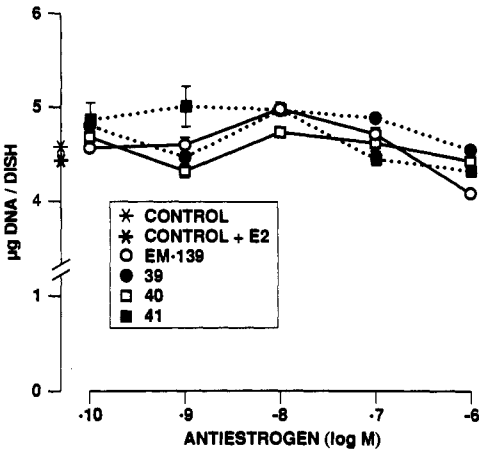


Figure 2. Comparison of the effects of diphenolic compounds **39–41** with those of the pure antiestrogen EM-139 in the absence of E_2 on cell proliferation of (ER^-) MDA-MB-231 human breast cancer cells. Data obtained in the absence of the indicated antiestrogen (control and control + 0.1 mM E_2) are indicated on the *y* axis. Two days after plating, cells were incubated for 9 days with indicated concentrations of antiestrogens alone. Media were changed every second day. Results are expressed as means ± SEM of triplicate dishes. When SEM overlaps with the symbol, only the symbol is shown.

compounds of series I and II (without phenol) were roughly similar to the results obtained for series III and IV (with phenol).

We next further compared the estrogenic and/or antiestrogenic activities of three compounds of the diphenolic series **39–41** to those of the pure antiestrogen EM-139. As expected from the data described above, it can be seen in Figure 1 that all these compounds failed to increase cell proliferation of ZR-75-1 cells. Moreover, it is of interest to observe that only EM-139 decreases basal cell proliferation at concentrations higher than 20 nM. The steroidal antiestrogen EM-139 causes a potent antiestrogenic activity, the half-maximal inhibitory activity (IC_{50}) being exerted at 5.4 nM, while the nonsteroidal derivatives **39–41** show respective IC_{50} values of 2000, 650, and 590 nM. For these compounds, we observed that the inhibition decreases slightly with the shortening of the side chain. Compound **41**, with a longer alkanamide side chain similar to that of EM-139 and ICI 164384, shows a better inhibition than the other thioether derivatives. For this compound, the antiestrogenic activity is approximately 100-fold lower than that of EM-139, in agreement with the RBA value which is also 100-fold lower (0.01% and 1.2%).

We also evaluated the effect of three compounds of the diphenolic series **39–41** and EM-139 on the estrogen-insensitive (ER^-) human breast cancer line MDA-MB-231. As illustrated in Figure 2, these compounds alone did not increase or decrease the basal cell proliferation in the range of concentration used (0.1–1000 nM). Similarly, no proliferative or antiproliferative effect was observed in this (ER^-) cell assay when E_2 (0.1 nM) was added.

Discussion

The newly synthesized compounds (Table 2) have a very low binding affinity for the crude estrogen receptor preparation (0–0.05%). Interestingly, these nonsteroidal derivatives have no estrogenic or proliferative activity in estrogen-sensitive (ER^+) ZR-75-1 cells up to the highest concentration used (1 µM), while a slight antiproliferative activity was observed for almost all compounds in this *in vitro* system. Compounds of series I and II, with no phenol group and no detectable binding affinity for the estrogen receptor, show an antiproliferative effect which cannot be explained readily by known mechanisms mediated by the estrogen receptor. For compounds of series III and IV, with phenol group and low binding affinity for the estrogen receptor, their slight antiproliferative activity can be at least partially explained by interaction with the estrogen receptor. It is also quite possible that metabolism of the compounds in intact cells could lead to compounds having more affinity for the estrogen receptor.

In the literature, several results obtained with antiestrogens cannot be explained exclusively by estrogen-receptor-mediated mechanisms and support the hypothesis of several mechanisms for *in vitro* antiproliferative activity. For nonsteroidal antiestrogens such as tamoxifen, data suggest that antiestrogen-binding sites (AEBS) may mediate the receptor-independent antiproliferative effect.[37,38] Moreover, Teo et al.[39] have recently reported the first demonstration that selective ligands of AEBS (other than the known nonsteroidal antiestrogens) interfere with cholesterol biosynthesis, an action that may contribute to their antiproliferative effect. However, it was also reported that the pure steroidal antiestrogen ICI 164384 does not compete with tamoxifen for binding to AEBS.[40]

In conclusion, the reaction of 1,2-diarylethanol and mercapto side chain catalyzed by ZnI_2 can be used as a key step in the short (three to five steps) and efficient synthesis of 17 diaryl thioether derivatives. Several of these compounds contain a methylbutylalkanamide chain for antiestrogenic activity and an hydroxyaryl part for binding affinity to the estrogen receptor. With these chemical characteristics, they can be compared to the pure antiestrogen ICI 164384 or EM-139. These newly synthetized compounds have a very low binding affinity (0–0.05%) for the cytosolic crude estrogen receptor prepa-

ration. Like the pure antiestrogen EM-139, these new compounds did not show estrogenic activity and inhibit the induction by E_2 of (ER^+) ZR-75-1 cell proliferation. Moreover, they did not cause proliferative and antiproliferative effects on the (ER^-) MDA-MB-231 cell line. Among the newly synthesized nonsteroidal compounds, the thioether 41, with a long methylbutylalkanamide side chain and a diphenolic nucleus, was selected as the best antiestrogen. However, compound 41 was about 100-fold less antiestrogenic in (ER^+) ZR-75-1 cells than EM-139. The results correlate with RBA values of 0.01% and 1.2%, respectively, obtained for compound 41 and EM-139.

Experimental Section

A. **Chemical Synthesis. General Procedure.** TLC was performed on 0.20-mm silica gel 60 F_{254} plates (E. Merck, Darmstadt, GE), while 230–400 mesh ASTM silica gel 60 (E. Merck, Darmstadt, GE) was used for flash column chromatography. When thioethers were submitted to biological tests, last-step chromatography was performed with freshly distilled or HPLC grade solvents. The purity of all tested compounds was found to be >99.5% by HPLC (Waters Associates, Milford, MA) with a reverse-phase column (Nova-pak, C-18, 4 μm, 0.5 cm × 10 cm) using an appropriate mixture of CH_3CN, MeOH, and H_2O as eluent. Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. Optical rotations were measured at room temperature on a Jasco DIP-360 polarimeter with $CHCl_3$ as solvent. NMR spectra were recorded on a Varian XL (200 MHz) or Bruker AC/F (300 MHz) spectrometer using TMS as internal standard. For ^{13}C NMR spectra of thioether derivatives with an alkanamide side chain, a representative example of the complete assignment of signals was furnished (see ref 41). Mass spectra (MS) were recorded with a V.G. Micromass 16 F spectrometer, while exact mass (EIMS or FABMS) (thioglycerol matrix) was provided by the Centre Régional de Spectrométrie de Masse (Université de Montréal, Montréal, Canada). Combustion analyses (C, H, N, S) were performed by Galbraith Laboratories Inc. (Knoxville, TN).

1. **Synthesis of Starting Alcohols: 8–11 (Scheme 1). Synthesis of 1-(4′-Methoxyphenyl)-2-[4′-(benzyloxy)phenyl]ethanone (5).** To a solution of desoxyanisoin (4) (3.0 g, 11.7 mmol) in dry CH_2Cl_2 (160 mL) at −78 °C was added dropwise boron tribromide (24.6 mL of a 1.0 M solution, 24.6 mmol) in dry CH_2Cl_2 (10 mL) over 0.5 h. At the end of the addition, the temperature of the mixture was raised and kept at −10 °C for 3 h. Then, the mixture was slowly poured into ice–water with stirring, and the product was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure. Without purification, the crude monophenolic compound was dissolved in acetone (140 mL) followed by addition of K_2CO_3 (1.76 g, 12.8 mmol) and benzyl chloride (3.5 mL, 30 mmol). The mixture was heated at reflux for 45 h. Additional K_2CO_3 (1.7 g, 12 mmol) was added after 5 h, while benzyl chloride (3 × 3 mL, 26 mmol) was added after 5, 22, and 28 h. The solid was then filtered and washed with acetone. Water was added to the organic solvent and acetone partially evaporated before extraction with CH_2Cl_2. The organic phase was dried ($MgSO_4$), the solvent removed, and the solid recrystallized from hexane–EtOAc to provide a light yellow solid (2.91 g, 75%): mp 121–123 °C; IR ν(KBr) 1675 (C=O, conjugated ketone); ^1H NMR δ ($CDCl_3$, 200 MHz) 3.85 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2CO), 5.03 (s, 2H, OCH_2Ph), 6.92 (d, J = 9.2 Hz, 4H, ArH *meta* to CO and to CH_2), 7.18 (d, J = 8.8 Hz, 2H, ArH *ortho* to CH_2), 7.3–7.5 (m, 5H, OCH_2 **Ph**), 7.99 (d, J = 8.8 Hz, 2H, ArH *ortho* to CO); MS *m/e* 332 (M^+, 47), 197 (9.3), 135 (100), 107 (37), 91 (100), 77 (62); EIMS calcd for $C_{22}H_{20}O_3$ (M^+), 332.1412, found, 332.1348.

Synthesis of 1-(4′-Methoxyphenyl)-2-[4′-(tetrahydro-2″*H*-pyran-2″-yloxy)phenyl]ethanone (6). Selective monodeprotection of desoxyanisoin (2.0 g, 7.8 mmol) was performed as reported in the first part of the synthesis of compound 5. Without purification, the crude monophenolic compound was dissolved in a mixture of dry benzene (100 mL) and 3,4-dihydro-2*H*-pyran (100 mL). A catalytic amount of *p*-TSA (60 mg) was added, and the mixture was stirred at room temperature for 2.5 h. The mixture was poured into a saturated $NaHCO_3$ solution, extracted with benzene, washed with water, and dried over $MgSO_4$. After partial evaporation of benzene, the THP derivative crystallized as a white powder (2.05 g, 80%): mp 104–105 °C; IR ν(KBr) 1670 (C=O, conjugated ketone); ^1H NMR δ ($CDCl_3$, 300 MHz) 1.5–2.1 (m, 6H, 3 × CH_2 of THP), 3.58 and 3.90 (2m, 2H, CH_2O of THP), 3.86 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2CO), 5.38 (t, J = 3.1 Hz, 1H, CH of THP), 6.92 (d, J = 8.9 Hz, 2H, ArH *meta* to CO), 7.00 (d, J = 8.7 Hz, 2H, ArH *meta* to CH_2), 7.17 (d, J = 8.6 Hz, 2H, ArH *ortho* to CH_2), 7.99 (d, J = 8.8 Hz, ArH *ortho* to CO); MS *m/e* 326 (M^+, 0.5), 243 (30), 135 (100), 107 (30), 85 (92); FABMS calcd for $C_{20}H_{23}O_4$ (M^+ + H), 327.1596; found, 327.1561.

Synthesis of 1,2-Bis[4′-(tetrahydro-2″*H*-pyran-2″-yloxy)phenyl]ethanone (7). Desoxyanisoin (4) was transformed to diphenol ketone by pyridine hydrochloride treatment according to the procedure of Buu-Hoi et al.[42] The diphenolic compound (6.0 g, 26 mmol) was dissolved in a mixture of benzene (50 mL) and 3,4-dihydro-2*H*-pyran (50 mL). A catalytic amount of *p*-TSA (450 mg) was added, and the mixture was stirred at 0 °C under argon for 1.5 h. The mixture was then poured into a saturated $NaHCO_3$ solution, extracted with EtOAc, washed with water, and dried over $MgSO_4$. After evaporation of the solvent, the crude compound was recrystallized in diethyl ether–CH_2Cl_2 to give 6.72 g (64%) of a white solid: mp 118–122 °C; IR ν(KBr) 1665 (C=O, conjugated ketone); ^1H NMR δ ($CDCl_3$, 300 MHz) 1.5–2.1 (m, 12H, 6 × CH_2 of THP), 3.6 and 3.9 (2m, 4H, 2 × CH_2O of THP), 4.15 (s, 2H, CH_2CO), 5.37 and 5.49 (2t, J = 3 Hz, 2H, 2 × CH of THP), 6.99 (d, J = 8.6 Hz, 2H, ArH *meta* to CH_2), 7.06 (d, J = 8.9 Hz, 2H, ArH *meta* to CO), 7.16 (d, J = 8.6 Hz, 2H, ArH *ortho* to CH_2), 7.96 (d, J = 8.8 Hz, 2H, ArH *ortho* to CO); MS *m/e* 313 (M^+ − DHP, 2.4), 228 (49), 121 (100), 107 (59), 85 (100); FABMS calcd for $C_{24}H_{29}O_5$ (M^+ + H), 397.2015; found, 397.2033.

General Procedure for Reduction of Ketones to Racemic Alcohols 8–11. A mixture of ketones 4–7 (5.9–7.7 mmol), methanol (100 mL), and sodium borohydride (1.1 equiv) was stirred at room temperature for 1 h. The reaction was quenched by addition of water, and methanol was evaporated under reduced pressure. The resulting white solid was filtered, washed with water, and dried under a vacuum pump for 1 or 2 days.

1,2-Bis(4′-methoxyphenyl)ethanol (8): white solid (96% yield), mp 107–109 °C; IR ν(KBr) 3520, 3350 (OH, alcohol free and H-bonded); ^1H NMR δ ($CDCl_3$, 300 MHz) 2.0 (br, 1H, OH), 2.92 (d_{app}, $J \sim 7$ Hz, 2H, CH_2CHOH), 3.77 and 3.79 (2s, 6H, 2 × OCH_3), 4.77 (t, J = 6.6 Hz, 1H, CH_2CHOH), 6.81 (d, J = 8.7 Hz, 2H, ArH *meta* to CH_2), 6.86 (d, J = 8.7 Hz, 2H, ArH *meta* to CHOH), 7.07 (d, J = 8.6 Hz, 2H, ArH *ortho* to CH_2), 7.24 (d, J = 8.6 Hz, 2H, ArH *ortho* to CHOH); ^{13}C NMR δ ($CDCl_3$, 75 MHz) 45.0, 55.2 (2×), 75.0, 113.7 (2×), 113.8 (2×), 127.1 (2×), 130.1, 130.4(2×), 136.0, 158.3, 159.0; MS *m/e* 240 (M^+ − H_2O, 100), 225 (60), 137 (67), 122 (61); EIMS calcd for $C_{16}H_{16}O_2$ (M^+ − H_2O), 240.1150; found, 240.1126. Anal. ($C_{16}H_{18}O_3$) C, H.

1-(4′-Methoxyphenyl)-2-[4′-(benzyloxy)phenyl]ethanol (9): white solid (96% yield), mp 108–110 °C; IR ν(KBr) 3400 (OH, alcohol); ^1H NMR δ ($CDCl_3$, 200 MHz) 2.0 (d, J = 2.9 Hz, 1H, OH), 2.94 (d, J = 6.6 Hz, 2H, CH_2CHOH), 3.80 (s, 3H, OCH_3), 4.79 (t, $J \sim 6$ Hz, 1H, CH_2CHOH), 5.04 (s, 2H, OCH_2Ph), 6.87 (d, J = 8.7 Hz, 2H, ArH *meta* to CHOH), 6.90 (d, J = 8.7 Hz, 2H, ArH *meta* to CH_2), 7.09 (d, J = 8.8 Hz, 2H, ArH *ortho* to CH_2), 7.26 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHOH), 7.3–7.5 (m, 5H, OCH_2Ph); ^{13}C NMR δ ($CDCl_3$, 50 MHz) 45.1, 55.3, 70.0, 75.0, 113.6 (2×), 114.8 (2×), 127.0 (2×), 127.4, 127.8 (2×), 128.4 (2×), 130.4 (3×), 135.9, 137.0, 157.4, 158.9; MS *m/e* 316 (M^+ − H_2O, 97), 225 (82), 91 (100); EIMS calcd for $C_{22}H_{20}O_2$ (M^+ − H_2O), 316.1463; found, 316.1425. Anal. ($C_{22}H_{22}O_3$) C, H.

1-(4′-Methoxyphenyl)-2-[4′-(tetrahydro-2″*H*-pyran-2″-yloxy)phenyl]ethanol (10): white solid (94% yield), mp 130–135 °C; IR ν(KBr) 3520, 3380 (OH, alcohol free and H-bonded); ^1H NMR δ ($CDCl_3$, 200 MHz) 1.5–2.1 (m, 6H, 3 × CH_2 of THP), 2.92 and 2.93 (2d, J = 5.1, 8.1 Hz, 2H, CH_2CHOH), 3.6 and 3.9 (2m, 2H, CH_2O of THP), 3.80 (s, 3H, OCH_3), 4.80 (t, J = 6.4 Hz, 1H, CH_2CHOH), 5.37 (t, J = 3.3 Hz, 1H, CH of THP), 6.87 (d, J = 8.8 Hz, 2H, ArH *meta* to CHOH), 6.97 (d, J = 8.4 Hz, 2H, ArH *meta* to CH_2), 7.09 (d, J = 8.4 Hz, 2H, ArH *ortho* to CH_2),

7.27 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHOH); ^{13}C NMR δ (acetone-d_6, 50 MHz) 19.7, 26.0, 31.2, 46.3, 55.5, 62.5, 75.5, 97.2, 114.2 (2×), 116.9 (2×), 128.1 (2×), 130.7, 131.3 (2×), 138.5, 156.5, 159.7; MS m/e 310 ($M^+ - H_2O$, 3.0), 244 (13), 226 (100), 211 (35), 137 (100), 107 (54), 85 (97); FABMS calcd for $C_{20}H_{23}O_4$ ($M^+ - H$), 327.1596; found, 327.1561. Anal. ($C_{20}H_{24}O_4$) C, H.

1,2-Bis[4′-(tetrahydro-2″*H*-pyran-2″yloxy)phenyl]ethanol (11): white solid (92% yield), mp 112–114 °C; IR ν(KBr) 3450 (OH, alcohol free and H-bonded); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.5–2.1 (m, 6 × CH_2 of THP), 2.94 (m, 2H, CH_2CHOH), 3.60 and 3.90 (2m, 4H, 2 × CH_2O of THP), 4.79 (t, $J \sim 3$ Hz, 1H, CH_2CHOH), 5.40 (m, 2H, 2 × CH of THP), 6.98 (d, J = 8.5 Hz, 2H, ArH *meta* to CH_2), 7.02 (d, J = 8.6 Hz, 2H, ArH *meta* to CHOH), 7.10 (d, J = 7.9 Hz, 2H, ArH *ortho* to CH_2), 7.26 (d, J = 8.5 Hz, 2H, ArH *ortho* to CHOH); ^{13}C NMR δ ($CDCl_3$, 75 MHz) 18.8, 25.2, 30.4, 45.2, 62.0 (2×), 75.0, 96.4 (2×), 116.3 (2×), 116.5 (2×), 127.0 (2×), 130.4 (2×), 131.2, 137.0, 155.8, 156.5; MS m/e 296 (M^+ - (H_2O + DHP), 1.2), 212 (100), 84 (53); FABMS calcd for $C_{24}H_{29}O_5$ ($M^+ - H$), 397.2015; found, 397.1997. Anal. ($C_{24}H_{30}O_5$) C, H.

2. Synthesis of Starting Side Chains. General Procedure for the Synthesis of Bromo Amides 18–21. Carboxylic acids 14–17 (3.7 g, 16.6 mmol) were dissolved in dry CH_2Cl_2 (200 mL) and tributylamine (20 mmol). After the mixture had cooled at −10 °C, isobutyl chloroformate (22 mmol) was added and allowed to react for 40 min. At this time, excess *N*-methylbutylamine (83 mmol) was added and the cooling bath was removed. After 3 h, CH_2Cl_2 was added and the organic phase was washed with HCl (1 N), saturated $NaHCO_3$, and water. After drying on $MgSO_4$, the solvent was removed and the crude amide was purified by column chromatography with hexane–EtOAc, 80:20, as eluent.

***N*-Butyl-*N*-methyl-6-bromohexanamide (18):** colorless oil (76% yield); IR ν(neat) 1620 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 0.84 and 0.86 (2t, J = 7.2 Hz, 3H, CH_2CH_3), 1.21–1.83 (m, 8H, 4 × CH_2), 1.79 (quintet, J = 7 Hz, 2H, CH_2), 2.27 (t, J = 7.4 Hz, 2H, CH_2CO), 2.83 and 2.91 (2s, 3H, CH_3NCO), 3.19 and 3.28 (2t, 2H, J = 7.5 Hz, CH_2NCO), 3.34 (t, J = 6.7 Hz, 2H, CH_2Br); MS m/e 265 (M^+, 1.1), 263 (M^+, 1.5), 184 (20), 142 (39), 129 (59), 114 (100), 87 (59).

***N*-Butyl-*N*-methyl-8-bromooctanamide (19):** colorless oil (89% yield); IR ν(neat) 1635 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 0.84 and 0.87 (2t, J = 7.3 Hz, 3H, CH_2CH_3), 1.15–1.60 (m, 12H, 6 × CH_2), 1.77 (quintet, J = 7 Hz, 2H, CH_2), 2.21 (m, 2H, CH_2CO), 2.83 and 2.89 (2s, 3H, CH_3NCO), 3.18 and 3.28 (2t, J = 7.5 Hz, 2H, CH_2NCO), 3.32 (t, J = 6.9 Hz, 2H, CH_2Br); MS m/e 293 (M^+, 2.7), 291 (M^+, 2.5), 212 (37), 142 (30), 129 (65), 114 (100), 87 (57).

***N*-Butyl-*N*-methyl-11-bromoundecanamide (20):** colorless oil (66% yield); IR ν(neat) 1630 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 0.90 and 0.93 (2t, J = 7.4 Hz, 3H, CH_2CH_3), 1.20–1.60 (m, 18H, 9 × CH_2), 1.83 (quintet, J = 7.3 Hz, 2H, CH_2), 2.26 (m, 2H, CH_2CO), 2.89 and 2.95 (2s, 3H, CH_3NCO), 3.23 and 3.34 (2t, J = 7.2 Hz, 2H, CH_2NCO), 3.38 (t, J = 6.8 Hz, 2H, CH_2Br); MS m/e 335 (M^+, 3.8), 333 (M^+, 3.9), 254 (25), 142 (51), 129 (91), 114 (100), 87 (68).

***N*-Butyl-*N*-methyl-12-bromododecanamide (21):** colorless oil (98% yield); IR ν(neat) 1635 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 0.83 and 0.92 (2t, J = 7.5 Hz, 3H, CH_2CH_3), 1.19–1.62 (m, 20H, 10 × CH_2), 1.75 (quintet, J = 7.2 Hz, 2H, CH_2), 2.20 (m, 2H, CH_2CO), 2.82 and 2.88 (2 s, 3H, CH_3NCO), 3.17 and 3.27 (2t, J = 7.7 Hz, 2H, CH_2NCO), 3.32 (t, J = 6.9 Hz, 2H, CH_2Br); MS m/e 349 (M^+, 1.3), 347 (M^+, 1.3), 268 (8.4), 142 (28), 129 (55), 114 (100), 87 (58).

General Procedure for the Synthesis of Thiols 13 and 22–25. The two-step procedure reported in *Organic Syntheses*[24] was used for the synthesis of thiols (mercapto side chain). However, when bromoalkanamide was used, the reaction times were increased to 15–24 h for the first step and 9–25 h for the second step. Purification of crude thiol was done by column chromatography with hexane–EtOAc, 80:20, as eluent.

11-Mercaptoundecanol (13): white solid from hexane (96% yield), mp 75–78 °C; IR ν(KBr) 3300 (OH, alcohol); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.2–1.4 (m, 14H, 7 × CH_2), 1.55 (m, 4H, 2 × CH_2), 1.9 (br, 1H, SH), 2.49 (q_{app}, J = 7.3 Hz, 2H, $HSCH_2$), 3.59 (t, J = 6.6 Hz, 2H, CH_2OH); MS m/e 406 (M^+ of dimeric form, 88), 185 ($M^+ - H_2O$, 61).

***N*-Butyl-*N*-methyl-6-mercaptohexanamide (22):** colorless oil (90% yield); IR ν(neat) 2520 vw (SH), 1625 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 0.84 and 0.87 (2t, J = 7.3 Hz, 3H, CH_2CH_3), 1.1–1.7 (m, 10H, 5 × CH_2), 2.22 (m, 2H, CH_2CO), 2.46 (q_{app}, J = 7.3 Hz, 2H, $HSCH_2$), 2.83 and 2.89 (2s, 3H, CH_3NCO), 3.18 and 3.28 (2t, J = 7.5 Hz, 2H, CH_2NCO); MS m/e 217 (M^+, 44), 184 (64), 142 (68), 129 (56), 114 (100), 87 (76).

***N*-Butyl-*N*-methyl-8-mercaptooctanamide (23):** colorless oil (78% yield); IR ν(neat) 2520 vw (SH), 1630 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 0.83 and 0.87 (2t, J = 7.3 Hz, 3H, CH_2CH_3), 1.2–1.6 (m, 14H, 7 × CH_2), 2.21 (m, 2H, CH_2CO), 2.43 (q_{app}, J = 7.4 Hz, 2H, $HSCH_2$), 2.81 and 2.88 (2s, 3H, CH_3NCO), 3.17 and 3.27 (2t, J = 7.5 Hz, 2H, CH_2NCO); MS m/e 245 (M^+, 15), 212 (66), 142 (43), 129 (33), 114 (100), 87 (58).

***N*-Butyl-*N*-methyl-11-mercaptoundecanamide (24):** colorless oil (62% yield); IR ν(neat) 2520 w (SH), 1640 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 0.90 and 0.94 (2t, J = 7 Hz, 3H, CH_2CH_3), 1.1–1.7 (m, 20H, 10 × CH_2), 2.27 and 2.28 (2t, J = 7.3 Hz, 2H, CH_2CO), 2.89 and 2.95 (2s, 3H, CH_3NCO), 3.23 and 3.34 (2t, J = 7.46 Hz, 2H, CH_2NCO); MS m/e 287 (M^+, 22), 254 (22), 142 (21), 129 (29), 114 (56), 87 (25), 44 (100).

***N*-Butyl-*N*-methyl-12-mercaptododecanamide (25):** colorless oil (53% yield); IR ν(neat) 2540 w (SH), 1640 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 0.88 and 0.92 (2t, J = 7.0 Hz, 3H, CH_2CH_3), 1.2–1.7 (m, 22H, 11 × CH_2), 2.25 and 2.26 (2t, J = 7.5 Hz, 2H, CH_2CO), 2.87 and 2.93 (2s, 3H, CH_3NCO), 3.22 and 3.32 (2 t, J = 7.4 Hz, 2H, CH_2NCO); MS m/e 301 (M^+, 46), 268 (52), 142 (82), 129 (62), 114 (100), 86 (51).

3. Synthesis of Racemic Thioethers: 26–42. Zinc iodide was added to a solution of racemic alcohols 8–11 and mercapto side-chain in dry 1,2-dichloroethane. The suspension was stirred at room temperature under an argon atmosphere for the appropriate time. Then, the reaction was quenched by addition of water and the mixture extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated to dryness, and the crude product was purified by column chromatography with a suitable mixture of hexane–EtOAc as eluent. Table 3 shows the conditions used for thioether formation.

Methyl-5,6-bis(4′-methoxyphenyl)-4-thiahexanoate (26): colorless oil; IR ν(neat) 1720 (C=O, ester); ^{1}H NMR δ ($CDCl_3$, 300 MHz), 2.42 and 2.52 ($2t_{app}$, J = 6.6 Hz, 4H, SCH_2CH_2CO), 3.03 (m, 2H, $PhCH_2CH$), 3.63 (s, 3H, $COOCH_3$), 3.75 and 3.79 (2s, 6H, 2 × OCH_3), 3.96 (t, 1H, CH_2CHS), 6.73 (d, J = 8.7 Hz, 2H, ArH *meta* to CH_2), 6.80 (d, J = 8.7 Hz, 2H, ArH *meta* to CHSR), 6.92 (d, J = 8.5 Hz, 2H, ArH *ortho* to CH_2), 7.16 (d, J = 8.6 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 50 MHz) 25.8, 34.0, 42.1, 51.3, 51.5, 54.7, 54.8, 113.1, 113.3 (2×), 128.6 (2×), 129.6 (2×), 130.5, 133.2, 157.6, 158.2, 171.5; MS m/e 360 (M^+, 4.9), 240 (100), 225 (13), 151 (72), 121 (67); FABMS calcd for $C_{20}H_{25}O_4S$ ($M^+ + H$), 361.1473; found 361.1510. Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.72; S, 8.88. Found: C, 66.00; H, 7.01; S, 9.07.

***N*-Butyl-*N*-methyl-10,11-bis(4′-methoxyphenyl)-9-thiaundecanamide (27):** colorless oil; IR ν(neat) 1640 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 0.90 and 0.92 (2t, J = 7.0 Hz, 3H, CH_2CH_3), 1.1–1.7 (m, 14H, 7 × CH_2), 2.23 (m, 4H, CH_2CO and SCH_2), 2.88 and 2.93 (2s, 3H, CH_3NCO), 3.02 (m, 2H, $PhCH_2CH$), 3.22 and 3.33 (2t, J = 7.3 Hz, 2H, CH_2NCO), 3.72 and 3.76 (2s, 6H, 2 × OCH_3), 3.90 (dd, J_1 = 6.6 Hz and J_2 = 8.1 Hz, 1H, CH_2CHS), 6.71 (d, J = 8.8 Hz, 2H, ArH *meta* to CH_2), 6.78 (d, J = 8.8 Hz, 2H, ArH *meta* to CHSR), 6.91 (d, J = 8.4 Hz, 2H ArH *ortho* to CH_2), 7.13 (d, J = 8.4 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 75 MHz) (see ref 41) 13.8, 20.0 (19.9), 253 (24.9), 28.7–29.3 (4×), 30.6 (29.3), 31.1, 33.5 (32.8), 35.2 (33.3), 42.5, 49.7 (47.3), 51.1, 55.2, 55.1, 113.4 (2×), 113.6 (2×), 128.9 (2×), 130.0 (2×), 131.2, 134.1, 157.9, 158.4, 172.8; MS m/e 485 (M^+, 0.1), 364 (100), 241 (25), 225 (11), 212 (21), 121 (34); FABMS calcd for $C_{29}H_{42}NO_3S$ ($M^+ - H$), 484.2885; found, 484.2904. Anal. ($C_{29}H_{43}NO_3S$) C, H, N.

***N*-Butyl-*N*-methyl-14,15-bis(4′-methoxyphenyl)-13-thiapentadecanamide (28):** colorless oil; IR ν(neat) 1640 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 0.90 and 0.93 (2t, J = 7.3 Hz, 3H, CH_2CH_3), 1.1–1.7 (m, 22H, 11 × CH_2), 2.26 (m, 4H, CH_2CO and SCH_2), 2.89 and 2.94 (2s, 3H, CH_3NCO), 3.03 (m, 2H, $PhCH_2CH$), 3.23 and 3.34 (2t, J = 7.4 Hz, 2H, CH_2NCO), 3.73 and 3.77 (2s, 6H, 2 × OCH_3), 3.91 (dd, J_1 = 6.6 Hz and J_2 = 8.3

Hz, 1H, CH_2CHS), 6.71 (d, J = 8.8 Hz, 2H, ArH *meta* to CH_2), 6.78 (d, J = 8.8 Hz, 2H, ArH *meta* to CHSR), 6.92 (d, J = 8.4 Hz, 2H, ArH *ortho* to CH_2), 7.14 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 13.9, 20.1 (20.0), 25.5 (25.1), 28.9–29.5 (8×), 30.7 (29.2), 31.3, 33.2 (33.0), 35.3 (33.7), 42.5, 49.7 (47.4), 51.1, 55.2, 55.1, 113.3 (2×), 113.5 (2×), 128.9 (2×), 130.0 (2×), 131.1, 134.0, 157.8, 158.3, 172.0; MS *m/e* 541 (M^+, 0.7), 420 (100), 300 (4.1), 268 (10), 241 (37), 225 (12), 121 (41); FABMS calcd for $C_{33}H_{52}NO_3S$ (M^+ + H), 542.3668; found, 542.3611. Anal. ($C_{33}H_{51}NO_3S$) C, H, N, S.

Methyl-6-[4′-(benzyloxy)phenyl]-5-(4′-methoxyphenyl)-4-thiahexanoate (29): white solid, mp 79–81 °C; IR ν(KBr) 1715 (C=O, ester); ^1H NMR δ ($CDCl_3$, 300 MHz) 2.43 and 2.53 ($2t_{app}$, J = 7.0 Hz, 4H, SCH_2CH_2CO), 3.04 (m, 2H, $PhCH_2CH$), 3.64 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 3.97 (dd, J_1 = 6.6 Hz and J_2 = 8.2 Hz, 1H, CH_2CHS), 5.00 (s, 2H, $PhCH_2O$), 6.82 (d, J = 8.7 Hz, 4H, ArH *meta* to CH_2 and to CHSR), 6.94 (d, J = 8.7 Hz, 2H, ArH *ortho* to CH_2), 7.17 (d, J = 8.7 Hz, 2H, ArH *ortho* to CHSR), 7.37 (m, 5H, $PhCH_2O$); ^{13}C NMR δ ($CDCl_3$, 75 MHz) 26.2, 34.3, 42.5, 51.4, 51.7, 55.2, 70.0, 113.8 (2×), 114.5 (2×), 127.5, 127.9, 128.5, 129.1 (2×), 130.2 (2×), 131.3, 133.6, 137.1, 157.4, 158.7, 172.4; MS *m/e* 436 (M^+, 0.7), 317 (36), 239 (100), 225 (58), 151 (51), 91 (100); EIMS calcd for $C_{28}H_{28}O_4S$ (M^+), 436.1708; found, 436.1673. Anal. Calcd for $C_{28}H_{28}O_4S$: C, 71.53; H, 6.46; S, 7.34. Found: C, 72.20; H, 7.01; S, 7.01.

***N*-Butyl-*N*-methyl-11-[4′-(benzyloxy)phenyl]-10-(4′-methoxyphenyl)-9-thiaundecanamide (30):** colorless oil; IR ν(neat) 1630 (C=O, amide); ^1H NMR δ ($CDCl_3$, 200 MHz) 0.91 and 0.94 (2d, J = 7.0 Hz, 3H, CH_2CH_3), 1.1–1.7 (m, 14H, 7 × CH_2), 2.25 (m, 4H, CH_2CO and SCH_2), 2.89 and 2.94 (2s, 3H, CH_3NCO), 3.03 (m, 2H, $PhCH_2CH$), 3.23 and 3.34 (2t, J = 7.4 Hz, 2H, CH_2CO), 3.78 (s, 3H, OCH_3), 3.92 (dd, J_1 = 6.5 Hz and J_2 = 8.2 Hz, 1H, CH_2CHS), 4.99 (s, 2H, $PhCH_2O$), 6.79 and 6.80 (2d, J = 8.4, 8.9 Hz, 4H, ArH *meta* to CH_2 and *meta* to CH_2SR), 6.93 (d, J = 8.8 Hz, 2H, ArH *ortho* to CH_2), 7.14 (d, J = 8.4 Hz, 2H, ArH *ortho* to CHSR), 7.35 (m, 5H, $PhCH_2O$); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 13.9, 20.1 (20.0), 25.4 (25.0), 28.8–29.3 (4×), 30.7 (29.1), 31.3, 33.3 (32.9), 35.4 (33.6), 42.6, 49.8 (47.4), 51.1, 55.2, 69.9, 113.5 (2×), 114.3 (2×), 127.4, 127.8, 128.4, 128.9 (2×), 130.0 (2×), 131.5, 134.1, 137.0, 157.1, 158.3, 170.3; MS *m/e* 561 (M^+, 0.4), 365 (99), 317 (25), 225 (64), 212 (51), 121 (52), 91 (100); FABMS calcd for $C_{35}H_{48}NO_3S$ (M^+ + H), 562.3355; found, 562.3378. Anal. ($C_{35}H_{47}NO_3S$) C, H, N.

***N*-Butyl-*N*-methyl-14-[4′-(benzyloxy)phenyl]-13-(4′-methoxyphenyl)-12-thiatetradecanamide (31):** colorless oil; IR ν(neat) 1635 (C=O, amide); ^1H NMR δ ($CDCl_3$, 200 MHz) 0.92 and 0.94 (2t, J = 7.0 Hz, 3H, CH_2CH_3), 1.1–1.7 (m, 20H, 10 × CH_2), 2.24 (m, 4H, CH_2CO and SCH_2), 2.90 and 2.95 (2s, 3H, CH_3NCO), 3.04 (m, 2H, $PhCH_2CH$), 3.24 and 3.35 (2t, J = 7.3 Hz, 2H, CH_2NCO), 3.78 (s, 3H, OCH_3), 3.92 (dd, J_1 = 6.5 Hz and J_2 = 8.2 Hz, 1H, CH_2CHS), 4.99 (s, 2H, $PhCH_2O$), 6.79 and 6.80 (2d, J = 8.4, 8.8 Hz, 4H, ArH *meta* to CH_2 and to CHSR), 6.93 (d, J = 8.8 Hz, 2H, ArH *ortho* to CH_2), 7.15 (d, J = 8.4 Hz, 2H, ArH *ortho* to CHSR), 7.36 (m, 5H, $PhCH_2O$); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 13.9, 20.1 (20.0), 25.5 (25.2), 28.9–29.5 (7×), 30.7 (29.2), 31.3, 33.3 (33.0), 35.3 (33.7), 42.6, 49.8 (47.4), 51.1, 55.2, 69.9, 113.5 (2×), 114.3 (2×), 127.3, 127.7, 128.4, 128.9 (2×), 130.0 (2×), 131.5, 134.0, 137.0, 157.1, 158.3, 172.8; MS *m/e* 603 (M^+, 0.4), 407 (100), 317 (29), 254 (20), 225 (52), 121 (55), 91 (99); FABMS calcd for $C_{38}H_{54}NO_3S$ (M^+ + H), 604.3824; found, 604.3849. Anal. ($C_{38}H_{53}NO_3S$) C, H, N, S.

14-[4′-(Benzyloxy)phenyl]-13-(4′-methoxyphenyl)-12-thiatetradecanol (32): white solid from hexane–ether, mp 60–62 °C; IR ν(KBr) 3330 (OH, alcohol); ^1H NMR δ ($CDCl_3$, 200 MHz) 1.1–1.7 (m, 18H, 9 × CH_2), 2.24 (m, 2H, SCH_2), 3.04 (m, 2H, $PhCH_2CH$), 3.63 (t, J = 6.6 Hz, 2H, CH_2OH), 3.78 (s, 3H, OCH_3), 3.92 (dd, J_1 = 6.2 Hz and J_2 = 8.4 Hz, 1H, CH_2CHS), 4.99 (s, 2H, $PhCH_2O$), 6.80 (d, J = 8.8 Hz, 4H, ArH *meta* to CH_2 and to CHSR), 6.94 (d, J = 8.8 Hz, 2H, ArH *ortho* to CH_2), 7.15 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHSR), 7.37 (m, 5H, $PhCH_2O$); ^{13}C NMR δ ($CDCl_3$, 50 MHz) 25.8, 28.9–29.6 (7×), 31.3, 32.8, 42.6, 51.1, 55.2, 63.1, 69.9, 113.5 (2×), 114.3 (2×), 127.4, 127.8, 128.4, 128.9 (2×), 130.0 (2×), 131.5, 134.1, 137.0, 157.1, 158.3; MS *m/e* 520 (M^+, 0.6), 324 (52), 225 (93), 152 (37), 120 (45), 91 (100); FABMS calcd for $C_{33}H_{45}O_3S$ (M^+ + H), 521.3089; found, 521.3140. Anal. ($C_{33}H_{44}O_3S$) C, H, S.

Methyl-6-(4′-hydroxyphenyl)-5-(4′-methoxyphenyl)-4-thiahexanoate (33): colorless oil; IR ν(neat) 3400 (OH, phenol), 1720 (C=O, ester); ^1H NMR δ ($CDCl_3$, 300 MHz) 2.17 (s, 1H, OH), 2.42 and 2.52 ($2t_{app}$, J = 6.5, 6.8 Hz, 4H, SCH_2CH_2CO), 3.00 (m, 2H, $PhCH_2CH$), 3.63 (s, 3H, $COOCH_3$), 3.76 (s, 3H, OCH_3), 3.95 (t, $J \sim 7$ Hz, 1H, CH_2CHS), 6.66 (d, J = 8.2 Hz, 2H, ArH *meta* to CH_2), 6.79 (d, J = 8.6 Hz, 2H, ArH *meta* to CHSR), 6.85 (d, J = 8.3 Hz, 2H, ArH *ortho* to CH_2), 7.14 (d, J = 8.6 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 75 MHz) 26.1, 34.3, 42.4, 51.4, 51.8, 55.2, 113.8 (2×), 115.1 (2×), 129.1 (2×), 130.0 (2×), 130.6, 133.6, 154.5, 158.6, 172.8; MS *m/e* 346 (M^+, 0.4), 239 (100), 227 (79), 151 (59); MS calcd for $C_{19}H_{22}O_4S$ (M^+), 346.1239; found, 346.1237. Anal. ($C_{19}H_{22}O_4S$) C, H, S.

***N*-Butyl-*N*-methyl-11-(4′-hydroxyphenyl)-10-(4′-methoxyphenyl)-9-thiaundecanamide (34):** colorless oil; IR ν(neat) 3200 (OH, phenol), 1605 (C=O, amide); ^1H NMR δ ($CDCl_3$, 200 MHz) 0.92 and 0.94 (2t, J = 7.3 Hz, 3H, CH_2CH_3), 1.05–1.75 (m, 14H, 7 × CH_2), 2.17 (t, J = 7 Hz, 2H, SCH_2), 2.28 (m, 2H, CH_2CO), 2.94 and 2.97 (2s, 3H, CH_3NCO), 3.00 (m, 2H, $PhCH_2CH$), 3.25 and 3.38 (2t, J = 7.5 Hz, 2H, CH_2NCO), 3.78 (s, 3H, OCH_3), 3.8 (m, 1H, CH_2CHS), 6.75 (d, J = 8.4 Hz, 2H, ArH *meta* to CH_2), 6.81, (d, J = 8.8 Hz, 2H, ArH *meta* to CHSR), 6.97 (d, J = 8.8 Hz, 2H, ArH *ortho* to CH_2), 7.14 (br, 1H, OH phenol), 7.19 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 14.0, 20.1 (20.0), 25.4 (25.1), 28.3–29.5 (4×), 30.7 (29.5), 31.6, 33.7 (33.0), 35.5 (33.7), 43.0, 50.0 (47.7), 51.6, 55.3, 113.7 (2×), 115.2 (2×), 128.5 (2×), 130.1 (2×), 130.8, 135.3, 154.9, 158.3, 173.5; MS *m/e* 471 (M^+, 0.1), 364 (100), 227 (36), 212 (26), 121 (28); FABMS calcd for $C_{28}H_{40}NO_3S$ (M^+ – H), 470.2729; found, 470.2775. Anal. ($C_{28}H_{41}NO_3S$) C, H, N.

***N*-Butyl-*N*-methyl-14-(4′-hydroxyphenyl)-13-(4′-methoxyphenyl)-12-thiatetradecanamide (35):** colorless oil; IR ν(neat) 3200 (OH, phenol), 1605 (C=O, amide); ^1H NMR δ ($CDCl_3$, 200 MHz) 0.91 and 0.95 (2t, J = 7.3 Hz, 3H, CH_2CH_3), 1.10–1.75 (m, 20H, 10 × CH_2), 2.27 (m, 4H, CH_2CO and SCH_2), 2.92 and 2.99 (2s, 3H, CH_3NCO), 3.03 (m, 2H, $PhCH_2CH$), 3.26 and 3.37 (2t, J = 7.3 Hz, 2H, CH_2NCO), 3.78 (s, 3H, OCH_3), 3.88 (t_{app}, J = 7.3 Hz, 1H, CH_2CHS), 6.73 (d, J = 8.4 Hz, 2H, ArH *meta* to CH_2), 6.81 (d, J = 8.8 Hz, 2H, ArH *meta* to CHSR), 6.91 (d, J = 8.4 Hz, 2H, ArH *ortho* to CH_2), 7.17 (d, J = 8.4 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 13.9, 20.1 (20.0), 25.7 (25.1), 28.4–29.4 (7×), 30.7 (29.4), 31.2, 33.7 (33.0), 35.5 (33.7), 42.8, 50.0 (47.7), 51.1, 55.2, 113.6 (2×), 115.0 (2×), 128.8 (2×), 130.0 (2×), 130.5, 134.6, 154.9, 158.2, 173.4; MS *m/e* 513 (M^+, 0.2), 406 (100), 392 (4.9), 286 (3.6), 254 (6.4), 227 (29), 121 (24); FABMS calcd for $C_{31}H_{48}NO_3S$ (M^+ + H), 514.3355; found, 514.3406.

***N*-Butyl-*N*-methyl-15-(4′-hydroxyphenyl)-14-(4′-methoxyphenyl)-13-thiapentadecanamide (36):** colorless oil; IR ν(neat) 3240 (OH, phenol), 1610 (C=O, amide); ^1H NMR δ ($CDCl_3$, 200 MHz) 0.90 and 0.94 (2t, J = 7.0 Hz, 3H, CH_2CH_3), 1.1–1.7 (m, 22H, 11 × CH_2), 2.27 (m, 4H, CH_2CO and SCH_2), 2.91 and 2.96 (2s, 3H, CH_3NCO), 3.00 (m, 2H, $PhCH_2CH$), 3.25 and 3.36 (2t, J = 7.3 Hz, 2H, CH_2NCO), 3.77 (s, 3H, OCH_3), 3.89 (t_{app}, J = 7 Hz, 1H, CH_2CHS), 6.71 (d, J = 8.4 Hz, 2H, ArH *meta* to CH_2), 6.78 (d, J = 8.8 Hz, 2H, ArH *meta* to CHSR), 6.85 (d, J = 8.4 Hz, 2H, ArH *ortho* to CH_2), 7.14 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHSR), 7.45 (br, 1H, OH phenol); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 13.9, 20.1 (20.0), 25.5 (25.2), 28.5–29.4 (8×), 30.7 (29.3), 31.1, 33.7 (33.0), 35.5 (33.7), 42.7, 50.0 (47.7), 51.0, 55.2, 113.5 (2×), 115.0 (2×), 128.8 (2×), 130.0 (2×), 130.2, 134.4, 154.8, 158.3, 173.4; MS *m/e* 527 (M^+, 0.5), 420 (100), 300 (5.8), 268 (10), 227 (36), 121 (24); FABMS calcd for $C_{32}H_{48}NO_3S$ (M^+ – H), 526.3355; found, 526.3409. Anal. ($C_{32}H_{49}NO_3S$) C, H, N, S.

14-(4′-Hydroxyphenyl)-13-(4′-methoxyphenyl)-12-thiatetradecanol (37): colorless oil; IR ν(neat) 3320 (OH, phenol and alcohol); ^1H NMR δ ($CDCl_3$, 200 MHz) 1.1–1.7 (m, 18H, 9 × CH_2), 2.23 (m, 2H, SCH_2), 3.01 (m, 2H, $PhCH_2CH$), 3.64 (t, J = 6.6 Hz, 2H, CH_2OH), 3.77 (s, 3H, OCH_3), 3.89 (dd, J_1 = 6.7 Hz and J_2 = 8.2 Hz, 1H, CH_2CHS), 5.5 (br, 1H, OH phenol) 6.64 (d, J = 8.4 Hz, 2H, ArH *meta* to CH_2), 6.79 (d, J = 8.8 Hz, 2H, ArH *meta* to CHSR), 6.87 (d, J = 8.8 Hz, 2H, ArH *ortho* to CH_2), 7.14 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 50 MHz) 25.7, 28.8–29.5 (7×), 31.3, 32.7, 42.6, 51.2, 55.2, 63.1, 113.6 (2×), 114.9 (2×), 128.9 (2×), 130.2 (2×), 131.1, 134.1, 154.1, 158.3;

MS *m/e* 323 (M^+ - $HOPhCH_2$, 70), 265 (72), 227 (100), 153 (80), 121 (88); FABMS calcd for $C_{27}H_{37}O_3S$ (M^+ - H), 429.2463; found, 429.2511. Anal. Calcd for $C_{26}H_{38}O_3S$: C, 72.51; H, 8.89; S, 7.44. Found: C, 71.90; H, 8.77; S, 7.29.

Methyl-5,6-bis(4'-hydroxyphenyl)-4-thiahexanoate (38): white solid, mp 116–118 °C; IR ν(KBr) 3350 (OH, phenol), 1710 (C=O, ester); ^1H NMR δ (acetone-d_6, 300 MHz) 2.42 and 2.53 (2t, J = 6.5, 7.0 Hz, 4H, SCH_2CH_2CO), 2.98 (m, 2H, $PhCH_2CH$), 3.62 (s, 3H, $COOCH_3$), 3.95 (t_{app}, J = 7.5 Hz, 1H, CH_2CHS), 6.67 (d, J = 8.5 Hz, 2H, ArH *meta* to CH_2), 6.76 (d, J = 8.5 Hz, 2H, ArH *meta* to CH_2SR), 6.85 (d, J = 8.3 Hz, ArH *ortho* to CH_2), 7.08 (d, J = 8.4 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ (acetone-d_6, 75 MHz) 26.7, 35.0, 42.9, 51.6, 51.7, 115.6 (2×), 115.8 (2×), 130.0 (2×), 130.8, 130.9 (2×), 133.6, 156.5, 157.1, 172.7; MS *m/e* 332 (M^+, 0.7), 225 (100), 213 (95), 137 (97), 107 (49); FABMS calcd for $C_{16}H_{21}O_4S$ (M^+ + H), 333.1161; found, 333.1172. Anal. ($C_{16}H_{20}O_4S$) C, H, S.

***N*-Butyl-*N*-methyl-8,9-bis(4'-hydroxyphenyl)-7-thianonanamide (39):** colorless oil; IR ν(neat) 3260 (OH, phenol), 1610 (C=O, amide); ^1H NMR δ ($CDCl_3$, 300 MHz) 0.89 and 0.94 (2t, J = 7.4 Hz, 3H, CH_2CH_3), 1.2–1.8 (m, 10H, 5 × CH_2), 2.23 (m, 4H, CH_2CO and SCH_2), 2.90 and 2.93 (2s, 3H, CH_3NCO), 2.99 (m, 2H, $PhCH_2CH$), 3.22 and 3.34 (2t, J = 7.5 Hz, 2H, CH_2NCO), 3.86 (m, 1H, CH_2CHS), 6.68 (d, J = 8.3 Hz, 2H, ArH *meta* to CH_2), 6.73 (d, J = 8.4 Hz, 2H, ArH *meta* to CHSR), 6.85 (d, J = 8.3 Hz, 2H, ArH *ortho* to CH_2), 7.04 (d, J = 8.4 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 75 MHz) (see ref 41) 13.8, 19.9 (19.8), 25.0 (24.6), 28.5, 28.9, 30.4 (29.2), 31.0, 33.7 (32.8), 35.5 (33.4), 42.5, 50.0 (47.8), 51.3, 115.1 (2×), 115.3 (2×), 129.0 (2×), 130.1 (2×), 130.9, 133.4, 154.6, 155.2, 173.9; MS *m/e* 322 (M^+ - $HOPhCH_2$, 5.1), 217 (11), 212 (100), 184 (31), 114 (51); FABMS calcd for $C_{25}H_{36}NO_3S$ (M^+ + H), 430.2416; found, 430.2393. Anal. ($C_{25}H_{35}NO_3S$) C, H, N.

***N*-Butyl-*N*-methyl-10,11-bis(4'-hydroxyphenyl)-9-thiaundecanamide (40):** colorless oil; IR ν(neat) 3250 (OH, phenol), 1610 (C=O, amide); ^1H NMR δ ($CDCl_3$, 300 MHz) 0.91 and 0.94 (2t, J = 7.3 Hz, CH_2CH_3), 1.0–1.6 (m, 14H, 7 × CH_2), 2.23 (m, 4H, CH_2CO and SCH_2), 2.93 and 2.96 (2s, 3H, CH_3NCO), 2.99 (m, 2H, $PhCH_2CH$), 3.25 and 3.37 (2t, J = 7.5 Hz, 2H, CH_2NCO), 3.85 (t, J = 7.4 Hz, 1H, CH_2CHS), 6.71 (d, J = 8.5 Hz, 2H, ArH *meta* to CH_2), 6.78 (d, J = 8.6 Hz, 2H, ArH *meta* to CHSR), 6.89 (d, J = 8.5 Hz, 2H, ArH *ortho* to CH_2), 7.08 (d, J = 8.6 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 75 MHz) (see ref 41) 13.8, 20.0 (19.9), 25.6 (25.2), 28.3–29.1 (4×), 30.5 (29.2), 31.0, 33.7 (33.0), 35.6 (33.8), 42.5, 50.1 (47.8), 51.6, 115.2 (2×), 115.5 (2×), 129.0 (2×), 130.2 (2×), 130.8, 133.8, 154.6, 155.3, 174.2; MS *m/e* 350 (M^+ - $HOPhCH_2$, 1.9), 245 (8.1), 212 (100), 114 (45); FABMS calcd for $C_{27}H_{40}NO_3S$ (M^+ + H), 458.2728; found, 458.2748. Anal. ($C_{25}H_{35}NO_3S$) C, H, N.

***N*-Butyl-*N*-methyl-13,14-bis(4'-hydroxyphenyl)-12-thiatetradecanamide (41):** colorless oil; IR ν(neat) 3250 (OH, phenol), 1610 (C=O, amide); ^1H NMR δ ($CDCl_3$, 300 MHz) 0.90 and 0.95 (2t, J = 7.2 Hz, 3H, CH_2CH_3), 1.1–1.7 (m, 20H, 10 × CH_2), 2.28 (m, 4H, CH_2CO and SCH_2), 2.94 and 2.98 (2s, 3H, CH_3NCO), 3.00 (m, 2H, $PhCH_2CH$), 3.27 and 3.38 (2t, J = 7.5 Hz, 2H, CH_2NCO), 3.88 (t, J = 7.3 Hz, 1H, CH_2CHS), 6.69 (d, J = 8.5 Hz, 2H, ArH *meta* to CH_2), 6.79 (d, J = 8.4 Hz, 2H, ArH *meta* to CHSR), 6.87 (d, J = 8.5 Hz, 2H, ArH *ortho* to CH_2), 7.08 (d, J = 8.5 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 75 MHz) (see ref 41) 13.8, 20.0 (19.9), 25.4 (25.1), 28.1–29.1 (7×), 30.5 (29.3), 30.8, 33.8 (32.9), 35.6 (33.6), 42.6, 50.1 (47.8), 51.3, 115.0 (2×), 115.2 (2×), 129.1 (2×), 130.1 (2×), 130.8, 133.3, 154.6, 155.5, 174.1; MS *m/e* 390 (M^+ - $HOPhCH_2$, 5.1), 287 (15), 254 (26), 212 (100), 114 (83); FABMS calcd for $C_{30}H_{49}NO_3S$ (M^+ + H), 500.3198; found, 500.3220. Anal. ($C_{30}H_{45}NO_3S$) C, H, N.

13,14-Bis(4'-hydroxyphenyl)-12-thiatetradecanol (42): colorless oil; IR ν(neat) 3250 (OH, phenol and alcohol); ^1H NMR δ ($CDCl_3$, 300 MHz) 1.2–1.6 (m, 18H, 9 × CH_2), 2.25 (m, 2H, SCH_2), 3.0 (m, 2H, $PhCH_2CH$), 3.60 (t, J = 6.5 Hz, 2H, CH_2OH), 3.91 (t_{app}, J = 7.4 Hz, 1H, CH_2CHS), 6.66 (d, J = 8.5 Hz, 2H, ArH *meta* to CH_2), 6.74 (d, J = 8.5 Hz, 2H, ArH *meta* to CHSR), 6.85 (d, J = 8.5 Hz, 2H, ArH *ortho* to CH_2), 7.07 (d, J = 8.5 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ (acetone-d_6, 75 MHz) 26.7, 29.1–31.1 (7×), 31.7, 33.8, 42.2, 51.7, 62.5, 115.7 (2×), 115.8 (2×), 130.0 (2×), 131.0 (2×), 131.1, 134.1, 156.6, 157.2; MS *m/e* 309 (M^+ - $HOPhCH_2$, 71), 212(100); FABMS calcd for $C_{25}H_{35}O_3S$ (M^+ - H) 415.2307; found, 415.2338. Anal. ($C_{25}H_{36}O_3S$) C, H, S.

4. Synthesis of Racemic Thioethers with a Short Alkanamide Side Chain: 43, 44, 47, and 48. Typical Procedure for Ester Hydrolysis Followed by Amide Formation (Synthesis of 43–46). To a solution of ester **29** (300 mg, 0.69 mmol) in MeOH (60 mL) was added an aqueous solution of KOH, 10% w/v (30 mL), and the mixture was refluxed under an argon atmosphere for 5 h. Thereafter, water was added and MeOH was evaporated under vacuum. The resulting solution was acidified with HCl and extracted with EtOAc. The organic phase was then washed with water and brine and dried over $MgSO_4$. Without purification, the crude carboxylic acid was dissolved in dry CH_2Cl_2 (110 mL) and tributylamine (0.68 mL, 2.8 mmol). After the mixture had cooled at −10 °C, isobutyl chloroformate (0.44 mL, 3.4 mmol) was added and allowed to react for 30 min. At this time, *N*-methylbutylamine in excess (2.6 mL, 22 mmol) was added and the cooling bath was removed. After 4 h, CH_2Cl_2 was added and the organic phase was washed with HCl (1 N) and dried over $MgSO_4$. The solvent was removed, and the crude amide was purified by column chromatography (hexane–EtOAc, 7:3) to give amide **44** in 91% yield.

Typical Procedure for Hydrolysis of Carbonates 45 and 46 to Phenols 47 and 48. To the carbonate derivative **46** (192 mg, 0.33 mmol) dissolved in MeOH (50 mL) was added K_2CO_3 (1% w/v) in aqueous MeOH (25:75 v/v) (50 mL), and the resulting solution was stirred at room temperature for 6 h. The reaction mixture was acidified with HCl (1 N), and MeOH was evaporated under vacuum. The residue was extracted with EtOAc and the organic phase dried ($MgSO_4$) and evaporated. Purification was done by column chromatography (hexane–EtOAc) to give the free phenolic derivative **48** at 80% yield.

***N*-Butyl-*N*-methyl-5,6-bis(4'-methoxyphenyl)-4-thiahexanamide (43):** colorless oil; IR ν(neat) 1630 (C=O, amide); ^1H NMR δ ($CDCl_3$, 200 MHz) 0.87 and 0.89 (2t, J = 7.3 Hz, 3H, CH_2CH_3), 1.15–1.50 (m, 4H, 2 × CH_2), 2.34 (m, 2H, CH_2CO), 2.60 (m, 2H, SCH_2), 2.77 and 2.82 (2s, 3H, CH_3NCO), 3.02 (m, 3H, $PhCH_2CH$ and one proton of CH_2NCO), 3.27 (t, J = 7.3 Hz, 1H, one proton of CH_2NCO), 3.70 and 3.73 (2s, 6H, 2 × OCH_3), 3.93 (t, $J \sim 7$ Hz, 1H, CH_2CHS), 6.69 (d, J = 8.4 Hz, 2H, ArH *meta* to CH_2), 6.76 (d, J = 8.4 Hz, 2H, ArH *meta* to CHSR), 6.91 (d, J = 8.1 Hz, 2H, ArH *ortho* to CH_2), 7.14 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 13.8, 19.9 (19.8), 26.9 (26.7), 30.3 (29.2), 33.6 (33.1), 34.9 (33.2), 42.3, 49.4 (47.3), 51.8, 55.0 (2×), 113.2 (2×), 113.5 (2×), 128.8 (2×), 129.9 (2×), 130.8, 134.0, 157.7, 158.3, 170.6; MS *m/e* 415 (M^+, 0.3), 294 (100), 241 (28), 142 (69), 121 (29), 83 (40); FABMS calcd for $C_{24}H_{54}NO_3S$ (M^+ + H), 416.2259; found, 416.2303.

***N*-Butyl-*N*-methyl-6-[4'-(benzyloxy)phenyl]-5-(4'-methoxyphenyl)-4-thiahexanamide (44):** colorless oil; IR ν(neat) 1630 (C=O, amide); ^1H NMR δ ($CDCl_3$, 200 MHz) 0.90 and 0.92 (2t, J = 7.0 Hz, 3H, CH_2CH_3), 1.2–1.5 (m, 4H, 2 × CH_2), 2.37 (m, 2H, CH_2CO), 2.60 (m, 2H, SCH_2), 2.80 and 2.85 (2s, 3H, CH_3NCO), 3.05 (m, 3H, $PhCH_2CH$ and one proton of CH_2NCO), 3.29 (t, J = 7.3 Hz, 1H, one proton of CH_2NCO), 3.78 (s, 3H, OCH_3), 3.96 (t, J = 7.3 Hz, 1H, CH_2CHS), 4.99 (s, 2H, $PhCH_2O$), 6.79 and 6.88 (2d, J = 8.8 Hz, 4H, ArH *meta* to CH_2 and to CHSR), 6.94 (d, J = 8.4 Hz, 2H, ArH *ortho* to CH_2) 7.17 (d, J = 8.4 Hz, 2H, ArH *ortho* to CHSR), 7.35 (m, 5H, $PhCH_2O$); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 13.9, 20.1 (20.0), 27.1 (26.8), 30.5 (29.4), 33.8 (33.2), 35.0 (33.4), 42.5, 49.6 (47.5), 51.9, 55.2, 69.9, 113.7 (2×), 114.3 (2×), 127.4, 127.8, 128.4, 128.9 (2×), 130.1 (2×), 131.3, 134.0, 137.0, 157.1, 158.4, 170.8; MS *m/e* 317 (M^+ - $HOPhCH_2$, 26), 295 (69), 225 (70), 142 (71), 91 (100); FABMS calcd for $C_{30}H_{38}NO_3S$ (M^+ - H), 490.2416; found, 490.2387. Anal. ($C_{30}H_{37}NO_3S$) C, H, N.

***N*-Butyl-*N*-methyl-6-(4'-hydroxyphenyl)-5-(4'-methoxyphenyl)-4-thiahexanamide (47):** colorless oil; IR ν(neat) 3250 (OH, phenol), 1600 (C=O, amide); ^1H NMR δ ($CDCl_3$, 200 MHz) 0.86 and 0.92 (2t, J = 6.7 Hz, 3H, CH_2CH_3), 1.25 and 1.43 (2m, 4H, 2 × CH_2), 2.38 (m, 2H, CH_2CO), 2.60 (m, 2H, SCH_2), 2.81 and 2.86 (2s, 3H, CH_3NCO), 3.05 (m, 3H, $PhCH_2CH$ and one proton of CH_2NCO), 3.30 (t, J = 7.3 Hz, 1H, one proton of CH_2NCO), 3.75 (s, 3H, OCH_3), 3.91 (t, J = 7.3 Hz, CH_2CHS), 6.68 (d, J = 8.8 Hz, 2H, ArH *meta* to CH_2), 6.75 (d, J = 8.6 Hz, 2H, ArH *meta* to CHSR), 6.85 (d, J = 8.4 Hz, 2H, ArH *ortho* to CH_2),

7.12 (d, J = 8.8 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 50 MHz) (see ref 41) 13.9, 20.0 (19.9), 27.2 (27.0), 30.5 (29.2), 33.7 (33.2), 35.4 (33.7), 42.4, 49.8 (47.8), 52.1, 55.2, 113.7 (2×), 115.0 (2×), 128.9 (2×), 130.1 (3×), 134.0, 154.7, 158.4, 171.3; MS *m/e* 294 (M^+ - $HOPhCH_2$, 99), 227 (55), 142 (100), 121 (30); EIMS calcd for $C_{23}H_{31}NO_3S$ (M^+), 401.2024; found, 401.1973.

***N*-Butyl-*N*-methyl-5,6-bis(4'-hydroxyphenyl)-4-thiahexanamide** (48): colorless oil; IR ν(neat) 3240 (OH, phenol), 1605 (C=O, amide); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 0.87 and 0.91 (2t, J = 7.0 Hz, 3H, CH_2CH_3), 1.26–1.44 (2m, 4H, 2 × CH_2), 2.42 (m, 2H, CH_2CO), 2.61 (m, 2H, SCH_2), 2.84 and 2.86 (2s, 3H, CH_3-NCO), 3.00 (m, 2H, $PhCH_2CH$), 3.13 and 3.30 (2t, J = 7.5 Hz, 2H, CH_2NCO), 3.92 (J = 7.5 Hz, 1H, CH_2CHS), 6.65 (d, J = 8.5 Hz, 2H, ArH *meta* to CH_2), 6.68 (d, J = 8.7 Hz, 2H, ArH *meta* to CHSR), 6.83 (d, J = 8.5 Hz, 2H, ArH *ortho* to CH_2), 7.02 (d, J = 8.2 Hz, 2H, ArH *ortho* to CHSR); ^{13}C NMR δ ($CDCl_3$, 75 MHz) (see ref 41) 13.8, 19.9 (19.8), 27.0 (26.8), 30.3 (29.2), 33.9 (33.1), 35.5 (33.7), 42.3, 50.0 (48.0), 52.1, 115.1 (2×), 115.4 (2×), 129.1 (2×), 130.2 (2×), 130.5, 133.1, 154.6, 155.4, 172.0; MS *m/e* 280 (M^+ - $HOPhCH_2$, 6.6), 212 (100), 142 (47), 114 (14); FABMS calcd for $C_{22}H_{30}NO_3S$ (M^+ + H), 388.1946; found, 388.1908.

B. Biological Assays. 1. Estrogen-Receptor-Binding Assay. Apparent affinities of the synthesized compounds for the estrogen receptor were determined by competition binding with [^{3}H]estradiol to the rat uterine cytosol receptor according to Asselin and Labrie.[43] The incubations were performed at 25 °C for 3 h, and nonspecific binding was determined using an excess (1000 nM) of radioinert estradiol. The apparent affinities are expressed as relative binding affinity (RBA = 100 IC_{50} of estradiol/IC_{50} of tested compound), where IC_{50} is the concentration which inhibits [^{3}H]estradiol binding by 50%. The RBA of estradiol is taken as 100%.

2. Proliferative and Antiproliferative Cell Assays. (a) Maintenance of Stock Cell Cultures. All media and supplements for cell culture were from Sigma Chemical Co., except for fetal bovine serum (FBS) which was obtained from Hyclone (Logan, UH). ZR-75-1 human breast cancer cells were obtained from the American Type Culture Collection (ATCC) (Rockville, MD) at their 83rd passage and routinely grown in phenol-red-free RPMI-1640 medium supplemented with 10 nM E_2, 2 mM L-glutamine, 1 mM sodium pyruvate, 15 mM HEPES, 100 IU of penicillin/mL, 100 μg of streptomycin sulfate/mL, and 10% (v/v) FBS. Cell cultures were used between passages 90 and 96 and subcultured weekly. MDA-MB-231 human breast cancer cells were obtained from ATCC at their 33rd passage and routinely grown in MEM and 5% (v/v) FBS supplemented as described above plus MEM nonessential amino acids (Gibco BRL).

(b) **Cell Growth Experiments.** The ZR-75-1 and MDA-MB-231 cells in their exponential growth were harvested with 0.05% trypsin–0.02% EDTA (w/v) and resuspended in RPMI-1640 medium (ZR-75-1) or MEM (MDA-MB-231) without phenol red supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 50 ng of insulin/mL, 15 mM HEPES, 100 IU of penicillin/mL, 100 μg of streptomycin sulfate/mL, and 5% (v/v) dextran-coated charcoal-treated fetal bovine serum (SD medium). The cells were plated in Falcon 24-well tissue culture plates (2 cm^2/well) with 10 000 cells/dish and allowed to adhere to substrate for 3 days. Estradiol (0.1 nM) and/or indicated concentrations of the tested compound, from 1000–10 000× stock solutions in 99% redistilled ethanol, were added into fresh SD medium. Control cells received only the ethanolic vehicle (0.1% EtOH, v/v). Cells were then incubated at 37 °C in an humidified atmosphere of 5% CO_2 and 95% air for 9 days with a change of medium every 2 or 3 days. At the end of the incubation period, cell proliferation was assessed by measurement of DNA content by a modification of the Fiszer–Szafarz method[44] as previously described.[45]

Calculations were performed according to the following equation and expressed in percent (%). Inhibition of E_2-induced cell proliferation = $100 - [(D-B)/(C-A)] \times 100$ where A = DNA content of control cells (ng), B = DNA content of cells treated with tested compound (ng), C = DNA content of E_2-treated cells (ng), and D = DNA content of E_2-treated cells incubated with tested compounds (ng).

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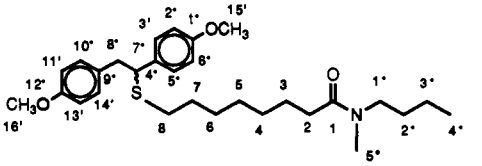
(41) ^{13}C NMR spectra of thioether derivatives with an alkanamide side chain show a duplication of the signal related to carbons neighboring the amide group. This pair of peaks was represented in NMR data by a second value indicated in parentheses. Herein, we report a representative example of the complete assignment of signals observed for compound **27**. Assignment was greatly facilitated by HETCOR analysis. This complete assignment is also representative of other alkanamide compounds, considering the modification of the aromatic nucleus. The ^{13}C numeration used herein was not the same as the nomenclature numeration.



δ (ppm): 13.8 [C-4″], 20.0 (19.9) [C-3″], 25.3 (24.9) [C-3], 28.7–29.3 [C-4–C-7], 30.6 (29.3) [C-2″], 31.1 [C-8], 33.5 (32.8) [C-2], 35.2 (33.3) [C-5″], 42.5 [C-8′], 49.7 (47.3) [C-1″], 51.1 [C-7′], 55.1 and 55.2 [C-15′,16′], 113.4 [C-11′,13′], 113.6 [C-2′,6′], 128.9 [C-3′,5′], 130.0 [C-10′,14′], 131.2 [C-9′], 134.1 [C-4′], 157.9 [C-12′], 158.4 [C-1′], 172.8 [C-1].

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