Flexible Estrogen Receptor Modulators: Design, Synthesis, and Antagonistic Effects in Human MCF-7 Breast Cancer Cells

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Although many series of estrogen receptor antagonists continue to be produced, the majority are direct structural analogues of existing modulators. To examine the tolerance of the estrogen receptor toward flexible ligands, a series of novel flexible estrogen receptor antagonists were prepared and their antiproliferative effects on human MCF-7 breast tumor cells investigated. Each of these compounds deviated from the traditional triphenylethylene backbone associated with common tamoxifen analogues through the introduction of a flexible methylene (benzylic) spacing group between one of the aryl rings and the ethylene group and through variations in the basic side chain moiety. The compounds prepared, when assayed in conjunction with a tamoxifen standard, demonstrated high potency in antiproliferative assays against an MCF-7 human breast cancer cell line with low cytotoxicity and high binding affinity. A computational study was undertaken to investigate the compounds' potential interactions with specific residues within the human estrogen receptor α ligand-binding domain (ER-LBD), predicting these compounds bind in an antiestrogenic fashion within the ER-LBD and interact with those important residues previously identified in the structures of ER-LBD agonist/antagonist cocrystals. These compounds further illustrate the eclectic nature of the estrogen receptor in terms of ligand flexibility tolerance.

Introduction

The estrogen receptor is responsible, among other functions as a ligand-inducible nuclear transcription factor, for the mediation of the physiological effects of estrogen steroid hormones.[1] Through binding to the ligand-binding domain (LBD) of the receptor, hormone ligands initiate a cascade of molecular and biochemical events which ultimately can express themselves in the growth of certain tissues through the activation or inactivation of particular genes.[2] Nonsteroidal antiestrogens, by definition, antagonize the activity of estrogenic species. One such compound is tamoxifen (**1a**, TAM, ((*Z*)-1-[4-(2-dimethylaminoethoxy)phenyl]-1,2-diphenyl-1-butene) (Figure 1), which has been used extensively in the treatment of hormone-sensitive breast cancers and has become the first-line endocrine therapy for all stages of breast cancer in pre- and postmenopausal women.[3] Now classified as a selective estrogen receptor modulator (SERM) by virtue of its estrogen-like effects in certain tissues, the antiestrogenic properties of this compound are related to its ability to compete for estrogen-binding sites in target tissues such as the breast: its resultant orientation within the LBD perturbs the receptor structure to inhibit coactivator recruitment and ultimate transcription regulation.[11] Given the importance of the estrogen receptor in several disease processes, the design of therapeutics which modulate this target continues to generate considerable interest, both industrial and academic.[4]

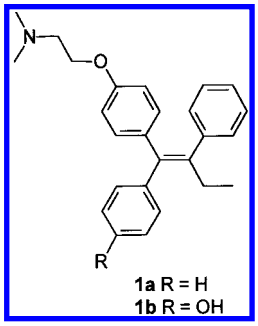

Figure 1. R = H, tamoxifen (**1a**, TAM); R = OH, hydroxytamoxifen (**1b**, OHT).

It has been suggested that building flexibility into the rigid backbone of antiestrogens could enhance their activity and binding affinity for the estrogen receptor.[5] To that end, this work describes the design, synthesis, and investigation of four series of compounds (**2**−**5**,**a**−**e**) which, while related structurally to TAM, deviate from the traditional approach of triarylethylene analogues through the introduction of a spacing methylene group between the aryl and vinylic systems associated with 'classical' analogues of TAM, imparting novel flexibility to this rigid class of antagonist.[3,6−9] The chemotherapeutic and antiestrogenic potential of the compounds prepared is determined through appropriate biochemical assays.[14−18] The availability of highly resolved crystal structure studies of the estrogen receptor α (ERα) allows the investigation of both actual and theoretical interactions of both estrogenic and antiestrogenic materials in the LBD.[10−12] A thorough computational investigation of the predicted orientation and interaction of representative compounds within the LBD of the human ERα is undertaken, with a view to

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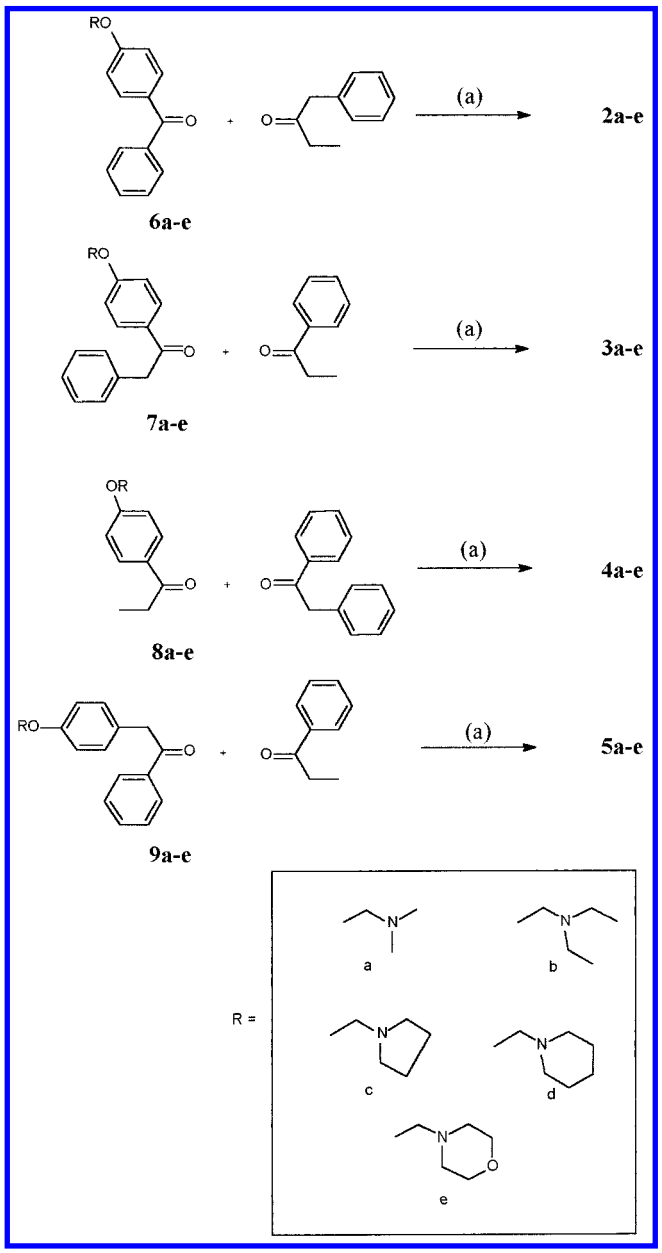
Scheme 1[a]



[a] (a) $TiCl_4$, Zn powder in dry dioxane/N_2 atmosphere, reflux.

rationalizing antiestrogenic activity observed through analyzing ligand−receptor interactions, to provide an insight into the basis for biological activity of the compounds prepared.[29] Such work further illustrates the eclectic liganding behavior of ERα and its tolerance for flexible antiestrogen systems.

Chemistry

A facile route to the target compounds (**2**−**5**,**a**−**e**) was afforded via implementation of the titanium tetrachloride/zinc-mediated McMurry coupling reaction,[13] illustrated in Scheme 1. Alkylated ketones (**6**−**9**,**a**−**e**) were readily prepared from phenol-containing parent ketones using standard methods.[32] All compounds were prepared and isolated in good yield. It was noted that during workup of the McMurry products, the yield of compound isolated was considerably increased wherein large quantities of water (ca. 1−2 L for reaction scale employed) were used in quenching the reaction mixture. All products were

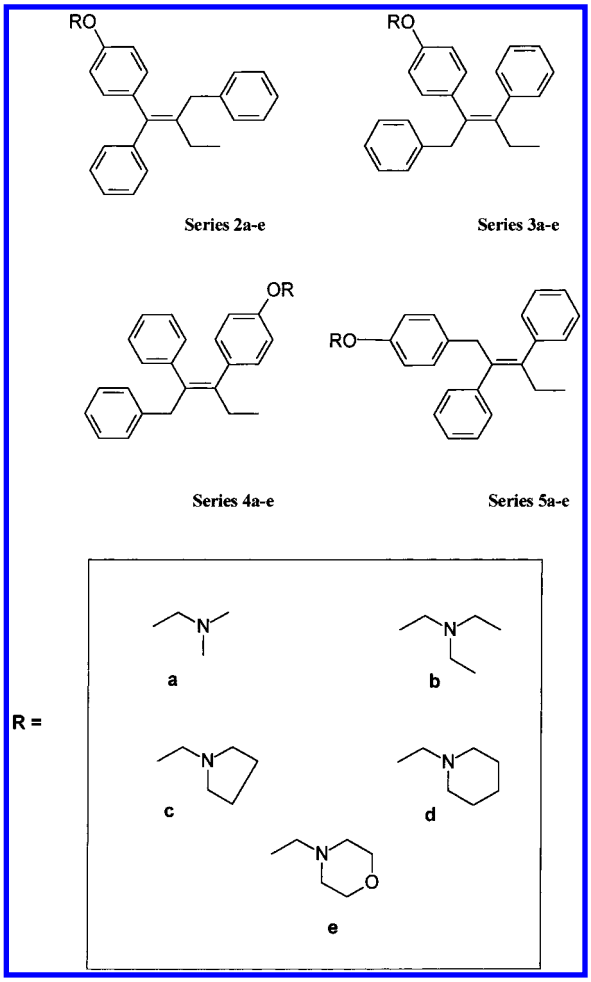


Figure 2. Target compounds. Compounds **2a**−**e**, **3a**−**e**, and **4a**−**e** are presented as *Z*-isomers; compounds **5a**−**e** are presented as *E*-isomers.

isolated and tested as oils containing the free base.[30] Table 3 lists each of the compounds formed, the percent (%) yields isolated, and the major:minor isomeric ratio attained for each compound. The assignment of isomeric ratios was made from relative peak heights in product ^{1}H NMR spectra. Given that it is known that only the *Z*-isomer of TAM is antiestrogenic (the *E*-isomer has been shown to act as an estrogen agonist),[31] the importance of the stereospecificity of the method employed must be considered.

Previous work on TAM and related analogues using the McMurry reaction has identified the propensity of phenolic, benzophenone-derived ketones used in the coupling reaction to favor the formation of that product which has a trans arrangement of the ethyl side chain relative to the original phenolic system across the double bond.[32,33] This literature data in conjunction with NMR peak assignment/analysis allowed the assignment of the major species prepared in series **2**−**4** as *Z*-isomers and those in series **5** as *E*-isomers, as illustrated in Figure 2. Spectral isomeric assignment interpretations were made based on the relative positions of those aryl proton signals arising from the A_2B_2 para system of the 4-substituted phenyl ring and/or on the relative chemical shifts observed for the OCH_2 signal arising from protons in the basic side chain.[34,35]

In series **2** a 33% isomeric (*Z*) excess is found across all five members. Series **3** has isomeric (*Z*) excesses in

Table 1. Mean IC_{50} Values of Compounds **2**−**5**,**a**−**e** for Their Antiproliferative Effects on the Human MCF-7 Breast Cancer Cell Line

compd	IC_{50} (μM)	compd	IC_{50} (μM)
1a	11.28[a]	**4a**	117.17
2a	14.94	**4b**	20.65
2b	12.83	**4c**	22.36
2c	3.57	**4d**	19.05
2d	4.62	**4e**	51.11
2e	45.52	**5a**	25.06
3a	21.66	**5b**	58.04
3b	19.00	**5c**	142.19
3c	10.34	**5d**	68.76
3d	76.58	**5e**	16.59
3e	2.53		

[a] The value recorded for TAM in this work is in good agreement with IC_{50} values reported in other works utilizing the MTT assay in MCF-7 cells.[9,15]

Table 2. ER Binding Affinities for Selected Compounds Compared to TAM (**1a**)

compd	K_i (mean ± SEM)
1a	157 ± 24 nM
2a	459 ± 230 nM
3a	503 ± 98 nM
4d	2.39 ± 0.35 μM
5e	2.48 ± 0.45 μM

Table 3. Yield and Isomeric Ratio Data for Compounds **2**−**5**,**a**−**e**

compd	% yield	isomeric ratio[a]	compd	% yield	isomeric ratio[a]
2a	69.0	2:1	**4a**	44.3	>100:1
2b	71.5	2:1	**4b**	34.7	>100:1
2c	68.4	2:1	**4c**	24.7	5:1
2d	65.1	2:1	**4d**	39.2	5:1
2e	67.9	2:1	**4e**	29.2	5:1
3a	49.0	4:1	**5a**	71.2	6:5
3b	41.9	6:5	**5b**	40.2	9:1
3c	74.8	2:1	**5c**	18.9	6:5
3d	80.3	2:1	**5d**	38.4	6:1
3e	40.5	2:1	**5e**	29.2	3:1

[a] Ratio determined as major:minor isomer present; *Z*-isomer for series **2**−**4**, *E*-isomer for series **5**, based on ^{1}H NMR assignment.

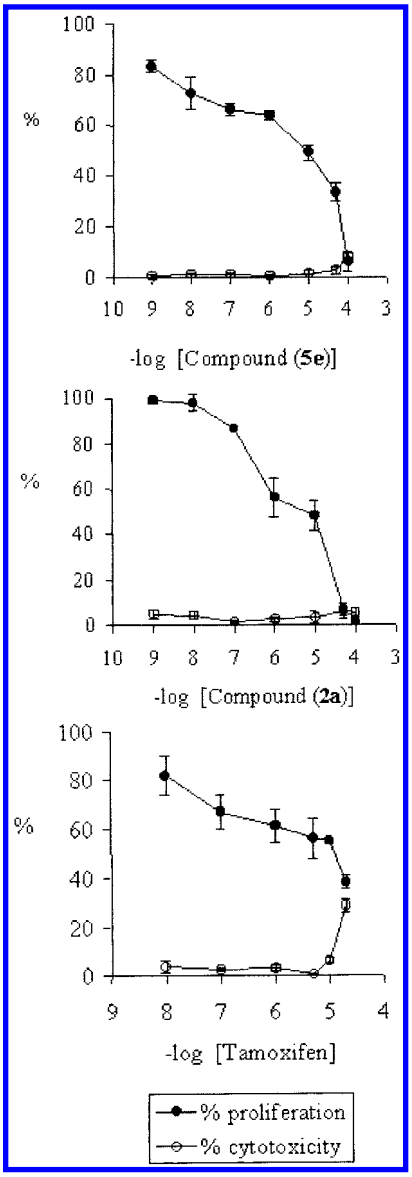


Figure 3. Inhibition of proliferation/cytotoxicity profiles for **1a**, **5e**, and **2a**.

the region of 9−60%. Series **4** has two members which were isolated as almost 100% isomerically pure *Z*-products, and the remaining members exhibit a 67% isomeric (*Z* over *E* assigned) excess. In series **5** the isomeric *E*-excess ranges 9−80%.

Variations in isomeric ratios across series are primarily attributed to the variation of basic side chains in the reacting ketone species. No ratio variation is in evidence across the members of series **2**, and indeed, this is the only compound series in which a benzophenone ketone backbone is preserved for the primary reactant. This observation may be indicative of the importance of aromatic conjugation in the determination of isomeric ratio outcome in the McMurray coupling of such systems, although the exact mechanism of the coupling is still unknown. As previously employed in similar work in the literature, compounds were assayed biologically as the indicated *E*−*Z* mixtures.[35]

Biochemistry

Inhibition of Proliferation. To determine the chemotherapeutic potential of the compounds prepared, their ability to inhibit the proliferation of the human breast tumor MCF-7 cell line was investigated using the standard MTT assay. The individual IC_{50} results for compounds (**2**−**5**,**a**−**e**) are recorded in Table 1 using a TAM reference standard for the assay. The data may be examined in two groupings: by structural series and by basic side chain present. When the activities are reviewed series **2** is overall the most active structure group. It can also seen from the side chain groupings that the *N*-diethyl basic side chain (**b**) compounds are, on average, the most active of the five units studied. If the structural diversification from **1a** which is manifest in series **2**−**5** is examined in conjunction with the average IC_{50} values obtained for the series as a whole, a 'ring order' to the compounds based on an arbitrary 'ring order' for TAM can be allocated. This is illustrated in Figure 5. In general series terms it is possible to determine the overall effect of the inclusion of a methylene (benzylic) spacing moiety into these compounds.

The average activity recorded per series indicates the average series IC_{50} values for series **2**−**5** to be 16.3, 26.0, 26.1, and 62.1 μM, respectively, in comparison to an IC_{50} of 11.3 μM recorded for **1a**, indicating the introduction of a spacing group (and the resulting flexibility this

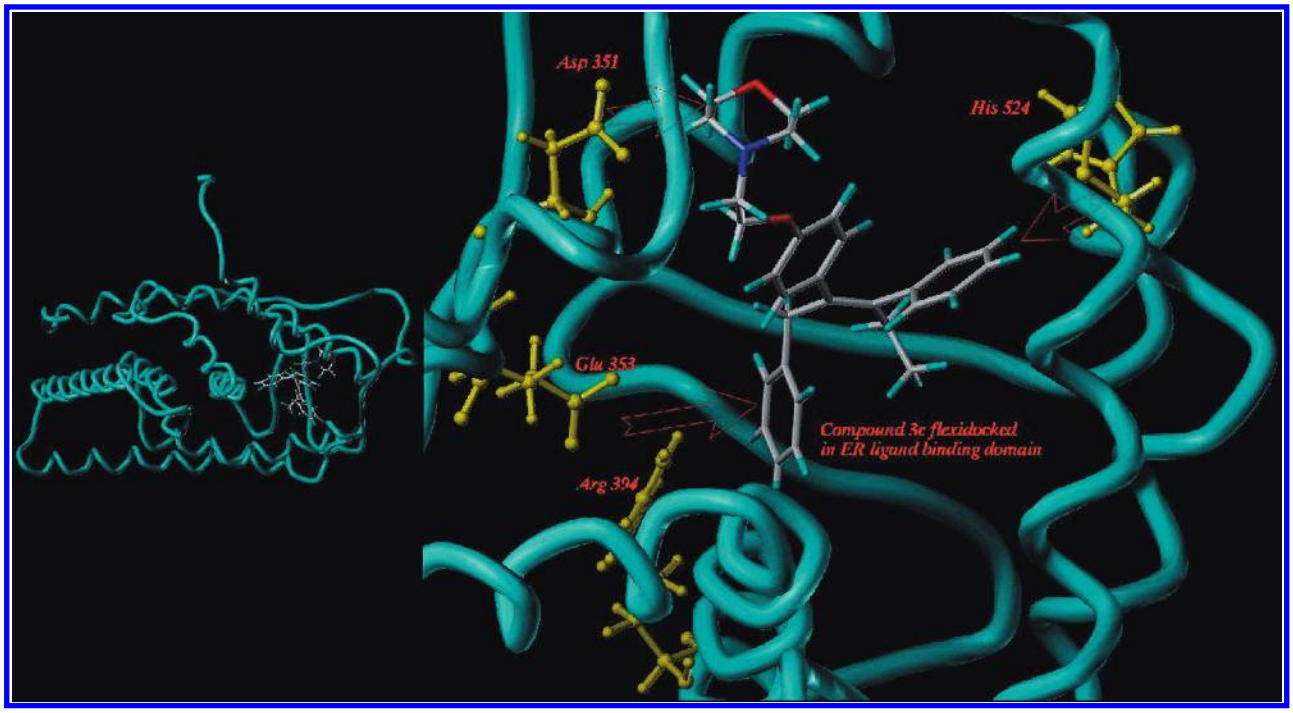


Figure 4. Docked 'model structure' obtained for compound **3e**. Left-hand side shows compound docking in 'normal' antiestrogenic mode in the ligand-binding domain (LBD) of the ER. The right-hand zoom highlights the ligand in the context of important residues within the LBD. Rendered through the biopolymer module of SYBYL 6.6.

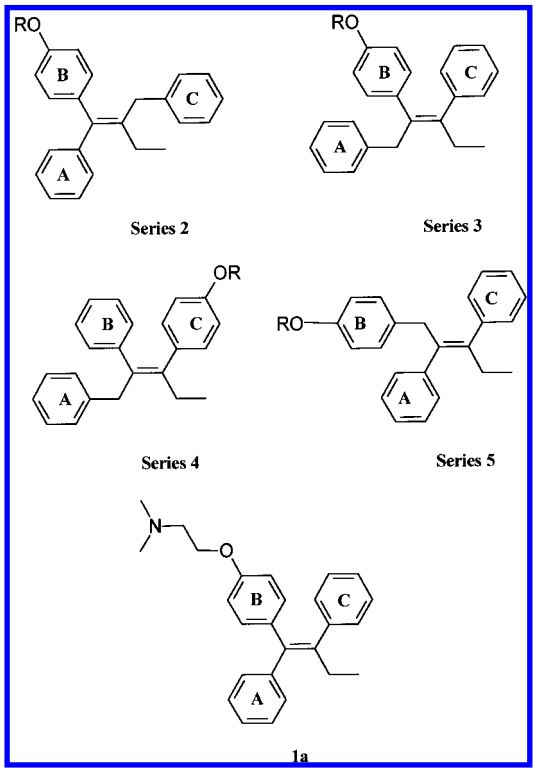


Figure 5. Assignment of 'ring order' for series **2**−**5** with reference to **1a**.

group confers to the molecule) is most beneficial when ring C is removed from the vinylic system. For series **2**, it is noted that two members, **2c**,**d**, have IC_{50} values which are considerably lower than that recorded for TAM. The values for **2b,a** are only marginally higher than the TAM value (13% and 32%, respectively), with only compound **2e** displaying a significantly weaker antiproliferative effect. When the A ring is displaced through the introduction of a methylene group as in series **3** and **4**, only a moderate reduction in efficacy is found, although it must be noted that the most active compound **3e** (IC_{50} 78% lower than that of TAM) stems from this grouping.

Within these series, it can be seen that the translocation of the basic side chain from ring B to C, as is present in series **4**, has no benefit for activity; indeed computational modeling predicts a 'flip' in the compound orientation upon ligand binding for compounds from series **4**, to facilitate 'normalized' antiestrogen-like binding. Series 4 is unique among the compound series prepared insofar as this series is not a direct homologue of TAM − translocation the basic side chain translocation effectively 'flips' the molecular geometry when considered from the geometry of TAM and the other compound series.

This investigation has shown that the least beneficial ring displacement arises when a flexible methylene group is introduced to space ring B from the vinyl system. All members of the B-spaced series, series **5**, demonstrated antiproliferative activity, although the results were collectively, on average, the least active of the compounds investigated. It can be concluded from these observations that the introduction of flexibility between the vinyl system and that ring bearing the basic side chain in these compounds is detrimental to antiestrogenic activity.

A direct comparison of those compounds containing the *N*-dimethyl basic side chain to that activity recorded for TAM, under the experimental conditions detailed, can be made. Compounds **2a**, **3a**, and **5a** are all directly derived structurally from TAM, insofar as the overall relative location of the basic side chain is conserved. As can be seen from the data presented, the increased molecular flexibility bestowed on these compounds does not detract from their potency as antiestrogenic inhibitors of proliferation.

Cytotoxicity Profiles. In terms of therapeutic practicality, the potency of any given compound in terms of its inhibition of cellular proliferation should not arise from its propensity for cellular necrosis. With the design of this series of flexible antiestrogenic compounds, the achievement of cytostasis through therapy was the primary objective. Previous research has indicated that the antiproliferative effects manifested by TAM are due in part to its inherent cytotoxicity[36] and more recently through its ability to induce apoptosis in cell lines.[37] To this end, all compounds assayed for antiproliferative effects were concurrently tested to assess the extent of their cytotoxicity using the LDH assay outlined in the Experimental Section.

Each of the flexible compounds (**2**−**5**,**a**−**e**) assayed demonstrated low cytotoxicity in conjunction with their inhibitory activity, and several possessed extremely low cytoxicity profiles, indicating their mode of action to be truly cytostatic rather than cytotoxic. As can be seen for compounds **2a** and **5e** (Figure 3) the level of cytotoxicity recorded remains almost constant across the concentration range studied. These graphs clearly show that at the concentration values studied, the activity for the compounds is not due to cytotoxic effects, which for **2a** rise only slightly at a concentration of about 50 μM and for **5e** show a small increase at 100 μM. Contrarily, a sharp (and significantly larger) increase in the cytotoxicity of TAM can be seen above a concentration of 20 μM. Indeed the level of cytotoxic-induced antiproliferation observed for TAM at the 20 μM concentration is approximately 28.6%, whereas, when examined at the corresponding concentration, both compound **5e**'s and **2a**'s cytotoxic contributions are less than 4%.

Binding Studies. Binding assays were carried out for selected compounds, representing highly potent members of their corresponding series. A novel radiolabeled estradiol displacement protocol was developed from existing studies.[14,18] ERα-rich cytosol isolated from rat uteri was used in the procedure. Binding affinity as determined by the K_i value was measured for compounds **2a**, **3a**, **4d,** and **5e** and is illustrated (with reference to TAM) in Table 2. Each of the active compounds assayed demonstrates good (nM or low-μM) binding affinity for the ER, comparable to that of **1a**, demonstrating competitive inhibitory activity. When the data is correlated with the inhibitory activity of the individual compound series, it is noted that the more active series **2** and **3** also demonstrate higher binding affinity for the ER. A similar binding affinity−inhibitory activity correlation is seen for series **4** and **5**. This relationship between binding affinity and antiproliferative potency observed for the series prepared is significant and may be of use in the development of further novel flexible ER modulators.

Computational Studies. To rationalize the observed biological activity in these compounds a variety of computational methods were employed. Upon computational docking it was noted that all compounds were liganded in the established estrogen antagonist mode, cf. Figure 4. Figure 6 illustrates a direct structural comparison of the docked geometries for compounds **2c**, **3e**, **4d**, and **5e** (representing each of the four parent series in their majority isomeric form) superimposed on the docked geometry obtained for **1a** (TAM) and the receptor-bound conformation observed for **1b** (OHT). It can be seen clearly from this figure where the incorporated methylene spacing groups bestow additional flexibility to the compounds prepared.

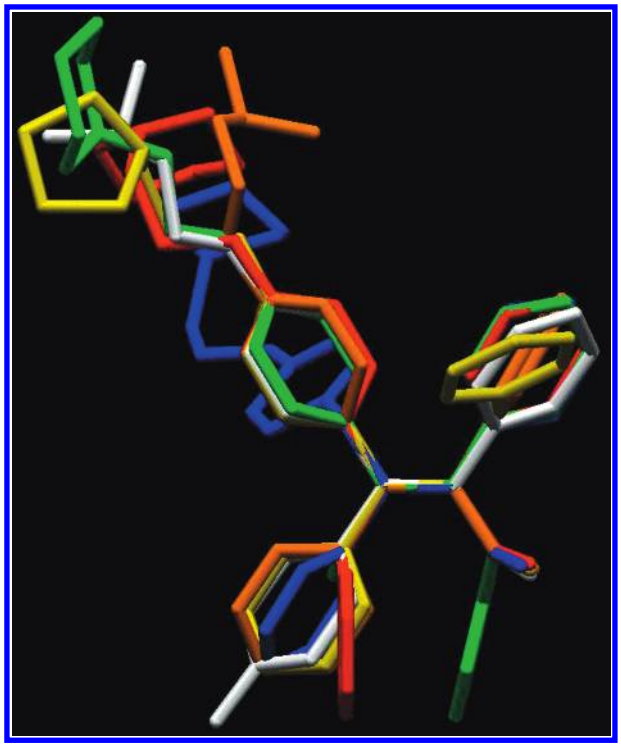


Figure 6. MacroModel superimposition of docked compounds and TAM with hydroxy-TAM. Legend: yellow, **2c**; red, **3e**; green, **4d**; blue, **5e**; orange, tamoxifen (**1a**, TAM); white, hydroxytamoxifen (**1b**, OHT).

In each case the overlap of the docked geometries for synthesized compounds with OHT and TAM is high, deviating only where the benzylic spacing group is introduced. While the basic side chain for **4d** is of course translocated to ring C (Figure 5) of the structure, docking analyses indicate that this series binds to the receptor in a 'normal' antiestrogenic mode; thus we have 'flipped' the structure (from its representation in Figure 2) so as to render true comparison. The location of the flexible benzylic group in **4d** is worthy of attention as this predicted docking conformation orientates the aromatic system of ring A toward those residues identified as playing a role in ligand anchoring.

It can be seen for all compounds that their respective basic side chains are orientated in a manner similar to that observed for OHT, with slight deviation noticed for **5e** (blue molecule) as the benzylic spacer between the vinylic system and ring B imparts additional flexibility in this region. This correlates with the overall lower activities recorded for this compound series as a whole.

Ligand−Protein Contacts. Hydroxy-TAM has been identified as the primary active metabolite derived in vivo from the parent TAM.[11] Work by Klinge et al. has described the similarities in the liganding behaviors of 4-hydroxy-TAM and TAM; thus the 4-hydroxy-TAM−ERα crystal system was an appropriate model for study.[23]

Initial docking of a minimized structure of TAM itself further validated our protocol, with ligand orientation and location reflecting typical antiestrogenic binding

Table 4. LPC Results for Specific Residues Compared to Known Estrogens and Antiestrogens[a]

compd	Asp 351	His 524	Arg 394	Glu 353
2c	34.1	12.1	13.0	26.7
3e	34.8	13.9	17.0	8.1
4d	35.7	11.9	17.5	6.5
5e	43.1	16.4	7.4	24.2
OHT	29.0	14.1	22.2	34.2
RAL	30.9	32.8	22.0	32.7
TAM	8.5	11.2	23.6	22.2
EST		40.4	18.0	35.9
DES		31.0	15.8	38.7

[a] Data given as overlap (Å^2) with key residues. OHT, 4-hydroxytamoxifen (**1b**) from PDB entry 3ERT; RAL, raloxifene from PDB entry 1ERR; TAM, tamoxifen (**1a**), LPC contacts generated from docked file; EST, estradiol from PDB entry 1ERE; DES, diethylstilbestrol from PDB entry 3ERD.

within the LBD, mirroring that observed in the crystal structure for hydroxy-TAM. Despite the absence of free phenolic groups in the compounds prepared, in-depth LPC analysis was concentrated primarily on the following specific residues: Glu 353 and Arg 394 (which are involved primarily in anchoring ligands in the active site), His 524 (identified as an important binding/'estrogenic' residue from studies with diethylstilbestrol[21] and estradiol[22]), and Asp 351 (identified by Brzozowski et al. as an important antiestrogenic residue). These particular residues were chosen so that specific reference could be made to the orientation and location of the test compounds relative to that predicted for TAM, which was itself directly validated and referenced back to the receptor crystal structure in the presence of hydroxy-TAM, as discussed above.

Table 4 illustrates the key predicted LPC data for compounds **2e**, **3e**, **4d,** and **5e** with the specific residues of choice, with reference made to those contacts calculated from existing crystal structures and the docked TAM 'model structure' data. These data gives some insight into the possible interactions occurring at the active site. It can be seen from the comparisons in Figure 6 and Table 4 that the flexible ligands, in their theoretical dockings, are orientated in much the same extent as known antiestrogenic and estrogenic compounds relative to the anchoring residues Arg 394 and Glu 353.

As detailed above, compound **4d** docks in a regular antiestrogenic mode (through flipping of the structure as illustrated in Figure 6). As one would expect, compound **4d**'s calculated proximity to and potential interaction with the Arg and Glu residues is the lowest of the four ligand types, although the difference when compared to other compound series is not very large. These figures are supported by the binding affinities measured for compounds of series **4** and the docking prediction that the flexible benzylic group imbues a molecular conformation so as to orientate aromatic ring A in closer proximity to the two anchoring residues Glu 353 and Arg 394 (cf. Figure 6). Overall, across the compound series, molecular interaction with the 'estrogenic' residue His 524 is low, comparable to that of the known antiestrogen OHT, whereas raloxifene (RAL)[20] is something of a special case stemming from its estradiol-mimicking backbone − its mode of action and LPC profile can best be described as an 'estrogen-like' antiestrogen.[38] Compound interaction with/proximity to the 'antiestrogenic' residue Asp 351 compares highly favorably with that calculated for the known antiestrogens; however, the value calculated from the predicted TAM model structure seems slightly low by comparison.

Given the correlation between model structure LPC data and observed activities, we deem this technique particularly useful for in silico evaluation of the potential benefits inherent to proposed functional or geometric changes in homologous drug candidate series prior to synthesis.

Conclusions

Synthetic details and data for four series of structurally novel, conformationally flexible compounds (**2**−**5**,**a**−**e**) derived from the structure of the known antiestrogen TAM have been presented. The 20 members prepared deviate from the traditional triphenylethylene structure of TAM analogues through the incorporation of a methylene (benzylic) spacing group stemming from the central vinylic system. These compounds have demonstrated high antiestrogenic potency through their inhibition of the proliferation of human MCF-7 breast cancer cells. They have been assayed for cytotoxic effects and demonstrate low cytoxicity profiles, indicating their mode of action to be cytostatic. Binding affinity studies were carried out using a modified assay developed for this work and showed the compounds to bind to the ER with similar affinity to known antiestrogenic species, with a correlation determined between series antiproliferative potency and binding affinity. To rationalize the biological data in the absence of a crystal structure, computational docking and ligand−protein contact studies were carried out which predict these molecules to dock in the same region of the ER in an antiestrogenic mode with orientation for interaction to the same extent with the same key residues as known antiestrogens. Although the docking and resulting LPC data are theoretical, until such time as a crystal structure is obtained for one of these novel compounds in the LBD of the ER, such tools will have to serve to furnish some measure of explanation for the biological results obtained. This work has highlighted the tolerance of the ER for flexible modulators. We are currently investigating the apoptotic potential of these compounds in MCF-7 and will present these data in a future publication. Further studies utilizing our established computational protocol for the presynthetic (in silico) modification of selected compounds and in the design of novel flexible ligands with a view to increasing specific residue interactions and antiestrogenic activity are underway.

Experimental Section

Chemistry. All reagents used were commercial grade chemicals from freshly opened containers. IR spectra were collected as thin films on NaCl plates on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance DPX 400 instrument at room temperature. All *J* values are quoted in Hz. Low-resolution mass spectra were run on a Hewlett-Packard 5973 MSD GC−MS system, while high-resolution accurate mass determinations were made on a Kratos Prohile HV-4 mass spectrometer using the direct insertion probe and electron impact ionization techniques by the High-Resolution Mass Spectrometry Service in the Department of Chemistry, University College Cork. Flash chromatography was carried out using standard silica gel 60 (230−400 mesh) obtained from Merck. Analytical HPLC work was performed on a chromato-

graphic system comprising a Waters 501 pump (flow rate 2 mL/min/sample loop 20 μL) and a Waters Spherisorb S5 ODS2 (4.6 × 250 mm) reversed-phase C18 analytical column. Detection was on a Waters 486 tunable absorbance detector with λ = 241 nm, chart recorder speed at 1/6 cm/min. The mobile phase used was prepared from HPLC grade solvents and comprised ACN:water:THF:18 M NH_3 buffer (30:12.5:7.5:2). Retention times are given in minutes. Unless otherwise stated all reactions were carried out under a nitrogen atmosphere.

4-(Dimethylaminoethoxy)benzophenone (6a).[39] 4-Hydroxybenzophenone (1.0 g, 5 mmol) was placed in a 100 mL two-necked round-bottomed flask equipped with a magnetic stirrer and dissolved in 30 mL dry acetone. To this solution, anhydrous K_2CO_3 (7 g, 5 mmol) was added with continual stirring. Stirring was maintained for 15 min. After this time 2-dimethylaminoethylchloride hydrogen chlorine (1.66 g, 11.5 mmol) was added. Stirring was continued for a further 10 min after which time the mixture was heated to reflux temperature for 6 h. The reaction was monitored by TLC and once the starting material was seen to be consumed, heating was halted and the reaction vessel allowed to cool to room temperature. The reaction mixture was vacuum filtered, and the residue washed with cold dry acetone. The filtrate was concentrated using reduced pressure rotary evaporation to yield a brown oil. The crude product was purified by column chromatography (silica gel) with CH_2Cl_2/MeOH (50:50) to yield the pure product (1.321 g, 98%) as a viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.32 (s, 6H, $(CH_3)_2$), 2.74 (t, 2H, J = 5.64, CH_2N), 4.15 (t, 2H, J = 5.66, CH_2O), 6.90−6.91 (dd, 2H, J = 7.00, 1.97, Ar), 7.36−7.75 (m, 7H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 45.61 ($(CH_3)_2$), 57.85 (NCH_2), 65.99 (OCH_2), 114.02−160.00 (Ar C), 191.11 (C=O) ppm. IR (film) ν = 2928.3, 1652.2 (C=O), 1601.4, 1507.8, 1445.3, 1281.4, 1258.0 (C−N), 1172.2 cm^{-1}.

4-(Diethylaminoethoxy)benzophenone (6b).[40] **6b** was prepared from 4-hydroxybenzophenone and 2-diethylaminoethoxychloride hydrochloride in the manner described for **6a** above. The product was isolated as an oil in 97% yield following flash chromatography with CH_2Cl_2/MeOH (60:40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.64 (m, 10H, $(CH_2CH_3)_2$), 2.97 (t, 2H, J = 6.02, CH_2N), 4.21 (t, 2H, J = 6.02, CH_2O), 6.97−6.99 (dd, 2H, J = 5.04, 2.00, Ar), 7.45−7.84 (m, 7H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 11.01 ($(CH_3)_2$), 47.34 (CH_2), 51.15 (NCH_2), 66.05 (OCH_2), 113.65−161.89 (Ar C), 195.04 (C=O) ppm. IR (film) ν = 2933.9, 1668.1 (C=O), 1601.0, 1572.3, 1508.0, 1494.2, 1446.4, 1371.4, 1281.3 (C−N), 1172.8 cm^{-1}.

4-(Pyrrolidinylethoxy)benzophenone (6c).[41] **6c** was prepared from 4-hydroxybenzophenone and 1-(2-chloroethyl)-pyrrolidine hydrochloride in the manner described for **6a** above. The product was isolated as an oil in 95% yield following flash chromatography with CH_2Cl_2/MeOH (60:40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.82 (m, 4H, (CH_2), 2.57 (m, 4H, (CH_2), 2.94 (t, 2H, J = 5.96, CH_2N), 4.20 (t, 2H, J = 6.02, CH_2O), 6.97−6.99 (dd, 2H, J = 8.52, 1.98, Ar), 7.45−7.90 (m, 7H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 23.47 (CH_2), 54.83 (CH_2), 57.86 (NCH_2), 67.37 (OCH_2), 113.67−162.08 (Ar C), 195.03 (C=O) ppm. IR (film) ν = 2963.5, 1651.4 (C=O), 1601.0, 1572.3, 1508.1, 1281.5 (C−N), 1173.2 cm^{-1}.

4-(Pipyridinylethoxy)benzophenone (6d).[42] **6d** was prepared from 4-hydroxybenzophenone and 1-(2-chloroethyl)-pipyridine hydrochloride in the manner described for **6a** above. The product was isolated as an oil in 89% yield following flash chromatography with CH_2Cl_2/MeOH (60:40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.49−2.73 (m, 10H, $(CH_2)_5$), 2.85 (t, 2H, J = 5.78, CH_2N), 4.19 (t, 2H, J = 5.76, CH_2O), 6.96−6.98 (dd, 2H, J = 8.52, 2.00, Ar), 7.45−7.82 (m, 7H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 40.22 (CH_2), 53.10 (CH_2), 53.64 (CH_2), 56.98 (NCH_2), 66.45 (OCH_2), 113.67−161.89 (Ar C), 194.97 (C=O) ppm. IR (film) ν = 2935.4, 1651.9 (C=O), 1600.0, 1508.0, 1281.4 (C−N), 1173.4 cm^{-1}.

4-(Morpholinylethoxy)benzophenone (6e).[41] **6e** was prepared from 4-hydroxybenzophenone and 4-(2-chloroethyl)-morpholine hydrochloride in the manner described for **6a** above. The product was isolated as an oil in 88% yield following flash chromatography with CH_2Cl_2/MeOH (60:40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.44−2.71 (m, 8H, $(CH_2)_4$), 2.79 (t, 2H, CH_2N), 4.17 (t, 2H, CH_2O), 6.96−6.98 (dd, 2H, Ar), 7.45−7.55 (m, 7H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 50.56 (CH_2), 55.05 (CH_2), 57.71 (NCH_2), 66.32 (OCH_2), 114.11−162.50 (Ar C), 195.43 (C=O) ppm. IR (film) ν = 2961.6, 1651.8 (C=O), 1600.0, 1508.3, 1281.5 (C−N), 1173.7 cm^{-1}.

2-Phenyl(4-dimethylaminoethoxyphenyl)ethan-1-one (7a).[43] **7a** was prepared from 2-phenyl(4-hydroxyphenyl)-ethan-1-one and 2-dimethylaminoethoxychloride hydrochloride in the manner described for **6a** above. The product was isolated as a viscous oil in 97% yield following flash chromatography with CH_2Cl_2/MeOH (40:60). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.37 (s, 6H, $N(CH_3)_2$), 2.77 (t, 2H, J = 5.04, CH_2N), 4.14 (t, 2H, J = 5.52, CH_2O), 4.23 (s, 2H, CH_2), 6.94−6.96 (d, 2H, J = 9.04, Ar), 7.24−7.32 (m, 5H, Ar), 7.98−8.00 (d, 2H, J = 9.04, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 44.76 (CH_2), 45.33 ($N(CH_3)_2$), 57.55 (NCH_2), 65.72 (OCH_2), 113.90−162.29 (Ar C), 195.69 (C=O) ppm. IR (film) ν = 3097.6, 2703.1, 1673.7 (C=O), 1601.2, 1574.5, 1510.5, 1496.9, 1456.1 ($N(CH_3)_2$), 1261.1 (C−N), 1174.9 cm^{-1}.

2-Phenyl(4-diethylaminoethoxyphenyl)ethan-1-one (7b).[43] **7b** was prepared from 2-phenyl(4-hydroxyphenyl)ethan-1-one and 2-diethylaminoethoxychloride hydrochloride in the manner described for **6a** above. The product was isolated as a viscous oil in 64% yield following flash chromatography with CH_2Cl_2/MeOH (40:60). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.10 (m, 6H, $(CH_3)_2$), 2.66 (m, 4H, $(CH_2)_2$), 2.91 (t, 2H, J = 6.26, CH_2N), 4.12 (t, 2H, J = 6.26, CH_2O), 4.24 (s, 2H, CH_2), 6.92−6.96 (d, 2H, J = 9.52, Ar), 7.23−7.33 (m, 5H, Ar), 8.01−8.19 (d, 2H, J = 9.54, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 11.33 ($(CH_3)_2$), 44.78 (CH_2), 47.41 ($N(CH_2)_2$), 51.15 (NCH_2), 66.42 (OCH_2), 113.88−162.39 (Ar C), 196.55 (C=O) ppm. IR (film) ν = 2939.0, 1668.1 (C=O), 1599.8, 1574.3, 1509.8, 1496.2, 1454.7, 1377.4, 1288.6 (C−N), 1168.9 cm^{-1}.

2-Phenyl(4-pyrrolidinylethoxyphenyl)ethan-1-one (7c).[43] **7c** was prepared from 2-phenyl(4-hydroxyphenyl)ethan-1-one and 1-(2-chloroethyl)pyrrolidine hydrochloride in the manner described for **6a** above. The product was directly isolated as an oil in 94% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.86 (m, 4H 2x(CH_2), 2.63 (m, 4H, 2x(CH_2)), 2.98 (m, 2H, CH_2N), 4.17 (m, 2H, CH_2O), 4.24 (m 2H, CH_2), 6.92 (m, 2H, Ar), 7.32−7.54 (m, 5H, Ar), 7.99−8.08 (m, 2H, Ar) ppm. IR (film) ν = 2958.5, 2858.3, 1667.6 (C=O), 1598.8, 1510.0, 1490.2, 1454.2, 1241.9 (C−N), 1173.1 cm^{-1}.

2-Phenyl(4-pipyridinylethoxyphenyl)ethan-1-one (7d).[43] **7d** was prepared from 2-phenyl(4-hydroxyphenyl)ethan-1-one and 1-(2-chloroethyl)pipyridine hydrochloride in the manner described for **6a** above. The product was directly isolated as a viscous gel in 99% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.58 (m, 6H, (−$CH_2CH_2CH_2$-)), 2.72 (m, 4H, ((−CH_2)$N(CH_2$-)), 2.79 (t, 2H, J = 6.02, NCH_2), 4.15 (t, 2H, J = 6.02, OCH_2), 4.24 (s, 2H, CH_2), 6.91−6.95 (d, 2H, J = 15.08, Ar), 7.23−7.41 (m, 5H, Ar), 7.98−8.12 (d, 2H, J = 15.08, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 24.01 (CH_2), 25.89 (CH_2), 44.78 (CH_2), 54.55 (CH_2), 54.95 (CH_2), 57.25 (NCH_2), 65.88 (CH_2O), 113.91−130.43 (Ar C), 156.58 (C=O) ppm. IR (film) ν = 3061.5, 2853.2, 1671.9 (C=O), 1599.8, 1575.1, 1509.4, 1496.1, 1450.4, 1265.8 (C−N), 1171.8 cm^{-1}.

2-Phenyl(4-morpholinylethoxyphenyl)ethan-1-one (7e). **7e** was prepared from 2-phenyl(4-hydroxyphenyl)ethan-1-one and 4-(2-chloroethyl)morpholine hydrochloride in the manner described for **6a** above. The product was isolated as a viscous gel following flash chromatography with 50/50 MeOH/CH_2Cl_2 in 98% yield (product homogeneous on TLC with R_f = 0.16; 80/20 pet. ether/EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.74 (t, 2H, J = 6.84, CH_2N), 2.84 (m, 4H, $(CH_2)N(CH_2)$), 3.61 (m, 4H, $(CH_2)O(CH_2)$), 4.18 (t, 2H, J = 6.52, CH_2O), 4.25 (s, 2H, CH_2), 6.93−6.96 (d, 2H, J = 8.56, Ar), 7.25−7.99 (m, 5H, Ar), 8.00−8.01 (d, 2H, J = 8.52, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 44.80 (CH_2), 53.11 ((CH)N), 53.63 (N(CH)), 59.73 (NCH_2), 65.78 (CH_2O), 66.38 ((CH_2)O(CH_2)), 66.42 ((CH_2)O-(CH_2)), 113.89−128.17 (8xAr C) ppm. IR (film) ν = 2943.9, 1665.0 (C=O), 1600.1, 1509.3, 1496.7, 1453.2, 1256.2 (C−N), 1172.5 cm^{-1}. HRMS calcd 325.1682, found 325.1678.

***p*-Dimethylaminoethoxypropiophenone (8a).**[44] **8a** was prepared from *p*-hydroxypropiophenone and 2-dimethylaminoethylchloride hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (90:10) as an oil in 83% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.20 (t, 3H, J = 7.28, CH_3), 2.34 (s, 6H, $N(CH_3)_2$), 2.75 (t, 2H, J = 5.28, NCH_2), 2.93 (q, 2H, J = 7.24, CH_2), 4.12 (t, 2H, J = 5.24, CH_2O), 6.95 (d, 2H, J = 8.52, Ar), 7.94 (d, 2H, J = 9.00, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 10.16 (CH_3), 33.10 (CH_2), 47.64 ($N(CH_3)_2$), 59.87 (NCH_2), 68.03 (OCH_2), 115.97−164.32 (Ar), 201.14 (C=O) ppm. IR (film) ν = 3066.6, 1679.3 (C=O), 1610.9, 1575.3, 1509.2, 1458.2, 1419.3, 1350.2, 1258.2 (C−N), 1172.5 cm^{-1}.

***p*-Diethylaminoethoxypropiophenone (8b).**[44] **8b** was prepared from *p*-hydroxypropiophenone and 2-diethylaminoethylchloride hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (80:20) as an oil in 92% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.09 (t, 3H, CH_3), 1.20 (t, 3H, J = 5.52, CH_3), 2.64 (m, 4H, $N(CH_2)_2$), 2.93 (m, 4H, NCH_2, $CH_2(C{=}O)$), 4.11 (t, 2H, J = 6.02, CH_2O), 6.91−6.94 (d, 2H, J = 9.00, Ar), 7.92−7.94 (d, 2H, J = 8.56, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 8.81 (CH_3), 12.22 ((CH_3)$_2$), 31.73 (CH_2), 48.27 ($N(CH_3)_2$), 52.02 (NCH_2), 67.28 (OCH_2), 114.68−163.01 (Ar), 199.76 (C=O) ppm. IR (film) ν = 2971.2, 1681.1 (C=O), 1602.1, 1575.0, 1458.2, 1419.0, 1375.1, 1350.3, 1259.1 (C−N), 1171.1 cm^{-1}.

***p*-Pyrrolidinylethoxypropiophenone (8c). 8c** was prepared from *p*-hydroxypropiophenone and 1-(2-chloroethyl)-pyrrolidine hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (80:20) as an oil in 91% yield (product homogeneous on TLC with R_f = 0.34; 60/40 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.21 (t, 3H, J = 7.28, CH_3), 1.84 (m, 4H, $(CH_2)_2$), 2.08 (m, 4H, $NCH_2)_2$), 2.91 (m, 2H, NCH_2), 2.98 (m, 2H, CH_2), 4.20 (t, 2H, J = 5.76, CH_2O), 6.94 (d, 2H, J = 8.52, Ar), 7.92 (d, 2H, J = 8.52, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 9.80 (CH_3), 24.87 (CH_2), 32.76 (CH_2), 56.07 ($N(CH_2)_2$), 56.84 (NCH_2), 68.46 (OCH_2), 115.03−163.85 (Ar), 200.81 (C=O) ppm. IR (film) ν = 2879.6, 1680.6 (C=O), 1601.4, 1575.0, 1509.0, 1459.1, 1419.1, 1351.3, 1259.0 (C−N), 1172.2 cm^{-1}. HRMS calcd 247.1572, found 247.1572.

***p*-Pipyridinylethoxypropiophenone (8d).**[44] **8d** was prepared from *p*-hydroxypropiophenone and 1-(2-chloroethyl)-pipyridine hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (90:10) as a solid (mp 61 °C)[44] in 64% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.21 (t, 3H, J = 7.52, CH_3), 1.45 (m, 2H, CH_2), 1.61 (m, 4H, $(CH_2)_2$), 2.51 (m, 4H, $NCH_2)_2$), 2.78 (t, 2H, J = 6.02, NCH_2), 2.95 (q, 2H, J = 7.49, CH_2), 4.16 (t, 2H, J = 6.02, CH_2O), 6.92 (d, 2H, J = 9.04, Ar), 7.92 (d, 2H, J = 8.52, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 9.06 (CH_3), 24.77 (CH_2), 26.53 (CH_2), 26.56 (CH_2), 32.00 (CH_2), 55.70 ($N(CH_2)_2$), 58.36 (NCH_2), 66.91 (OCH_2), 114.88−163.01 (Ar), 198.76 (C=O) ppm. IR (film) ν = 2989.3, 2783.0, 1674.8 (C=O), 1600.3, 1574.9, 1558.0, 1540.0, 1455.4, 1437.8, 1351.9, 1262.0 (C−N), 1174.0 cm^{-1}.

***p*-Pipyridinylethoxypropiophenone (8e).**[44] **8e** was prepared from *p*-hydroxypropiophenone and 4-(2-chloroethyl)-morpholine hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (85:15) as a solid (mp 48 °C)[44] in 85% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.22 (t, 3H, J = 7.28, CH_3), 2.61 (m, 4H, $NCH_2)_2$), 2.83 (t, 2H, J = 5.52, NCH_2), 2.96 (q, 2H, J = 7.69, CH_2), 3.73 (m, 4H, $(CH_2)_2$), 4.16 (t, 2H, J = 5.56, CH_2O), 6.93 (d, 2H, J = 8.56, Ar), 7.93 (d, 2H, J = 9.00, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 8.36 (CH_3), 31.33 (CH_2), 53.50 ($N(CH_2)_2$), 57.38 (NCH_2), 65.38 (OCH_2), 114.17−160.01 (Ar), 199.46 (C=O) ppm. IR (film) ν = 3017.6, 2855.2, 1679.0 (C=O), 1601.4, 1575.3, 1455.3, 1419.3, 1356.0, 1256.4 (C−N), 1172.4 cm^{-1}.

2-(4-Dimethylaminoethoxyphenyl)-1-phenylethanone (9a). 9a was prepared from 2-(4-hydroxyphenyl)-1-phenylethanone and 2-dimethylaminoethylchloride hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (90:10) as an oil in 90% yield (product homogeneous on TLC with R_f = 0.43; 50/50 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.34 (s, 6H, $(CH_3)_2$), 2.56 (t, 2H, J = 5.76, NCH_2), 3.69 (s, 2H, CH_2), 4.13 (t, 2H, J = 5.78, CH_2O), 6.93−6.96 (d, 2H, J = 9.04, Ar), 7.26−7.73 (m, 5H, Ar), 7.96−7.99 (d, 2H, J = 8.58, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 40.79 (CH_2), 45.11 ($N(CH_3)_2$), 57.18 (NCH_2), 65.76 (OCH_2), 113.61−162.32 (Ar C), 171.12 (C=O) ppm. IR (film) ν = 3061.3, 2931.9, 1670.1 (C=O), 1599.9, 1576.5, 1453.9, 1374.3, 1251.8 (C−N), 1169.4 cm^{-1}. HRMS calcd 283.1576, found 283.1572.

2-(4-Diethylaminoethoxyphenyl)-1-phenylethanone (9b).[34] **9b** was prepared from 2-(4-hydroxyphenyl)-1-phenylethanone and 2-diethylaminoethylchloride hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (90:10) as an oil in 90% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.02 (m, 6H, $(CH_3)_2$), 2.55 (m, 4H, $N(CH_2)_2$), 2.71 (t, 2H, J = 6.28, NCH_2), 3.64 (s, 2H, CH_2), 4.19 (t, 2H, J = 6.26, CH_2O), 6.76−6.96 (d, 2H, J = 9.04, Ar), 7.28−7.54 (m, 5H, Ar), 7.96−7.99 (d, 2H, J = 9.04, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 11.39 (CH_3), 40.93 (CH_2), 47.93 ($N(CH_3)_2$), 50.56 (NCH_2), 66.76 (OCH_2), 113.21−131.87 (Ar C), 171.05 (C=O) ppm. IR (film) ν = 2941.2, 2930.0, 1654.3 (C=O), 1600.0, 1508.4, 1452.5, 1376.8, 1252.5 (C−N), 1168.8 cm^{-1}.

2-(4-Pyrrolidinylethoxyphenyl)-1-phenylethanone (9c). 9c was prepared from 2-(4-hydroxyphenyl)-1-phenylethanone and 1-(2-chloroethyl)pyrrolidinemonochloride hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (95:5) as an oil in 91% yield (product homogeneous on TLC with R_f = 0.36; 50/50 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.76 (m, 4H, $(CH_2)_2$), 2.53 (m, 4H, $N(CH_2)_2$), 2.73 (t, 2H, J = 6.04, NCH_2), 3.64 (s, 2H, CH_2), 4.24 (t, 2H, J = 6.18, CH_2O), 6.93−6.95 (d, 2H, J = 9.00, Ar), 7.22−7.61 (m, 5H, Ar), 7.97−7.99 (d, 2H, J = 8.52, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 23.03 (CH_2), 40.88 (CH_2), 53.89 ($N(CH_2)_2$), 53.98 (NCH_2), 63.32 (OCH_2), 113.89−130.44 (Ar C), 171.03 (C=O) ppm. IR (film) ν = 3063.1, 2877.8, 1670.3 (C=O), 1599.7, 1508.7, 1454.8, 1257.2, (C−N), 1160.0 cm^{-1}. HRMS calcd 309.1741, found 309.1728.

2-(4-Pipyridinylethoxyphenyl)-1-phenylethanone (9d). 9d was prepared from 2-(4-hydroxyphenyl)-1-phenylethanone and 1-(2-chloroethyl)pipyridinemonochloride hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (90:10) as an oil in 92% yield (product homogeneous on TLC with R_f = 0.45; 50/50 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.53 (m, 6H, $(CH_2)_3$), 2.40 (m, 4H, $N(CH_2)_2$), 2.60 (t, 2H, J = 5.76, NCH_2), 3.62 (d, 2H, J = 4.04, CH_2), 4.20 (t, 2H, J = 5.78, CH_2O), 6.88−6.98 (d, 2H, J = 8.52, Ar), 7.19−7.26 (m, 5H, Ar), 7.90−7.92 (d, 2H, J = 8.52, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 23.31 (CH_2), 24.93 (CH_2), 25.29 (CH_2), 40.63 (CH_2), 53.99 ($N(CH_2)_2$), 56.45 (NCH_2), 61.53 (OCH_2), 113.90−132.75 (Ar C), 170.15 (C=O) ppm. IR (film) ν = 2938.5, 2854.4, 1664.3 (C=O), 1599.7, 1509.5, 1495.4, 1254.4, (C−N), 1159.9 cm^{-1}. HRMS calcd 323.1881, found 323.1885.

2-(4-Morpholinylethoxyphenyl)-1-phenylethanone (9e). 9e was prepared from 2-(4-hydroxyphenyl)-1-phenylethanone and 4-(2-chloroethyl)morpholine hydrochloride in the manner described for **6a** above. The pure product was isolated by flash chromatography CH_2Cl_2/MeOH (85:15) as a mustard gel in 84% yield (product homogeneous on TLC with R_f = 0.10; 80/20 pet. ether/EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.24 (m, 4H, $(CH_2)_2$), 1.43 (t, 2H, J = 6.52, NCH_2), 2.26 (t, 2H, J = 6.52, OCH_2), 2.30 (m, 4H, $(CH_2)_2O$), 2.80 (s, 2H, CH_2), 5.39−5.48(d, 2H, J = 8.76, Ar), 5.80−6.14 (m, 5H, Ar), 5.80−6.14 (d, 2H, J = 8.78, Ar) ppm. ^{13}C NMR (MeOD, 76.7 MHz) δ = 37.29 (CH_2), 42.54 (NCH_2), 51.07 ($N(CH_2)_2$), 57.58 (OCH_2), 63.83 ($O(CH_2)_2$), 113.00−130.31 (Ar C), 160.59 (C=O) ppm. IR (film) ν = 2925.7, 1654.2 (C=O), 1599.7, 1508.1, 1458.1, 1222.1, (C−N), 1165.4 cm^{-1}. This compound was used in subsequent reactions without further purification.

2-Benzyl-1-phenyl-1-[4-(dimethylaminoethoxy)phenyl]-but-1-ene (2a). 6a (1.20 g, 4.5 mmol) was placed in a three-

necked round-bottomed flask equipped with a magnetic stirrer. To this 1-phenyl-2-butanone (0.662 mL, 4.5 mmol) and absolute dioxane (25 mL) were added and the mixture stirred in an ice bath (0−5 °C, 15 min). Titanium tetrachloride (0.99 mL, 9.1 mmol) was slowly added via syringe over 10 min, while maintaining stirring and the lowered temperature. Upon completion of addition the reaction mixture left stirring for a further 30 min, after which time Zn powder (1.86 g, 28 mmol, particle size < 10 μm) was added in a single portion and stirring continued for 15 min. The ice bath was removed and the reaction mixture allowed to reach room temperature, at which stage the apparatus was arranged for reflux and the reaction brought to reflux temperature for 4 h. The reaction was allowed to cool to room temperature, filtered (residue washed with ethyl acetate), washed, first with 10% K_2CO_3 solution, then a large volume of deionized water and extracted (3 × 30 mL) into dichloromethane. The organic extracts were combined and consecutively washed with 20 mL 3 M HCl and deionized water before being dried over anhydrous sodium sulfate. The resulting solution was filtered to remove drying agent and concentrated under reduced pressure rotary evaporation. The crude product was purified using column chromatography CH_2Cl_2/MeOH (60:40) to yield pure **2a** (0.41 g, 23%) (product homogeneous on TLC with R_f = 0.32; 60/40 CH_2Cl_2/pet. ether). HPLC t_R = 15.0, 16.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.99 (m, 3H, CH_3), 2.07 (m, 2H, CH_2), 2.48 (d, 6H, J = 7.95, $(CH_3)_2$), 2.90 (m, 2H, NCH_2), 3.56 and 3.59 (2 x s, 2H, CH_2), 4.16 (m, 2H, OCH_2), 6.82−6.84 (d, 2H, J = 8.74, Ar), 7.14−7.32 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 12.81 (CH_3), 24.20 (CH_2), 36.72 (CH_2), 44.75 ($N(CH_3)_2$), 57.34 (CH_2N), 64.67 (OCH_2), 113.67−140.19 (Ar C) ppm. IR (film) ν = 3007.5, 2997.8, 1606.6 (C═C), 1506.5, 1461.5, 1371.4, 1275.7, 1173.4 cm^{-1}. HRMS calcd 385.2405, found 385.2406.

2-Benzyl-1-phenyl-1-[4-(diethylaminoethoxy)phenyl]-but-1-ene (2b). 2b was prepared from **6b** and 1-phenyl-2-butanone in the manner described for **2a** above. The pure product was isolated in 40% yield following flash chromatography (CH_2Cl_2/MeOH (75:25) (product homogeneous on TLC with R_f = 0.45; 60/40 MeOH/CH_2Cl_2)). HPLC t_R = 18.0, 19.5 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.95 (m, 3H, CH_3), 2.05 (m, 2H, CH_2), 2.51 (m, 5H, (CH_2CH_3)), 2.71 (m, 5H, (CH_2CH_3)), 2.91 (m, 2H, NCH_2), 3.60 and 3.64 (2 x s, 2H, CH_2), 4.10 (m, 2H, OCH_2), 6.80−6.86 (d, 2H, J = 8.34, Ar), 7.18−7.41 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 11.14 (CH_3), 24.30 (CH_2), 36.86 (CH_2), 47.33 ($N(CH_2)_2$), 51.20 (CH_2N), 65.15 (OCH_2), 113.60−135.20 (Ar C) ppm. IR (film) ν = 3027.2, 2969.4, 1600.0 (C═C), 1508.0, 1454.0, 1243.7, 1175.8 cm^{-1}. HRMS calcd 413.2725, found 413.2719.

2-Benzyl-1-phenyl-1-[4-(pyrrolidinylethoxy)phenyl]-but-1-ene (2c). 2c was prepared from **6c** and 1-phenyl-2-butanone in the manner described for **2a** above. The pure product was isolated in 40% yield following flash chromatography (CH_2Cl_2/MeOH (90:10) (product homogeneous on TLC with R_f = 0.49; 60/40 MeOH/CH_2Cl_2)). HPLC t_R = 21.0, 22.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.02 (m, 3H, CH_3), 1.84 (m, 4H, $(CH_2)_2$), 2.12 (m, 2H, CH_2), 2.71 (m, 4H, $(CH_2)_2$), 2.94 (m, 2H, NCH_2), 3.63 and 3.67 (2 x s, 2H, CH_2), 4.13 (m, 2H, OCH_2), 6.85−6.95 (d, 2H, J = 8.04, Ar), 7.21−7.38 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 12.93 (CH_3), 23.50 (CH_2), 24.79 (CH_2), 37.25 (CH_2), 54.60 ($N(CH_2)_2$), 55.01 (CH_2N), 66.77 (OCH_2), 113.84−138.18 (Ar C) ppm. IR (film) ν = 3026.2, 2964.3, 1708.6 (C═C), 1507.5, 1454.0, 1243.8, 1175.1 cm^{-1}. HRMS calcd 411.2573, found 411.2562.

2-Benzyl-1-phenyl-1-[4-(pipyridinylethoxy)phenyl]but-1-ene (2d). 2d was prepared from **6d** and 1-phenyl-2-butanone in the manner described for **2a** above. The pure product was isolated in 24% yield following flash chromatography (CH_2Cl_2/MeOH (70:30) (product homogeneous on TLC with R_f = 0.49; 60/40 MeOH/CH_2Cl_2)). HPLC t_R = 15.0, 16.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.97 (m, 3H, CH_3), 1.47 (m, 2H, CH_2), 1.62 (m, 4H $(CH_2)_2$), 2.03 (m, 2H, CH_2), 2.49 (m, 4H, $(CH_2)_2$), 2.81 (m, 2H, NCH_2), 3.57 and 3.61 (2 x s, 2H, 15.04, CH_2), 4.09 (m, 2H, OCH_2), 6.82−6.88 (d, 2H, J = 8.52, Ar), 7.15−7.17 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 12.81 (CH_3), 23.66 (CH_2), 24.29 (CH_2), 25.36 (CH_2), 36.85 (CH_2), 54.54 ($N(CH_2)_2$), 57.48 (CH_2N), 65.30 (OCH_2), 113.76−138.13 (Ar C) ppm. IR (film) ν = 3026.1, 2932.8, 1708.6 (C═C), 1506.8, 1453.2, 1241.7, 1174.9 cm^{-1}. HRMS calcd 425.2718, found 425.2719.

2-Benzyl-1-phenyl-1-[4-(morpholinylethoxy)phenyl]-but-1-ene (2e). 2e was prepared from **6e** and 1-phenyl-2-butanone in the manner described for **2a** above. The pure product was isolated in 34% yield following flash chromatography (CH_2Cl_2/MeOH (90:10) (product homogeneous on TLC with R_f = 0.49; 90/10 pet. ether/EtOAc)). HPLC t_R = 22.8, 24.0 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.95 (m, 3H, CH_3), 2.04 (m, 2H, CH_2), 2.58 (m, 4H $(CH_2)_2$), 2.81 (m, 2H, NCH_2), 3.56 and 3.59 (2 x s, 2H, CH_2), 3.71 (m, 4H, $(CH_2)_2$), 4.07 (m, 2H, OCH_2), 6.82−6.87 (d, 2H, J = 8.52, Ar), 7.15−7.29 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 13.20 (CH_3), 37.14 (CH_2), 54.03 (NCH_2), 57.65 (CH_2), 65.66 (OCH_2), 66.87 (CH_2), 114.16−138.53 (Ar C) ppm. IR (film) ν = 3026.8, 2963.1, 1712.6 (C═C), 1507.9, 1453.2, 1243.8, 1175.1 cm^{-1}. HRMS calcd 427.2517, found 427.2511.

1-Benzyl-2-phenyl[4-(dimethylaminoethoxy)phenyl]-but-1-ene (3a). 3a was prepared from **7a** and propiophenone in the manner described for **2a** above. The pure product was isolated in 49% yield following flash chromatography (CH_2Cl_2/MeOH (40:60) (product homogeneous on TLC with R_f = 0.41; 60/40 MeOH/CH_2Cl_2)). HPLC t_R = 12.6, 15.6 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.01 (m, 3H, CH_3), 2.31 (s, 6H, $N(CH_3)_2$), 2.39 (m, 2H, CH_2), 2.64 (m, 2H, CH_2N), 2.70 (m, 2H, CH_2O), 3.95 and 3.97 (2 x s, 2H, CH_2), 6.55 (d, 2H, J = 8.52, Ar), 6.81−7.45 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 12.81 (CH_3), 27.51 (CH_3), 39.55 (CH_2), 45.25 ($N(CH_3)_2$), 57.72 (NCH_2), 65.07 (OCH_2), 113.02−156.05 (23x Ar C) ppm. IR (film) ν = 3057.2, 2871.2, 1605.2 (C═C), 1574.2, 1508.8, 1493.1, 1453.3, 1372.6, 1242.0, 1176.8 cm^{-1}. HRMS calcd 385.2405, found 385.2506.

1-Benzyl-2-phenyl[4-(diethylaminoethoxy)phenyl]but-1-ene (3b). 3b was prepared from **7b** and propiophenone in the manner described for **2a** above. The pure product was isolated in 41% yield following flash chromatography (CH_2Cl_2/EtOAc (90:10) (product homogeneous on TLC with R_f = 0.27; 60/40 MeOH/CH_2Cl_2)). HPLC t_R = 12.0, 15.0 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.99 (m, 3H, CH_3), 1.21 (m, 6H, $N(CH_3)_2$), 1.73 (m, 2H, CH_2), 2.10 (m, 4H, $N(CH_2)_2$), 2.84 (m, 2H, CH_2N), 3.66, (m, 2H, CH_2O), 4.23 and 4.25 (2 x s, 2H, CH_2), 6.90−6.94 (d, 2H, J = 8.78, Ar), 7.08−7.62 (m, 10H, Ar), 7.91−8.08 (d, 2H, J = 8.56, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 10.78 (CH_3), 27.56 (CH_2), 45.17 (CH_2), 47.47 ($N(CH_2)_2$), 51.25 (CH_2N), 65.49 (OCH_2), 113.86−139.93 (Ar C) ppm. IR (film) ν = 3058.9, 2874.2, 1600.9 (C═C), 1575.5, 1510.5, 1494.8, 1453.7, 1378.3, 1249.0, 1170.5 cm^{-1}. HRMS calcd 413.2725, found 413.2719.

1-Benzyl-2-phenyl[4-(pyrrolidinylethoxy)phenyl]but-1-ene (3c). 3c was prepared from **7c** and propiophenone in the manner described for **2a** above. The pure product was isolated in 74% yield following flash chromatography (CH_2Cl_2/MeOH (90:10) (product homogeneous on TLC with R_f = 0.35; 60/40 MeOH/CH_2Cl_2)). HPLC t_R = 15.6, 19.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.93 (t, 3H, J = 7.52, CH_3), 1.83 (m, 4H, ((CH_2)−(CH_2)), 2.08 (q, 2H, J = 7.54, CH_2), 2.67 (m, 4H (CH_2)-N−(CH_2)), 3.02 (m, 2H, NCH_2), 4.11 (m, 2H, CH_2O), 4.25 (s, 2H CH_2), 6.53−6.55 (d, 2H, J = 8.56, Ar), 6.99−7.25 (m, 12H, Ar), 8.01−8.03 (d, 2H, J = 8.84, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 8.01 (CH_3), 23.96 (CH_2), 28.25 (CH_2), 28.42 (CH_2), 55.36 (CH_2), 66.24 (OCH_2), 11426−144.09 (Ar C) ppm. IR (film) ν = 3058.3, 2875.0, 2225.8, 1601.9 (C═C), 1576.3, 1509.8, 1494.2, 1453.6, 1375.3, 1245.1, 1176.8 cm^{-1}. HRMS calcd 411.2573, found 411.2562.

1-Benzyl-2-phenyl[4-(pipyridinylethoxy)phenyl]but-1-ene (3d). 3d was prepared from **7d** and propiophenone in the manner described for **2a** above. The pure product was isolated in 80% yield following flash chromatography (CH_2Cl_2/MeOH (90:10) (product homogeneous on TLC with R_f = 0.48; 60/40 MeOH/CH_2Cl_2)). HPLC t_R = 12.6, 15.0 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.95 (m, 3H, CH_3), 1.48 (m, 6H, ((CH_2)−(CH_2)−

(CH_2))), 2.05 (m, 2H, CH_2), 2.70 (m, 4H, (CH_2)-N−(CH_2)), 2.78 (m, 2H NCH_2), 4.13 (m, 2H, OCH_2), 4.20 (s, 2H, CH_2), 6.49−6.51 (d, 2H, J = 8.52, Ar), 6.89−7.49 (m, 10H, Ar), 7.91−7.98 (d, 2H, J = 8.56, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 7.83 (CH_3), 24.40 (CH_2), 25.89 (CH_2), 26.10 (CH_2), 27.67 (CH_2), 45.63 (CH_2), 55.35 (CH_2), 58.09 (N(CH_2), 65.67 (OCH_2), 113.89−130.19 (Ar C) ppm. IR (film) ν = 3058.2, 2852.5, 1600.4 (C═C), 1575.3, 1509.3, 1494.0, 1452.7, 1372.8, 1245.1, 1175.5 cm^{-1}. HRMS calcd 425.2718, found 425.2719.

1-Benzyl-2-phenyl[5-(morpholinylethoxy)phenyl]but-1-ene (3e). 3e was prepared from **7e** and propiophenone in the manner described for **2a** above. The pure product was isolated in 40% yield following flash chromatography (CH_2Cl_2/MeOH (90:10) (product homogeneous on TLC with R_f = 0.72; 60/40 MeOH/CH_2Cl_2)). HPLC t_R = 15.0, 16.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.98 (t, 3H, J = 7.52, CH_3), 1.73 (q, 2H, J = 7.54, CH_2), 2.84 (m, 2H, NCH_2), 3.02 (m, 4H, (CH_2)-N−(CH_2)), 3.61 (m, 2H, OCH_2), 4.12 (m, 4H, (CH_2)-O−(CH_2)), 4.25 (s, 2H, CH_2), 6.83−6.86 (d, 2H, J = 8.52, Ar), 6.93−7.58 (m, 10H, Ar), 7.97−7.98 (d, 2H, J = 8.52, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 7.08 (CH_3), 27.23 (CH_2), 44.24 (CH_2), 53.11 ((CH_2)-N), 53.62 (N−(CH_2)), 57.25 (CH_2N), 65.61 (OCH_2), 66.43 (2xCH_2), 113.89−130.48 (Ar C) ppm. IR (film) ν = 3059.0, 2856.4, 1600.5 (C═C), 1510.1, 1493.3, 1453.3, 1358.2, 1247.0, 1175.3 cm^{-1}. HRMS calcd 427.2517, found 427.2511.

1-Benzyl-1-phenyl-2-[4-(dimethylaminoethoxy)phenyl]-but-1-ene (4a). 4a was prepared from **8a** and desoxybenzoin in the manner described for **2a** above. The pure product was isolated in 24% yield following flash chromatography (CH_2Cl_2/MeOH (90:10) (product homogeneous on TLC with R_f = 0.13; 50/10/40 CH_2Cl_2/MeOH/EtOAc)). HPLC t_R = 12.0, 15.0 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.99 (t, 3H, J = 7.54, CH_3), 2.45 (s, 6H, (CH_3)$_2$), 2.63 (q, 2H, J = 7.52, CH_2), 2.86 (m, 2H, NCH_2), 3.96 (s, 2H, CH_2), 4.07 (m, 2H, OCH_2), 6.65−6.67 (d, 2H, J = 8.52, Ar), 6.94−7.56 (m, 10H, Ar), 8.07−8.07 (d, 2H, J = 9.04, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 12.52 (CH_3), 27.47 (CH_2), 39.59 (CH_2), 44.65 (N(CH_3)$_2$), 57.20 (CH_2N), 64.61 (OCH_2), 113.89−156.03 (Ar C) ppm. IR (film) ν = 3083.3, 2871.1, 1604.5 (C═C), 1508.6, 1494.3, 1452.8, 1381.1, 1282.4, 1177.3 cm^{-1}. HRMS calcd 385.2405, found 385.2406.

1-Benzyl-1-phenyl-2-[4-(diethylaminoethoxy)phenyl]-but-1-ene (4b). 4b was prepared from **8b** and desoxybenzoin in the manner described for **2a** above. The pure product was isolated in 34% yield following flash chromatography (CH_2Cl_2/MeOH (80:20) (product homogeneous on TLC with R_f = 0.11; 50/10/40 CH_2Cl_2/MeOH/EtOAc)). HPLC t_R = 15.0, 19.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.01 (t, 3H, J = 7.54, CH_3), 1.14 (m, 6H, (CH_3)$_2$), 2.68 (m, 6H, CH_2, N(CH_2)$_2$), 2.90 (t, 2H, J = 6.26, CH_2N), 3.98 (s, 2H, CH_2), 4.03 (t, 2H, J = 6.04, OCH_2), 6.66−6.68 (d, 2H, J = 8.52, Ar), 6.94−7.31 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 11.06 (CH_3), 12.54 (CH_3), 27.49 (CH_2), 39.16 (CH_2), 47.31 (N(CH_2)$_2$), 51.12 (CH_2N), 65.48 (OCH_2), 113.89−156.26 (Ar C) ppm. IR (film) ν = 3080.2, 2931.2, 1605.6 (C═C), 1508.7, 1493.6, 1453.0, 1372.6, 1283.2, 1176.4 cm^{-1}. HRMS calcd 413.2725, found 413.2719.

1-Benzyl-1-phenyl-2-[4-(pyrrolidinylethoxy)phenyl]-but-1-ene (4c). 4c was prepared from **8c** and desoxybenzoin in the manner described for **2a** above. The pure product was isolated in 24% yield following flash chromatography (CH_2Cl_2/MeOH (85:15) (product homogeneous on TLC with R_f = 0.30; 50/10/40 CH_2Cl_2/MeOH/EtOAc)). HPLC t_R = 12.6, 17.6 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.99 (t, 3H, J = 7.00, CH_3), 1.95 (m, 4H, (CH_2)$_2$), 2.65 (q, 2H, J = 7.01, CH_2), 2.98 (m, 4H, N(CH_2)$_2$), 3.14 (t, 2H, J = 5.04, NCH_2), 3.96 (s, 2H, CH_2), 4.17 (t, 2H, J = 5.26, OCH_2), 6.64−6.66 (d, 2H, J = 8.52, Ar), 6.91−7.58 (m, 10H, Ar), 8.03−8.05 (d, 2H, J = 8.52, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 12.50 (CH_3), 22.86 (CH_2), 22.92 (CH_2), 27.46 (CH_2), 39.59 (CH_2), 45.05 (CH_2N), 53.81, 53.93 (N(CH_2)$_2$), 64.75 (OCH_2), 113.58−155.69 (Ar C) ppm. IR (film) ν = 3059.8, 2928.2, 1603.2 (C═C), 1509.1, 1494.6, 1451.0, 1377.5, 1277.7, 1177.5 cm^{-1}. HRMS calcd 411.2573, found 411.2562.

1-Benzyl-1-phenyl-2-[4-(pipyridinylethoxy)phenyl]but-1-ene (4d). 4d was prepared from **8d** and desoxybenzoin in the manner described for **2a** above. The pure product was isolated in 39% yield following flash chromatography (CH_2Cl_2/MeOH (90:10) (product homogeneous on TLC with R_f = 0.40; 50/10/40 CH_2Cl_2/MeOH/EtOAc)). HPLC t_R = 13.2, 16.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.96 (t, 3H, J = 7.52, CH_3), 1.51 (m, 2H, CH_2), 1.75 (m, 4H, (CH_2)$_2$), 2.66 (q, 2H, J = 7.54, CH_2), 2.75 (m, 4H, N(CH_2)$_2$), 2.98 (m, 2H, NCH_2), 3.95 (s, 2H, CH_2), 4.14 (m, 2H, OCH_2), 6.63−6.65 (d, 2H, J = 8.56, Ar), 6.75−7.56 (m, 10H, Ar), 8.02−8.10 (d, 2H, J = 8.64, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 12.90 (CH_3), 23.40 (CH_2), 24.72 (CH_2), 27.86 (CH_2), 39.99 (CH_2), 54.39 (N(CH_2)$_2$), 57.13 (CH_2N), 64.64 (OCH_2), 113.59−156.19 (Ar C) ppm. IR (film) ν = 3060.0, 2856.9, 1604.9 (C═C), 1509.1, 1494.5, 1452.9, 1379.9, 1281.5, 1177.7 cm^{-1}. HRMS calcd 425.2718, found 425.2719.

1-Benzyl-1-phenyl-2-[4-(morpholinylethoxy)phenyl]-but-1-ene (4e). 4e was prepared from **8e** and desoxybenzoin in the manner described for **2a** above. The pure product was isolated in 29% yield following flash chromatography (CH_2Cl_2/MeOH (90:10) (product homogeneous on TLC with R_f = 0.58; 50/10/40 CH_2Cl_2/MeOH/EtOAc)). HPLC t_R = 12.6, 15.6 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.99 (t, 3H, J = 7.54, CH_3), 2.63 (m, 4H, N(CH_2)$_2$), 2.83 (t, 2H, J = 5.52, NCH_2), 2.89 (q, 2H, J = 7.03, CH_2), 3.75 (m, 4H, O(CH_2)$_2$), 3.96 (s, 2H, CH_2), 4.06 (t, 2H, J = 5.52, OCH_2), 6.65−6.67 (d, 2H, J = 8.56, Ar), 6.92−7.56 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz), δ = 12.52 (CH_3), 27.48 (CH_2), 39.61 (CH_2), 55.44 (CH_2), 57.09 (NCH_2), 64.92 (OCH_2), 66.22 ((CH_2)$_2$O), 113.22−156.18 (Ar C) ppm. IR (film) ν = 3059.4, 2929.2, 1605.8 (C═C), 1509.1, 1494.4, 1453.3, 1370.4, 1282.0, 1177.3 cm^{-1}. HRMS calcd 427.2517, found 427.2511.

1,2-Diphenyl-2-[2-(dimethylaminoethoxy)benzyl]but-1-ene (5a). 5a was prepared from **9a** and propiophenone in the manner described for **2a** above. The pure product was isolated in 21% yield following flash chromatography (CH_2Cl_2/MeOH (95:5) (product homogeneous on TLC with R_f = 0.50; 50/50 CH_2Cl_2/MeOH)). HPLC t_R = 13.2, 15.6 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.46 (t, 3H, J = 6.86, CH_3), 2.07 (s, 6H, (CH_3)$_2$), 2.74 (m, 2H, NCH_2), 3.76 (q, 2H, J = 6.85, CH_2), 3.94 (s, 2H, CH_2), 4.14 (m, 2H, OCH_2), 6.52−6.56 (m, 2H, Ar), 6.83−7.54 (m, 12H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 14.19 (CH_3), 29.68 (CH_2), 38.67 (CH_2), 47.43, 47.54 (N(CH_3)$_2$), 58.48 (CH_2N), 60.38 (OCH_2), 113.89−164.59 (Ar C) ppm. IR (film) ν = 3120.4, 2885.6, 1603.7 (C═C), 1508.7, 1496.1, 1450.5, 1382.3, 1282.4 cm^{-1}. HRMS calcd 385.2405, found 385.2406.

1,2-Diphenyl-2-[2-(diethylaminoethoxy)benzyl]but-1-ene (5b). 5b was prepared from **9b** and propiophenone in the manner described for **2a** above. The pure product was isolated in 40% yield following flash chromatography (CH_2Cl_2/MeOH (96:4) (product homogeneous on TLC with R_f = 0.33; 50/50 CH_2Cl_2/MeOH)). HPLC t_R = 13.2, 15.0 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.86 (m 6H (CH_3)$_2$), 0.98 (t, 3H, J = 7.52, CH_3), 2.36 (s, 4H, (CH_2)$_2$), 2.66 (q, 2H, J = 7.52, CH_2), 2.76 (m, 2H, NCH_2), 3.92 (s, 2H, CH_2), 4.08 (m, 2H, OCH_2), 6.54−6.56 (d, 2H, J = 9.00, Ar), 6.80−7.35 (m, 12H, Ar) ppm. IR (film) ν = 3059.2, 2850.6, 1604.9 (C═C), 1509.9, 1494.2, 1454.2, 1373.2, 1283.2, 1172.4 cm^{-1}. HRMS calcd 413.2725, found 413.2719.

1,2-Diphenyl-2-[4-(pyrrolidinylethoxy)benzyl]but-1-ene (5c). 5c was prepared from **9c** and propiophenone in the manner described for **2a** above. The pure product was isolated in 19% yield following prep thin-layer chromatography (CH_2Cl_2/EtOAc/MeOH (50:40:10) (product homogeneous on TLC with R_f = 0.65; 50/50 CH_2Cl_2/MeOH)). HPLC t_R = 12.6, 14.4 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.90 (t, 3H, J = 7.28, CH_3), 2.63 (m, 4H, (CH_2)$_2$), 2.28 (q, 2H, J = 7.04, CH_2), 3.65 (m, 4H, (CH_2)$_2$), 3.78 (m, 2H, NCH_2), 4.15 and 4.16 (2 x s, 2H, CH_2), 4.35 (m, 2H, OCH_2), 7.25−7.47 (m, 14H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ = 17.58 (CH_3), 24.17 (CH_2), 29.21 (CH_2), 39.50 (CH_2), 47.07 (NCH_2), 63.28 (N(CH_2)$_2$), 66.36 (OCH_2), 116.39−146.26 (Ar C) ppm. IR (film) ν = 3104.7, 2973.9, 1600.4 (C═C), 1492.4, 1448.6, 1370.4, 1246.1, 1166.0 cm^{-1}. HRMS calcd 411.2573, found 411.2562.

1,2-Diphenyl-2-[4-(pipyridinylethoxy)benzyl]but-1-ene (5d). 5d was prepared from **9d** and propiophenone in the

manner described for **2a** above. The pure product was isolated in 38% yield following flash chromatography (CH_2Cl_2/MeOH (97:3) (product homogeneous on TLC with $R_f = 0.55$; 50/50 CH_2Cl_2/MeOH)). HPLC $t_R = 12.0$, 15.0 min. ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 1.01$ (t, 3H, $J = 7.54$, CH_3), 2.07 (m, 2H, CH_2), 2.31 (m, 4H, $(CH_2)_2$), 2.58 (t, 2H, $J = 7.52$, CH_2), 2.74 (m, 4H, $(CH_2)_2$), 3.03 (m, 2H, NCH_2), 3.63 (s, 2H, CH_2), 4.30 (m, 2H, OCH_2), 6.79−7.18 (m, 12H, Ar), 7.92−8.00 (d, 2H, $J = 9.04$, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) $\delta = 13.61$ (CH_3), 23.11 (CH_2), 26.81 (CH_2), 27.22 (CH_3), 31.45 (CH_2), 40.91 (CH_2), 53.66 ($N(CH_2)_2$), 56.08 (CH_2N), 61.07 (OCH_2), 115.09−142.76 (Ar C) ppm. IR (film) $\nu = 3060.7$, 2927.1, 1601.2 (C═C), 1511.1, 1494.5, 1451.1, 1377.6, 1247.2 cm^{-1}. HRMS calcd 425.2718, found 425.2719.

1,2-Diphenyl-2-[4-(morpholinylethoxy)benzyl]but-1-ene (5e). **5e** was prepared from **9e** and propiophenone in the manner described for **2a** above. The pure product was isolated in 29% yield following prep thin-layer chromatography (pet. ether (40−60)/EtOAc (90:10) (product homogeneous on TLC with $R_f = 0.40$; 80/20 EtOAc/pet. ether)). HPLC $t_R = 13.2$, 16.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 0.99$ (t, 3H, $J = 7.52$, CH_3), 2.27 (m, 4H, $(CH_2)_2$), 2.68 (q, 2H, $J = 7.48$, CH_2), 2.74 (t, 2H, $J = 6.26$, NCH_2), 3.89 (m, 4H, CH_2), 4.64 (t, 2H, $J = 6.26$, OCH_2), 4.72 (s, 2H, CH_2), 6.46−6.48 (d, 2H, $J = 8.52$, Ar), 6.66−7.32 (m, 10H, Ar), 7.38−7.39 (d, 2H, $J = 8.52$, Ar) ppm. ^{13}C NMR ($CDCl_3$, 76.7 MHz) $\delta = 13.34$ (CH_3), 29.63 (CH_2), 39.89 (CH_2), 41.45 (NCH_2), 55.45 ($O(CH_2)_2$), 63.71 ($(CH_2)_2N$), 64.17 (OCH_2), 114.29−128.86 (Ar C) ppm. IR (film) $\nu = 3083.0$, 2973.7, 1600.4 (C═C), 1509.8, 1492.8, 1462.8, 1370.5, 1256.7, 1142.9 cm^{-1}. HRMS calcd 427.2517, found 427.2511.

Biochemistry. All assays were performed in triplicate for the determination of mean values reported.

Antiproliferation Studies. Premise: MTT is a yellow tetrazolium salt which is taken up only by metabolically active cells and subsequently cleaved by mitochondrial dehydrogenases to yield a purple crystalline formazan dye. On solubilization this purple color may be read spectrophotometrically at 570 nm. The absorbance measured at this wavelength is directly proportional to the amount of viable cells present.

Procedure: The human breast tumor MCF-7 cell line was cultured in Eagles minimum essential medium in a 5% CO_2 atmosphere with 10% fetal calf serum. The medium was supplemented with 1% nonessential amino acids. The cells were trypsinized and seeded at a density of 1.5×10^4 into a 96-well plate and incubated at 37 °C, 5% CO_2 atmosphere for 24 h. After this time they were treated with 2 μL volumes of test compound which had been pre-prepared as stock solutions in ethanol to furnish the concentration range of study, 1 nM−100 μM, and reincubated for a further 72 h. Control wells contained the equivalent volume of the vehicle ethanol (1% v/v). The culture medium was then removed and the cells washed with 100 μL PBS and 50 μL MTT added, to reach a final concentration of 1 mg/mL MTT added. The cells were incubated for 2 h in darkness at 37 °C. At this point solubilization was begun through the addition of 200 μL DMSO and the cells maintained at room temperature in darkness for 20 min to ensure thorough color diffusion before reading the absorbance. The absorbance value of control cells (no added compound) was set to 100% cell viability and from this graphs of absorbance versus cell density/well were prepared to assess cell viability and from these graphs of percentage cell viability versus concentration of subject compound added were drawn.

Cytotoxicity Studies. Premise: Lactate dehydrogenase (LDH) is a cytosolic enzyme released upon cell lysis (death). Through the use of a commercial LDH assay kit, released LDH converts a substrate tetrazolium salt into a soluble red formazan product. The absorbance of this dye can be measured directly at 490 nm, the color formed is proportional to the number of lysed cells, and as such the extent of cytotoxic activity for the compound added may be assessed.

Procedure: As with the cell proliferation assay, human MCF-7 breast cancer cells were plated at a density of 1.5×10^4/well in a 96-well plate, then incubated at 37 °C, 5% CO_2 atmosphere for 24 h. The cells were treated with the compound of choice at varying concentrations (1nM−100 μM), then incubated for a further 72 h. Following incubation 50 μL aliquots of medium were removed to a fresh 96-well plate. A 50 μL/well LDH substrate mixture was added and the plate left in darkness at room temperature for equilibration. Stop solution (50 μL) was added to all wells before reading the absorbance at 490 nm. A control of 100% lysis was determined for a set of untreated cells which were lysed through the addition of 20 μL lysis solution to the media 45 min prior to harvesting. Data were presented following calculation, as percentage cell lysis versus concentration of subject compound.

Receptor Binding Assay. Premise: Binding affinity (K_i value) for the ER is measured by the ability of the study compound to displace tritium-labeled estradiol from the receptor site.

Procedure: ER-rich cytosol was obtained from the uteri of humanely sacrificed Sprague−Dawley immature rats (100−150 g mass). Briefly, the uteri were homogenized in 0.01 M sodium phosphate buffer, pH 7.3, containing 0.15 M NaCl, 0.1% gelatin and 0.01% sodium azide. The homogenate was then centrifuged at 100000*g*, 4 °C. The cytosol thus isolated was pretreated with dextran coated charcoal (DCC on ice)[45] and reisolated using centrifugation, before freezing at −20 °C for later use. The protein concentration of cytosol samples was determined using a standard Bradford protein assay and an appropriate protein concentration range (150 μg protein in a total volume of 0.14 mL) for assay prepared. The required amounts of tritium-labeled (hot) and nonlabeled (cold) estradiol were calculated using standard saturation curve techniques. A fresh buffer solution was prepared (Tris [tris(hydroxymethyl)aminomethane] buffer − 10 mM, pH 7.4, containing 1.5 mM EDTA and 3 mM sodium azide). Displacement testing of the compounds of choice was facilitated through the incubation of a buffered solution of a known concentration of the test compound with hot estradiol solution (specific activity 157 Ci/mmol, final concn 5 nM/tube), followed by the addition of ER-rich cytosol (150 μg protein). Total and nonspecific binding control assays were determined in the absence and presence of 14 μL of a 0.2 mM cold estradiol solution respectively, properly corrected for the presence of ethanol in the test (displacement) samples. Samples were vortexed to ensure homogeneity and refrigerated at 4 °C for 16−20 h. After this time the samples were retreated with DCC on ice and centrifuged for 10 min at 3500*g*. A 170 μL sample was pipetted from each vial and diluted with 10 mL scintillation fluid (Ecoscint). A scintillation control containing 28 μL of 5 nM hot estradiol in 10 mL scintillation fluid was also prepared to facilitate theoretical activity calculations. The samples thus prepared were counted for radioactivity by liquid scintillation counting. Binding values were obtained as counts/minute (cpm) and were converted to disintegrations/minute (dpm) and computationally analyzed using sigmoidal curve fitting programs EBDA and LIGAND[46] to fit the displacement curves and to calculate binding affinity values (K_i) for the test compounds.

Computational Procedures. Hardware and Software: All manipulations and calculations were carried out on Silicon Graphics O2 workstations (two workstations running IRIX 6.5: 1 × 200 MHz MIPS R5000 (IP32) processor and 128 Mb RAM, 1 × 300 MHz MIPS R12000 (IP32) processor and 256 Mb RAM). Text editing was performed using the SGI proprietary 'NEdit' program, version 4.0.3i. Model building and structural superimpositions were carried out using MacroModel 6.5.[24] Rigid docking was performed using LIGIN,[27] flexible docking was facilitated through the *flexidock* utility in the *Biopolymer* module of SYBYL 6.6,[28] with final ligand−protein contact data generated by LPC.[29] Visualizations were rendered from both MacroModel and SYBYL.

Molecular Modeling: Structures for compounds **1a** and **2**−**5**,**a**−**e** were built in MacroModel 6.5. Initial energy minimization[25] was performed through sequential minimization steps using Steepest Decent (SD), Polak-Ribier Conjugate Gradient (PRCG) and Full Matrix Newton Raphson (FMNR)

techniques. A global energy minimization protocol utilizing a Monte Carlo conformational search technique under a PRCG method. In all cases the MacroModel MM3* force field was applied. This protocol was evaluated through comparison of the geometries of receptor-bound 4-hydroxy-TAM[26] and its energy-minimized counterpart from Marcomodel (rms structural deviation of 0.061). The protocol was applied to all compounds (**2**−**5**,**a**−**e**) so as to ensure a standardized initial geometry for docking simulations.

Docking: PDB entry was downloaded from the Brookhaven database and modified to remove crystallographic waters. LIGIN was evaluated on its ability to reinsert OHT to 3ERT[19] (5000 starting points for ligand defined within a search box 15 × 15 × 15 Å in size). For subsequent analyses, using MacroModel the compound of interest was manually positioned in the vicinity of the LBD, using the bound ligand OHT as a reference for orientation. OHT was removed and the file saved in PDB format. Ligand atom types were assigned in the appropriate input file for the LIGIN program and a docking simulation initiated. (1000 starting points/ligand defined within a search box 5 × 5 × 5 Å in size). The results output contained detailed ligand−residue close contact data from the docking run. The PDB coordinate output files for each ligand from the LIGIN were reinserted to the corresponding 3ERT shell and visually checked using MacroModel for docking abnormalities. The best-scored results were chosen as docked structures. These rigid-docked structure files were imported to SYBYL 6.6 and treated to a fully flexible docking routine using the *flexidock* command in the *Biopolymer* module. For consistency, during the flexible docking analyses the protein was held rigid while allowing the ligand to flex according to its structural makeup. The default SYBYL *flexidock* parameters were utilized in all cases, with iterations set to 30 000. This protocol generated a final series of 'model structures' for the compounds. Following visual confirmation of docking mode the structures were further analyzed using LPC to generate general protein−ligand interaction data.

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