Synthesis and Biological Evaluation of a Novel Series of Furans: Ligands Selective for Estrogen Receptor α

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A variety of nonsteroidal systems can function as ligands for the estrogen receptor (ER), in some cases showing selectivity for one of the two ER subtypes, ERα or ER*β*. We have prepared a series of heterocycle-based (furans, thiophenes, and pyrroles) ligands for the estrogen receptor and assessed their behavior as ER ligands. An aldehyde enone conjugate addition approach and an enolate alkylation approach were developed to prepare the 1,4-dione systems that were precursors to the trisubstituted and tetrasubstituted systems, respectively. All of the diones were easily converted into the corresponding furans, but formation of the thiophenes and pyrroles from the more highly substituted 1,4-diones was problematical. Of the systems investigated, the tetrasubstituted furans proved to be most interesting. They were ERα binding- and potency-selective agents, with the triphenolic 3-alkyl-2,4,5-tris(4-hydroxyphenyl)furans (**15a**−**d**) displaying generally higher subtype binding selectivity than the bisphenolic analogues (**15f**−**i**). Binding selectivity for ERα was as high as 50−70-fold, and transcriptional activation studies showed that several members of this series were ERα selective agonists, with the best compound [3-ethyl-2,4,5-tris(4-hydroxyphenyl)furan, **15b**] having full transcriptional activity on ERα while being inactive on ER*β*. Comparative binding affinity analysis and molecular modeling were used to investigate the preferred binding mode adopted by the furan ligands, which appears to have the C(2) phenol mimicking the important role of the A-ring of estradiol. These ligands should be useful in studying the biological roles of both ERα and ER*β*, and they might form the basis for the development of novel estrogen pharmaceuticals.

The estrogen receptor (ER) is a ligand-regulated transcription factor whose activity as an inducer or repressor of gene transcription depends on the nature of the ligand with which it is bound, as well as the nature of the coregulator proteins with which it associates.[1] Estrogen action is important in many tissues, and ER is involved in the development and function of the reproductive system and plays a role in bone density maintenance,[2−4] regulation of blood-lipid profiles,[3−7] and brain function.[8,9] Not surprisingly, ER is a target for the discovery of new drugs for treating or regulating a variety of hormone-related conditions.

There are two ER genes, the well-known gene that produces subtype ERα and the more recently discovered gene that produces the subtype ER*β*.[10,11] The tissue distribution of ERα and ER*β* differ, though the biological significance of this difference is not yet well understood.[12] A number of previously known ER ligands,[12−15] as well as some recently developed novel ligand systems,[16] have different potencies[17] or are able to effect different response levels through ERα and ER*β*.[18] Ligands having very high ER subtype selectivity would be effective probes of the respective biological roles of ERα and ER*β* and might also function as tissue-selective agents having improved endocrine profiles.

The ER subtypes α and *β* have only 55% amino acid identity in the ligand binding domain, yet all but two of the residues that define the ligand binding pocket are the same.[19] The two differences are conservative substitutions, with Met421 in ERα corresponding to an isoleucine in ER*β* and, similarly, Leu384 in ERα being replaced with a methionine in ER*β*. These subtle changes in the ligand-binding pocket of the two ER subtypes do not provide a definitive basis for understanding the selectivity in either binding or potency that is seen with some ligands, so further structural analyses will be required.

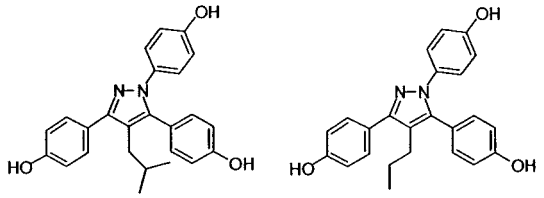

Figure 1. Structures and binding affinity data for pyrazoles **1** and **2**.

In previous investigations, we found that certain pyrazoles, particularly those displaying a 1,3,5-triaryl-4-alkyl substitution pattern, were very selective for ERα, in terms of affinity, potency, and efficacy.[20−25] Pyrazole **1** was found to have the highest ERα binding affinity, but pyrazole **2** had the greatest ERα subtype selectivity (Figure 1). While certain azoles, such as oxazoles, thiazoles, isoxazoles, and imidazoles, did not produce good ER ligands in our hands,[20] we wondered

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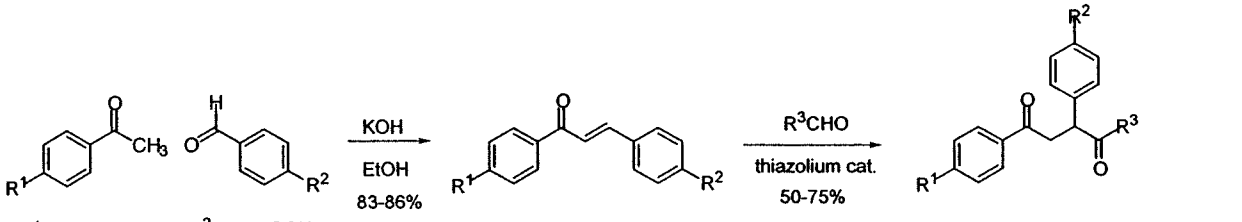
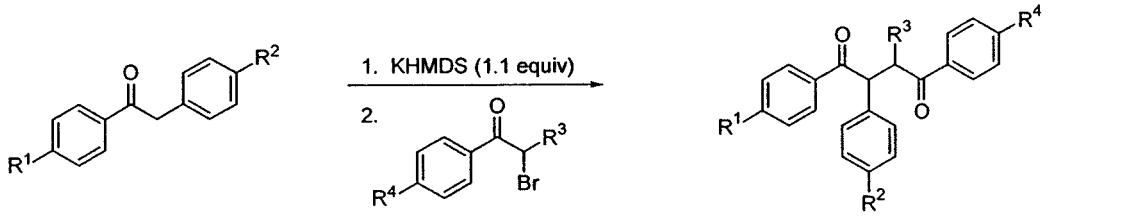
Scheme 1. Preparation of 1,2,4-Trisubstituted Diones **10a**−**c**



9	R^1	R^2
a	OCH_3	H
b	OCH_3	OCH_3
c	H	OCH_3

10	R^1	R^2	R^3
a	OCH_3	H	*p*-CH_3O-C_6H_4
b	OCH_3	OCH_3	C_6H_5
c	H	OCH_3	C_2H_5

Scheme 2. Preparation of 1,2,3,4-Tetrasubstituted Diones **13a**−**l**



11	R^1	R^2
a	H	OCH_3
b	OCH_3	H
c	OCH_3	OCH_3
d	H	H

12	R^3	R^4
a	CH_3	OCH_3
b	C_2H_5	OCH_3
c	C_3H_7	OCH_3
d	C_4H_9	OCH_3
e	C_2H_5	H
f	*p*-CH_3O-C_6H_4	OCH_3

13	R^1	R^2	R^3	R^4
a	OCH_3	OCH_3	CH_3	OCH_3
b	OCH_3	OCH_3	C_2H_5	OCH_3
c	OCH_3	OCH_3	C_3H_7	OCH_3
d	OCH_3	OCH_3	C_4H_9	OCH_3
e	OCH_3	OCH_3	*p*-CH_3O-C_6H_4	OCH_3
f	H	OCH_3	C_2H_5	OCH_3
g	H	OCH_3	C_3H_7	OCH_3
h	OCH_3	H	C_2H_5	OCH_3
i	OCH_3	OCH_3	C_2H_5	H
j	H	H	C_2H_5	OCH_3
k	H	OCH_3	C_2H_5	H
l	OCH_3	H	C_2H_5	H

whether other five-membered ring heterocycles bearing only one heteroatom, namely, furans, thiophenes, and pyrroles, might provide ER ligands with interesting biological character. Several furans (**3**−**5**) and pyrroles (**6**−**8**) have been described as potential antifertility agents.[26−29] Few, however, showed significant activity, the most active being the furans (**3**−**5**), and binding and transcriptional activity were reported only in one instance.[26]

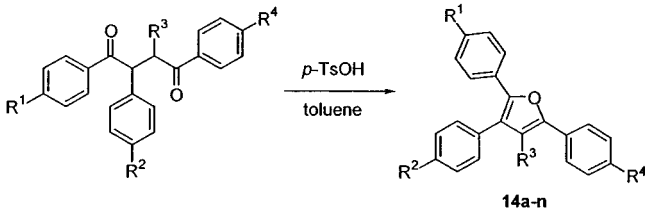
In this report we describe an investigation of single heteroatom-containing five-membered ring heterocyclic analogues of the high-affinity pyrazole ligands. We find that certain furans are ER ligands that display ERα-selective biological character equivalent to that of the pyrazoles. We have also developed a structure−activity relationship within the furan series to optimize ligand affinity and selectivity and to investigate the binding mode adopted by this class of ligands.

Results

Synthesis of Ligands. While the literature provides a plethora of approaches to furans, thiophenes, and pyrroles, we wished to prepare all three of these heterocycles from a common precursor, namely, a 1,4-dione. The trisubstituted 1,4-diketones **10a**−**c** were prepared by the conjugate addition of an aldehyde to an α,*β*-unsaturated ketone **9a**−**c** (Scheme 1). Treatment of commercially available acetophenones and aromatic aldehydes with ethanolic KOH afforded chalcones **9a**−**c**. The α,*β*-unsaturated ketones **9a**−**c** then underwent conjugate addition reactions with commercially available aldehydes, utilizing Stetter's thiazolium salt catalysts, either 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide for aromatic aldehydes or 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride for aliphatic aldehydes.[30] The Stetter reactions produced the desired 1,2,4-trisubstituted butane-1,4-diones **10a**−**c** in good yields. However, all of our attempts to use this approach with an α-substituted enone to produce the desired tetrasubstituted diones were unsuccessful.

The 1,2,3,4-tetrasubstituted butanediones were instead prepared by the alkylation of an enolate with an α-bromo ketone (Scheme 2). Treatment of the 1,2-diarylethanones **11a**−**d** with potassium hexamethyldisilyl amide (KHMDS), followed by the addition of an α-bromo ketone **12a**−**f**, provided the desired 1,3,4-triaryl-2-alkylbutane-1,4-diones **13a**−**l**. These reactions afforded the product diones as mixtures of diastereomers, which in some cases were separable by crystallization. Separation was not required, however, because these centers become trigonal in the final products. The α-bromo ketones **12a**−**f** were produced in nearly quan-

Table 1. Synthesis of Furans **14a**−**n**



14a-n

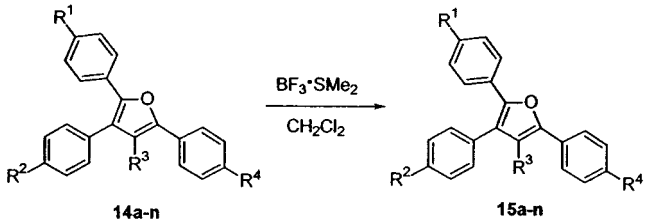
dione	furan	R^1	R^2	R^3	R^4	% yield
13a	**14a**	OCH_3	OCH_3	CH_3	OCH_3	74
13b	**14b**	OCH_3	OCH_3	C_2H_5	OH	70
13c	**14c**	OCH_3	OCH_3	C_3H_7	OCH_3	85
13d	**14d**	OCH_3	OCH_3	C_4H_9	OCH_3	98
13e	**14e**	OCH_3	OCH_3	p-$CH_3OC_6H_4$	OCH_3	85
13f	**14f**	H	OCH_3	C_2H_5	OCH_3	87
13g	**14g**	H	OCH_3	C_3H_7	OCH_3	83
13h	**14h**	OCH_3	H	C_2H_5	OCH_3	95
13i	**14i**	OCH_3	OCH_3	C_2H_5	H	73
13j	**14j**	H	H	C_2H_5	OCH_3	42
13k	**14k**	H	OCH_3	C_2H_5	H	75
13l	**14l**	OCH_3	H	C_2H_5	H	25
10a	**14m**	OCH_3	H	H	OCH_3	88
10b	**14n**	H	OCH_3	H	OCH_3	92

titative yields from the parent ketones upon treatment with bromine and a catalytic amount of aluminum chloride.

Furans. The 1,4-diketones were converted into furans upon treatment with catalytic *p*-toluenesulfonic acid in refluxing toluene. Table 1 lists the yields for conversion of diones **13a**−**l** and **10a**−**b** to furans **14a**−**n**. The methyl ether protecting groups of furans **14a**−**n** were removed using boron trifluoride−dimethyl sulfide complex, to afford furans **15a**−**n** as free phenols. The demethylation reactions and yields for conversion of **14a**−**n** to **15a**−**n** are listed in Table 2.

Thiophenes. Upon treatment with Lawesson's reagent, diones **10a**−**b** were converted into thiophenes **16a**-**b**.[31,32] Furan formation was found to be a competing process in these reactions, sometimes giving a furan-to-thiophene ratio as high as a 1:1 when the 1,4-diones were treated with Lawesson's reagent alone. Competing furan formation not only reduced yields, but the furan byproducts could not be separated from the corresponding thiophenes by flash column chromatography or recrystallization. Fortunately, the addition of solid potassium carbonate as an acid scavenger minimized furan formation, so the thiophenes could be isolated in pure form. Demethylation of **16a**−**b** with boron trifluoride−dimethyl sulfide complex afforded the phenolic thiophene analogues **17a**−**b** in good yields (Scheme 3).

Table 2. Demethylation of Furans **14a**−**n** to **15a**−**n**



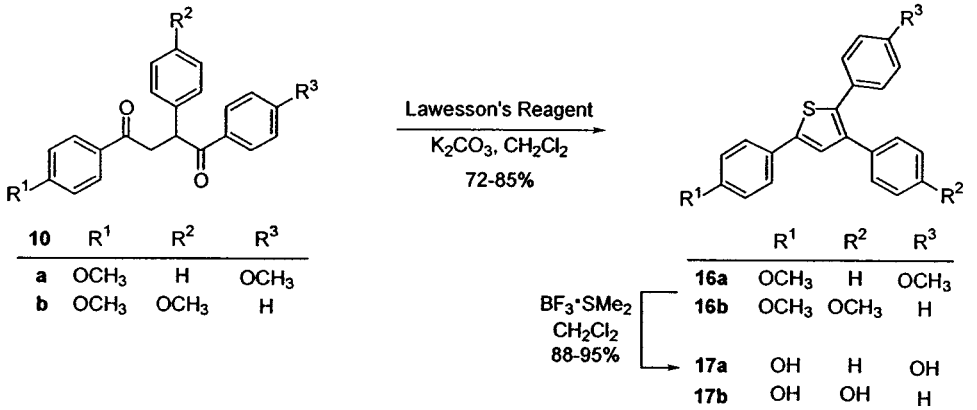
14a-n **15a-n**

furan	deprot. furan	R^1	R^2	R^3	R^4	% yield
14a	**15a**	OH	OH	CH_3	OH	77
14b	**15b**	OH	OH	C_2H_5	OH	93
14c	**15c**	OH	OH	C_3H_7	OH	93
14d	**15d**	OH	OH	C_4H_9	OH	88
14e	**15e**	OH	OH	p-HOC_6H_4	OH	85
14f	**15f**	H	OH	C_2H_5	OH	94
14g	**15g**	H	OH	C_3H_7	OH	88
14h	**15h**	OH	H	C_2H_5	OH	93
14i	**15i**	OH	OH	C_2H_5	H	84
14j	**15j**	H	H	C_2H_5	OH	55
14k	**15k**	H	OH	C_2H_5	H	70
14l	**15l**	OH	H	C_2H_5	H	78
14m	**15m**	OH	H	H	OH	75
14n	**15n**	H	OH	H	OH	77

Unfortunately, all attempts to convert the 1,2,3,4-tetrasubstituted butanediones into thiophenes afforded solely furan products. Even with the addition of potassium carbonate, Lawesson's reagent gave only quantitative yields of the furans. An alternate approach using hydrogen sulfide−hydrogen chloride also failed to give the desired thiophenes, instead producing furan in low yield and leaving unreacted starting material. It is known that these latter reagents can be used to produce disubstituted thiophenes either from 1,4-diones[33,34] or directly from the corresponding furans.[33] However, these conditions were reported not to work for the conversion of tetrasubstituted systems, such as 1,4-diaryl-2,3-dibromobutane-1,4-diones, into the corresponding thiophenes.[34] While our failure to convert tetrasubstituted 1,4-diones into thiophenes was disappointing, it is not surprising considering the ample precedent for preferential furan formation from hindered 1,4-diones.[33−36] In fact, to our knowledge, there has been only one report of the formation of thiophenes from 1,2,3,4-tetrasubstituted-1,4-dicarbonyl precursors.[37]

Pyrroles. Treatment of diones **10c** with *p*-anisidine and *p*-toluenesulfonic acid produced pyrrole **18** in modest yield; however, unreacted dione may be recycled to increase production of the desired heterocycle. Demethylation of **18** provided the target pyrrole **19** (Scheme 4). As was the case with the thiophenes, all attempts

Scheme 3. Preparation of Thiophenes **17a**−**b**



10	R^1	R^2	R^3
a	OCH_3	H	OCH_3
b	OCH_3	OCH_3	H

	R^1	R^2	R^3
16a	OCH_3	H	OCH_3
16b	OCH_3	OCH_3	H
17a	OH	H	OH
17b	OH	OH	H

Scheme 4. Preparation of Pyrrole **19**

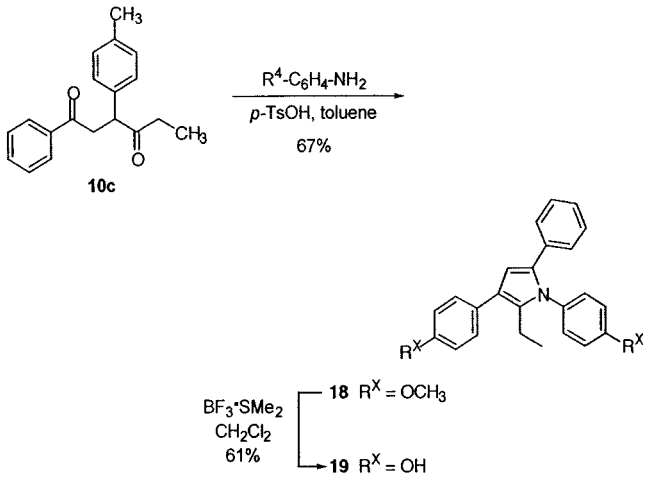


Table 3. Relative Binding Affinity (RBA)[a] Data for Furans **15a**−**n**, Thiophenes **17a**−**b**, and Pyrrole **19**

ligand	cytosol	ER-α	ER-β	α/β selectivity
15a	2.9 ± 0.09	40 ± 6.5	0.62 ± 0.02	65-fold
15b	6.5 ± 0.8	140 ± 38	2.9 ± 0.1	48-fold
15c	3.6 ± 0.6	100 ± 14	1.8 ± 0.65	56-fold
15d	1.3 ± 0.7	21 ± 0.6	3.9 ± 1.1	5.4-fold
15e	0.84 ± 0.07	8.7 ± 1.1	0.25 ± 0.01	36-fold
15f	4.6 ± 0.5	82 ± 20	7.1 ± 1.2	12-fold
15g	3.6 ± 0.3	140 ± 13	15 ± 4.1	9.5-fold
15h	0.7 ± 0	16.5 ± 1.9	3.0 ± 0.6	5.5-fold
15i	0.45 ± 0	14.8 ± 3.1	4.5 ± 1.2	3.3-fold
15j	0.44 ± 0.09	10.8 ± 2.6	3.4 ± 1.2	3.8-fold
15k	0.02 ± 0.01	0.15 ± 0.01	0.07 ± 0.02	2.1-fold
15l	0.10 ± 0.04	6.8 ± 2.1	2.0 ± 0.4	3.4-fold
15m	0.13	NA	NA	NA
15n	0.04	NA	NA	NA
17a	0.03	NA	NA	NA
17b	0.04	NA	NA	NA
19	0.50	NA	NA	NA

[a] Determined by a competitive radiometric binding assay with [^{3}H]estradiol using methods described in the Experimental Section. Where indicated, values represent the average (±SD or range) of multiple determinations. In our hands, RBA values are reproducible with a coefficient of variation of less than 0.3.

to convert 1,2,3,4-tetrasubstituted butane-1,4-diones into pyrroles resulted in quantitative furan formation.

Biological Studies. Relative Binding Affinities. The relative binding affinity of the heterocyclic ligands was determined by a competitive radiometric receptor binding assay first using lamb uterine cytosol as a source of receptor.[38] (The uterus is thought to contain almost exclusively ERα.)[12] The higher affinity ligands were then studied further with purified human ERα and ERβ.[18,39] The results of these studies, given as relative binding affinity (RBA) values where the affinity of estradiol is considered to be 100%, are summarized in Table 3.

While the members of these series of heterocycles displayed somewhat lower affinities for uterine cytosol ER than did those of the pyrazole class,[20] they showed good affinity nevertheless, with the highest RBA of 6.5% being observed for the 2,4,5-tris(4-hydroxyphenyl)-3-ethylfuran **15b**. As was the case with the pyrazoles,[20] the trisubstituted ligands, furans **15m,n** and thiophenes **17a,b**, showed very low affinities and thus were not assayed further with ERα and ERβ. The one pyrrole we prepared (**19**) also had low affinity; this was unexpected, considering that it is a tetrasubstituted ligand that is a close structural analogue to a high-affinity pyrazole (cf., Figure 1).[20]

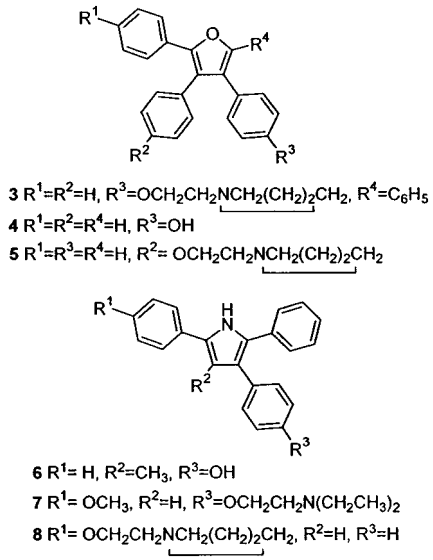


Figure 2. Representative furans and pyrroles explored as antifertility agents.[26−29]

All of the tetrasubstituted furans (**15a**−**l**) were assayed for binding to ERα and ERβ, and a number of structure−affinity trends are of note. All of these furans had much higher affinity for purified ERα than for ER from lamb uterine cytosol. We believe that this is due to reduced nonspecific binding of these relatively lipophilic ligands in the assays with the purified receptor, ERα, which are performed at much lower total protein concentrations than are the assays using uterine cytosol. While all of the furans proved to be ERα binding selective ligands, the data indicates that the presence of a third phenolic hydroxyl is required to achieve the highest binding selectivity for ERα versus ERβ (compare tris-phenols vs the corresponding bisphenols: **15c** vs **15g**, and **15b** vs **15f,h,i**, respectively). As the size of the 3-alkyl substituent is changed in the triphenols, the highest ERα binding affinity is found with the ethyl and propyl analogues (**15b** and **15c** with of RBAs 100−140), but the highest ERα binding selectivity was found with the methylfuran **15a** (RBA ERα/ERβ = 65). The symmetrical tetrakis(4-hydroxyphenyl)furan (**15e**) has respectable ERα affinity and selectivity, but is not as good as the best of the 3-alkyl analogues. The homologous series of bisphenols (**15f,h,i**) and monophenols (**15j**−**l**) were prepared to investigate the orientation of these furans in the ligand binding pocket of ER; their affinities are lower, and the structure−affinity correlations are considered further in the Discussion section.

Transcriptional Activation Assays. Four high-affinity tetrasubstituted furan ligands (**15a,b,c,g**) were assessed for transcriptional activation activity through both ERα and ERβ. These cotransfection assays are conducted in human endometrial carcinoma (HEC-1) cells, using expression plasmids for full-length human ERα or ERβ and an estrogen-responsive luciferase reporter gene system.[16] The results of these initial screening assays are summarized in Figure 3.

All four ligands tested were more potent on ERα than ERβ, and they were fully efficacious on ERα. On ERβ, however, the three triphenols (**15a**−**c**) were inactive, but

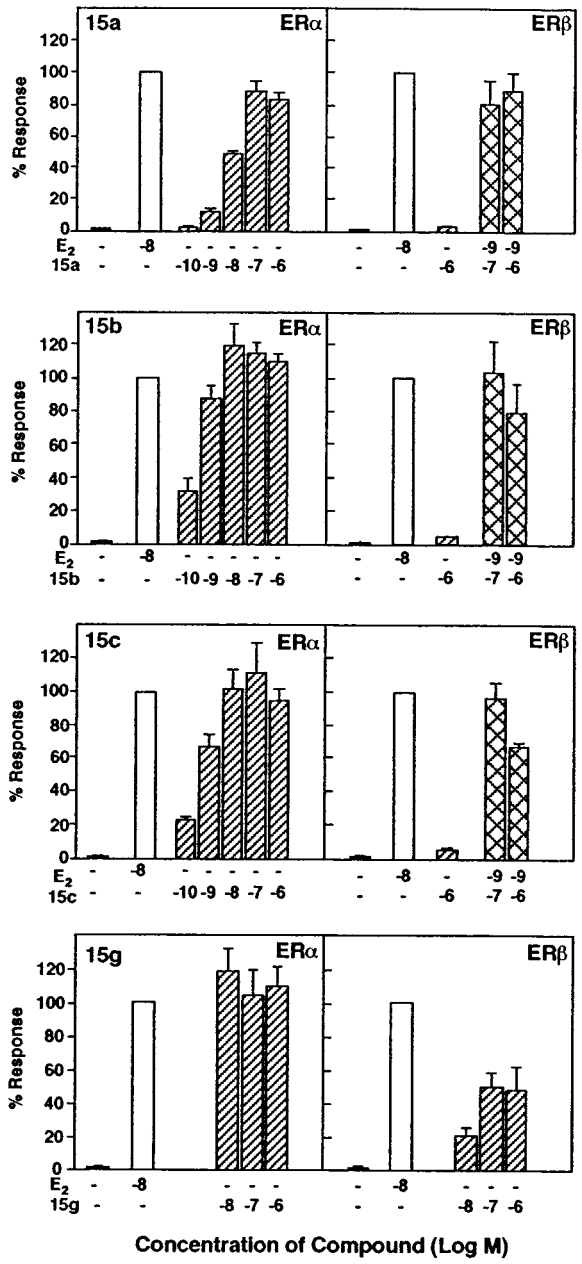


Figure 3. Transcriptional activation data for furans **15a**−**c** and **15g** through ERα and ERβ. Human endometrial cancer (HEC-1) cells were transfected with expression vectors for ERα or ERβ and an estrogen responsive reporter gene and were treated with indicated concentrations of estradiol or ligand for 24 h to assay for agonism (diagonal slashed bars) or antagonism (crosshatched bars). Transcriptional activity was normalized to an internal β-gal control plasmid using the luciferase reporter assay system. Values are expressed as a percent of the ERα or ERβ response with 10 nM E_2, which is set at 100% (open bars).[29] For details, see the Experimental Section.

the bisphenol (**15g**) showed partial agonist activity. Thus, while having a third phenol on the C(5) phenyl group is not essential for high ERα binding affinity (Table 3), it does appear to be important to ensure that the furans are highly selective for ERα and not efficacious on ERβ.

A full dose−response curve for transcriptional activation through ERα and ERβ for one of the most selective of the ligands assayed, 3-ethyl-2,4,5-tris(4-hydroxyphenyl)furan (**15b**), is shown in Figure 4. This furan is highly selective in its activation of ERα, having an $EC_{50} = 0.33$ nM for ERα and having essentially no agonist or antagonist activity on ERβ at concentrations up to 1 μM.

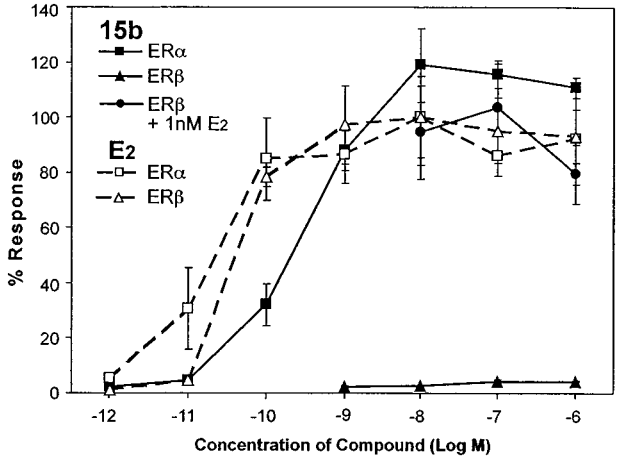


Figure 4. Dose−response curve for transcriptional activation by furan **15b** though ERα (solid squares) and ERβ (solid triangles). Antagonist activity through ERβ (circles) was also assayed. The activation curves for estradiol on those two receptors is shown for reference (open squares and triangles, respectively; dotted lines). For details, see the Experimental Section.

Discussion

We have prepared a series of aryl-substituted five-membered ring heterocycles containing a single heteroatom, namely, furans, thiophenes, and pyrroles, and we have assessed them as ligands for the estrogen receptor (ER). Certain tetrasubstituted furans proved to be very selective for ERα, in terms of binding affinity and potency as agonists, with the triphenolic 3-alkyl-2,4,5-tris(4-hydroxyphenyl)furans (**15a**−**d**) displaying generally higher subtype binding selectivity than the bisphenolic analogues (**15f**−**i**) (Table 3). The highest ERα binding selectivity (65-fold) was obtained with the 2,4,5-tris(4-hydroxyphenyl)-3-methylfuran **15a**, but the best overall combination of high affinity and ERα selectivity was given by the corresponding 3-ethyl and 3-propyl analogues, furans **15b** and **15c** (Table 3). The ethylfuran **15b** is sufficiently ERα selective to be used to activate ERα fully at concentrations (10−100 nM) where it has no agonist or antagonist activity on ERβ (Figure 4).

Structure−Activity Relationships in the Triarylfuran Series. The heterocycles most closely related to the furans, thiophenes, and pyrroles studied here are the pyrazoles that we have investigated extensively (Figure 1),[20,22−25] and certain features that we noted in the behavior of the pyrazoles are also found with the new heterocycles. The triaryl-substituted systems have low binding affinity, as was the case with the pyrazoles (and other related heterocycles), and high affinity and ERα selectivity was engendered by having a fourth group that was aliphatic and moderate in size.[20] With the furans, the most favorable substituents at this position were ethyl and propyl, whereas with the pyrazoles it was a propyl substituent. The best furan (RBA 140 for furan **15b**) has considerably higher ERα binding affinity than the best pyrazole (RBA 75 for pyrazole **1**),[24] but in both series, the trend of affinity increasing with substituent size up to a point, beyond

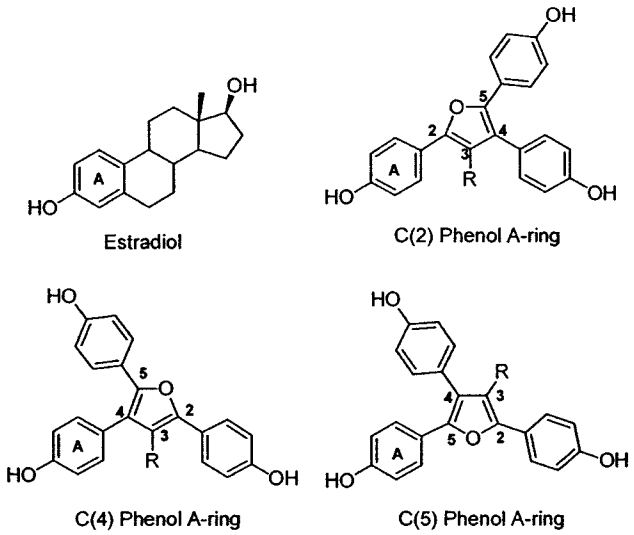


Figure 5. Three possible mimics for the A-ring of estradiol. Note, with each A-ring mimic, there are two possible orientations of the furan core (only one is shown).

which further increase proves detrimental, was noted. Such trends are well precedented in both steroidal and nonsteroidal systems,[40,41] and they have been interpreted to indicate the filling of a preformed pocket of limited volume within the receptor.[40]

Where it is possible to make direct comparisons between furans and thiophenes (**15m** vs **17a** and **15n** vs **17b**), it appears that the furans might be higher affinity ligands. However, this comparison remains limited by difficulties we encountered in the preparation of tetrasubstituted thiophenes. We prepared only one pyrrole (**19**), and though it was tetrasubstituted, its affinity was disappointing. This was unexpected, because it has strong structural analogy to other heterocycles that have high affinity.[20] The higher polarity of the pyrrole compared to the furans and pyrazoles could account for its lower binding affinity.[20]

Investigation of the Orientation of the Triarylfurans in the ER Ligand Binding Pocket. We have been interested in the manner in which nonsteroidal ER ligands having more than one phenol are oriented within the ligand binding pocket of ER.[42] Most of the furans we studied here that show high binding selectivity for ERα (**15a**−**c**) have three phenols, any one of which could be serving as the analogue of the phenolic A-ring of estradiol, a ring that is known to be important for the high affinity of this natural estrogen (see Figure 5).[40] While multiple binding modes could be operative, we used comparative binding affinity considerations and molecular modeling to see whether we could determine which of these three phenols might most likely be functioning as the A-ring mimic. One should note that for each of the three potential A-ring mimics, there are two possible binding modes for the rest of the furan (i.e., the ligands could be bound in the orientations shown in Figure 5 or in alternative binding modes, flipped 180° around the bond connecting the A-ring mimic phenol to the furan core, not shown, giving a total of six basic binding orientations).[42]

Comparative Binding Analysis. In the comparative binding affinity approach, we prepared furan bisphenols (**15f,h,i**) and monophenols (**15j**−**l**) to investigate the effect that removing phenolic hydroxyl groups had on binding affinity. We imagined that deletion of the hydroxy group from the furan phenol substituent that was playing the role of the A-ring of estradiol would have the greatest effect on binding affinity.[40] Also, if two phenols were deleted, we imagined that the monophenol having the highest affinity would be the one that retained the hydroxyl on the phenyl substituent in the furan that mimics the estradiol A-ring. The ERα binding affinities of the mono- and diphenols are given in Table 3, but are schematized in Figure 6 for ready analysis.

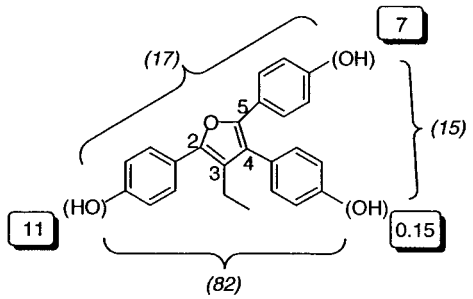


Figure 6. Summary of ERα binding data for furan monophenols and bisphenols for comparative binding analysis. The binding affinity of the three monophenols is shown in the shadowed box by each of the three hydroxyl groups, and the affinity of the three bisphenols is indicated by the italicized number in parentheses on braces linking two hydroxyl groups. For a discussion, see the text.

In the monophenols (**15j**−**l**) (See RBA values shown in boxes in Figure 6) the C(4) monophenol (**15k**) has a very low affinity, so it is unlikely that the C(4) aryl group is the mimic of the estradiol A-ring. However, it is difficult to choose between the C(2) and C(5) phenols (**15j,l**), because their affinities are quite comparable. So, from the monophenols, it appears that either the C(2) or C(5) phenol rings could be the A-ring mimic. The highest affinity bisphenol (**15f**) (see the RBA values shown in parentheses in italics, Figure 6) has hydroxyl groups on both the C(2) and C(4) phenyl groups, consistent with the importance of the C(2) phenol, noted above. However, the other two bisphenols (**15h,i**) again have very similar affinities, so a definitive distinction cannot be made between the importance of the other two phenols, at C(4) and C(5).

On the basis of these data, we make the following tentative conclusions: (a) the C(4) phenol is unlikely to be the A-ring mimic (based on the affinity pattern of the monophenols), (b) the C(2) phenol is most likely to be the A-ring mimic (based on the higher affinity of the 2,4-bisphenol (**15f**) than the 2,5- and 4,5-bisphenols (**15h,i**), but (c) the C(5) phenol might also function as the A-ring mimic. This tentative conclusion is the same as the one we reached in our analysis of the binding orientations of the pyrazoles,[24] and it is supported by further work we have done, both in the pyrazole and the furan series, to develop ERα-selective antagonists by attaching basic side chains to these heterocyclic systems.[25,43] Thus, we believe that the furan triphenols bind with the C(2) phenol in the A-ring binding pocket, but that the C(5) phenol can play this role in certain analogues (notably furan antagonists).[43]

Molecular Modeling Studies. We have also used molecular modeling to investigate the binding orienta-

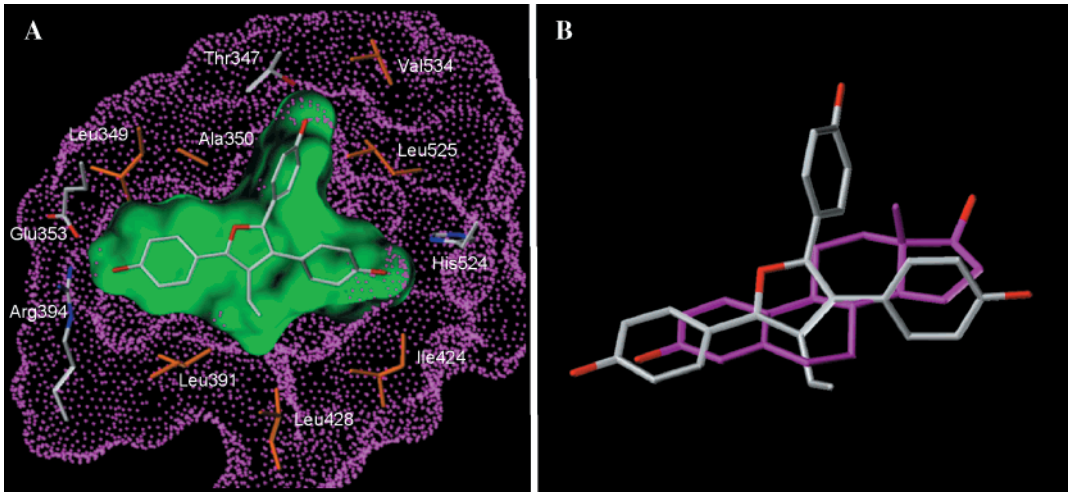


Figure 7. (A) Model of furan **15b** in the ERα ligand binding pocket. The surface of the ligand is shown as a continuous green shape; the surface of the ERα pocket is shown as purple dots. (B) Comparison of the orientation of the furan (gray) with respect to that of estradiol (purple) in the ERα ligand binding pocket. For details, see the text and Experimental Section.

tion of a furan ligand in ERα. Using the FlexiDock routine in the modeling program SYBYL, according to a modification of the protocol we described previously for the pyrazoles (See Experimental),[24] we docked the ERα-selective furan **15b** into the ligand-binding pocket of ERα, positioning the furan initially in each of six possible orientations (cf., Figure 5 and earlier discussion). In each case, the FlexiDock routine oriented the molecule so that the C(2) phenol remained or returned to the position so as to be the A-ring mimic. With the C(2) phenol in the A-ring orientation, we obtained the best fit when the C(3) ethyl group projected downward in roughly the direction of a 6α- or 7α-substituent in estradiol. The result of this docking-minimization study is shown in Figure 7. The purple dots represent the solvent-accessible surface of the ligand binding pocket, and the green surface is the molecular volume for the furan ligand. At the right of the figure is an overlay of furan **15b** (gray) onto estradiol (purple), illustrating their relative position within the ligand binding pocket.

This final minimized model shows that the hydrogen-bond contacts found between the phenol and the Glu353 and Arg394 residues in the ERα/estradiol and ERα/diethylstilbestrol crystal structures[44,45] persist with the C(2) phenol of the furan ligand. However, because of the overall greater length of the furan, we found that the phenol appears to be driven more deeply into the A-ring binding pocket in the furan structure than in the estradiol structure. The second phenol on C(4) of the furan makes a hydrogen bond with His524, as is also found with the distal hydroxyl groups of ligands in the crystal structures.[44,45] The third phenol on C(5) appears to be making a hydrogen bond with the hydroxy group of Thr347, which is the only other polar residue in the ligand binding pocket. As was the case with the pyrazoles, it is not clear what interactions are responsible for the high ERα binding selectivity of this ligand, although this is obviously a very interesting issue.[24]

The novel heterocyclic systems we have investigated here, the 3-alkyl-2,4,5-triarylfurans, in particular, are ligands for the estrogen receptor that have very high selectivity for ERα in terms of affinity and potency in transcription assays. These ligands should be useful in studying the biological role of both of the ER subtypes, and they might form the basis for the development of novel estrogen pharmaceuticals.

Experimental Section

General Methods. All reagents and solvents were purchased from Aldrich or Fischer. Solvents were distilled prior to use. THF was distilled over sodium/benzophenone. Methylene chloride was distilled over calcium hydride. Hexane was distilled over calcium sulfate. Triethylamine was distilled over calcium hydride. Reactions were all monitored by TLC, performed on 0.25 mm silica gel glass plates containing F-254 indicator (Merck). Visualization on TLC was achieved by UV light or phosphomolybdic acid indicator. Column chromatography was performed with Woelm 32−63 μm silica gel packing. Melting points were measured using a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra chemical shifts are reported in parts per million downfield from TMS and referenced to either TMS internal standard for chloroform-d_1 or acetone- d_6 solvent peak. NMR coupling constants are reported in hertz. All compounds used in structure−activity relationship considerations gave either satisfactory microanalyses or satisfactory exact mass determinations by high-resolution mass spectrometry and were shown to be pure by HPLC under two distinct reversed phase conditions.

Chemical Synthesis. General Procedure for the Preparation of Trisubstituted Butane-1,4-diones by the Stetter Reaction. Aldehyde, α,β unsaturated ketone, triethlyamine, and either 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (with aliphatic aldehydes) or 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (with aromatic aldehydes) were combined and heated to reflux in ethanol for 60−96 h. Solvent was removed under reduced pressure, and the resulting residue was taken up into CH_2Cl_2 and extracted with 3 M HCl (aq), water, saturated NaCl, and dried over sodium sulfate. Solvent was removed under reduced pressure and crude product was purified by flash column chromatography and recrystallization to afford 1,4 diones.

General Procedure for the Preparation of Tetrasubstituted Butane-1,4-diones. A solution of KHMDS (1.1 equiv, 0.5 M in toluene) was added to a stirring solution of diarylethanone (1 equiv) in THF (2−5 mL), at −78 °C. The mixture was stirred for 1 h followed by the dropwise addition of α-bromo ketone (1.1 equiv). The reaction mixture was allowed to stir at −78 °C for 1 h and then allowed to gradually warm to room temperature, with stirring from 5 h to overnight (monitored for disappearance of starting material) and then quenched with the addition of H_2O. The reaction was further diluted with EtOAc and washed with H_2O and saturated NaCl. Organic extract was dried over Na_2SO_4 and filtered and solvent

removed under reduced pressure. Purification by flash column chromatography afforded diones as mixtures of diastereomers (by NMR).

General Procedure for Furans. In toluene, the 1,4-dione and *p*-toluenesulfonic acid monohydrate (catalytic amount) were heated to reflux for 3−12 h. The reaction was cooled and filtered, the solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography.

General Demethylation Procedure Using BF_3·SMe_2. To a stirring solution of the methyl ether precursor (1 equiv) in CH_2Cl_2 (∼8 mL) at room temperature was added BF_3·SMe_2 complex (75 equiv). After stirring for 12−18 h, solvent and excess reagent were evaporated under nitrogen stream in hood. Residue was taken up in EtOAc and washed with H_2O and saturated NaCl. Organic extract was dried over Na_2SO_4 and filtered and solvent removed under reduced pressure. The resulting residue was purified by silica gel flash column chromatography.

General Demethylation Procedure Using BBr_3. The methyl ether protected compound was dissolved in CH_2Cl_2 and stirred at room temperature. A solution of 1 M boron tribromide in CH_2Cl_2 was added via syringe, and the reaction was left to stir overnight or until all starting material had been consumed. The reaction was poured into a separatory funnel, extracted with H_2O (3 × 10 mL) and saturated NaCl, and dried over sodium sulfate. Solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography and recrystallization to afford deprotected phenols.

2,3,5-Tris(4-hydroxyphenyl)-4-methylfuran (15a). Furan **14a** (58.0 mg, 0.14 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15a**. The crude material was purified by flash column chromatography (1:2 EtOAc:hexanes) and recrystallized from EtOAc:hexanes to give **15a** (40.2 mg, 77% yield): mp 231−233 °C (dec); ^{1}H NMR (500 MHz, acetone-d_6) δ 2.05 (3H, s, C*H*$_3$), 6.74 (2H, AA′XX′, J_{AX} = 8.77, $J_{AA'}$ = 2.48, Ar*H* ortho to OH), 6.94 (2H, AA′XX′, J_{AX} = 8.46, $J_{AA'}$ = 2.42, Ar*H* ortho to OH), 6.95 (2H, AA′XX′, J_{AX} = 8.83, $J_{AA'}$ = 2.49, Ar*H* ortho to OH), 7.16 (2H, AA′XX′, J_{AX} = 8.81, $J_{XX'}$ = 2.39, Ar*H* meta to OH), 7.34 (2H, AA′XX′, J_{AX} = 8.99, $J_{XX'}$ = 2.50, Ar*H* meta to OH), 7.61 (2H, AA′XX′, J_{AX} = 8.77, $J_{XX'}$ = 2.46, Ar*H* meta to OH), 8.44 (1H, bs, O*H*), 8.48 (1H, bs, O*H*), 8.51 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 10.5, 116.1(2), 116.4(2), 116.6(2), 117.5, 124.1, 124.6, 124.7, 125.8, 127.5(2), 127.7(2), 132.2(2), 147.4, 147.9, 157.4, 157.5, 157.7; MS (EI, 70 eV) *m*/*z* 358.1 (M^+); HRMS calcd for $C_{23}H_{18}O_4$ 358.120 51, found 358.120 40.

3-Ethyl-2,4,5-tris(4-hydoxyphenyl)furan (15b). Furan **14b** (28.0 mg, 0.07 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15b**. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) and recrystallized from EtOAc:hexanes to give **15b** (16.3 mg, 93% yield): mp 219−220 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 1.01 (3H, t, J = 7.52, C*H*$_3$-CH$_2$), 2.51 (2H, q, J = 7.52, CH$_3$C*H*$_2$), 6.72 (2H, AA′XX′, J_{AX} = 8.99, $J_{AA'}$ = 2.52, Ar*H* ortho to OH), 6.95 (2H, AA′XX′, J_{AX} = 8.85, $J_{AA'}$ = 2.54, Ar*H* ortho to OH), 6.96 (2H, AA′XX′, J_{AX} = 8.67, $J_{AA'}$ = 2.55, Ar*H* ortho to OH), 7.17 (2H, AA′XX′, J_{AX} = 8.89, $J_{XX'}$ = 2.41, Ar*H* meta to OH), 7.31 (2H, AA′XX′, J_{AX} = 9.01, $J_{XX'}$ = 2.47, Ar*H* meta to OH), 7.60 (2H, AA′XX′, J_{AX} = 8.95, $J_{XX'}$ = 2.49, Ar*H* meta to OH), 8.39 (1H, bs, O*H*), 8.46 (1H, bs, O*H*), 8.49 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 14.1, 17.1, 115.2(2), 115.6(2), 115.7(2), 123.2, 123.4, 123.5, 123.6, 125.1, 126.5(2), 126.8(2), 131.3(2), 146.5, 146.7, 156.5, 156.7, 156.9; MS (EI, 70 eV) *m*/*z* 372.2 (M^+); HRMS calcd for $C_{24}H_{20}O_4$ 372.136 159, found 370.136 761. Anal. Calcd for $C_{24}H_{20}O_4$·(0.5H_2O): C, 74.43; H, 6.12. Found: C, 74.82; H, 5.86.

2,3,5-Tris(4-hydroxyphenyl)-4-propylfuran (15c). Furan **14c** (40.0 mg, 0.09 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15c**. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) to provide **15c** (32.0 mg, 93% yield) as a white powder: ^{1}H NMR (500 MHz, acetone-d_6) δ 0.79 (3H, t, J = 7.24, C*H*$_3$CH$_2$CH$_2$), 1.42 (2H, m, CH$_3$C*H*$_2$-CH$_2$), 2.48 (2H, m, CH$_3$CH$_2$C*H*$_2$), 6.73 (2H, AA′XX′, J_{AX} = 8.89, $J_{AA'}$ = 2.53, Ar*H* ortho to OH), 6.95 (4H, AA′XX′, J_{AX} = 8.55, $J_{AA'}$ = 2.53, Ar*H* ortho to OH), 7.16 (2H, AA′XX′, J_{AX} = 8.82, $J_{XX'}$ = 2.41, Ar*H* meta to OH), 7.31 (2H, AA′XX′, J_{AX} = 8.86, $J_{XX'}$ = 2.47, Ar*H* meta to OH), 7.60 (2H, AA′XX′, J_{AX} = 9.02, $J_{XX'}$ = 2.42, Ar*H* meta to OH), 8.42 (1H, bs, O*H*), 8.48 (1H, bs, O*H*), 8.51 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 14.4, 23.8, 26.8, 116.0(2), 116.4(2), 116.6(2), 122.9, 124.1, 124.4, 124.5, 126.1, 127.3(2), 127.7(2), 132.2(2), 147.5, 147.7, 157.4, 157.5, 157.7; MS (EI, 70 eV) *m*/*z* 386.2 (M^+); HRMS calcd for $C_{25}H_{22}O_4$ 386.151 81, found 386.152 74.

3-Butyl-2,4,5-tris(4-hydroxyphenyl)furan (15d). Furan **14d** (50.0 mg, 0.11 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15d**. The crude material was purified by flash column chromatography (1:1 EtOAc:hexanes) to provide **15d** (39.5 mg, 88% yield) as a solid. A small amount of **15d** for biological testing was further purified by reverse phase HPLC: ^{1}H NMR (500 MHz, acetone-d_6) δ 0.76 (3H, t, J = 7.41, C*H*$_3$CH$_2$CH$_2$CH$_2$), 1.22 (2H, sextet, J = 7.39, CH$_3$C*H*$_2$CH$_2$CH$_2$), 1.39 (2H, m, CH$_3$CH$_2$C*H*$_2$-CH$_2$), 2.50 (2H, m, CH$_3$CH$_2$CH$_2$C*H*$_2$), 6.72 (2H, AA′XX′, J_{AX} = 8.72, $J_{AA'}$ = 2.53, Ar*H* ortho to OH), 6.949 (2H, AA′XX′, J_{AX} = 8.83, $J_{AA'}$ = 2.49, Ar*H* ortho to OH), 6.952 (2H, AA′XX′, J_{AX} = 8.63, $J_{AA'}$ = 2.53, Ar*H* ortho to OH), 7.16 (2H, AA′XX′, J_{AX} = 8.67, $J_{XX'}$ = 2.41, Ar*H* meta to OR), 7.31 (2H, AA′XX′, J_{AX} = 9.11, $J_{XX'}$ = 2.45, Ar*H* meta to OR), 7.60 (2H, AA′XX′, J_{AX} = 9.01, $J_{XX'}$ = 2.53, Ar*H* meta to OR), 8.47 (1H, bs, O*H*), 8.52 (1H, bs, O*H*), 8.56 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 13.9, 23.2, 24.3, 32.7, 116.0(2), 116.4(2), 116.6(2), 123.0, 124.1, 124.4, 124.5, 126.1, 127.3(2), 127.7(2), 132.2(2), 147.5, 147.6, 157.4, 157.5, 157.7; MS (EI, 70 eV) *m*/*z* 400.2 (M^+); HRMS calcd for $C_{26}H_{24}O_4$ 400.167 46, found 400.167 43.

2,3,4,5-Tetrakis(4-hydroxyphenyl)furan (15e). Furan **14e** (40.0 mg, 0.10 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15e**. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) and recrystallized from EtOAc:hexanes to give **15e** (49.0 mg, 85% yield): mp 247−250 °C (dec); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.76 (4H, AA′XX′, J_{AX} = 8.72, $J_{AA'}$ = 2.45, Ar*H* ortho to OH), 6.77 (4H, AA′XX′, J_{AX} = 8.65, $J_{AA'}$ = 2.45, Ar*H* ortho to OH), 7.37 (4H, AA′XX′, J_{AX} = 8.62, $J_{XX'}$ = 2.32, Ar*H* meta to OH), 8.38 (4H, AA′XX′, J_{AX} = 8.73, $J_{XX'}$ = 2.44, Ar*H* meta to OH), 8.38 (2H, bs, O*H*), 8.53 (2H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 116.08(4), 113.12(4), 123.9(2), 124.2(2), 125.5(2), 127.7(4), 132.4(4), 147.7(2), 157.4(2), 157.6(2); MS (EI, 70 eV) *m*/*z* 436.2 (M^+); HRMS calcd for $C_{28}H_{20}O_5$ 436.131 07, found 436.131 24.

3-Ethyl-2,4-bis(4-hydroxyphenyl)-5-phenylfuran (15f). Furan **14f** (20.0 mg, 0.05 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15f**. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) followed by recrystallization from CH_2Cl_2:hexanes to give **15f** as a solid (17.4 mg, 94% yield). mp 226−230 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 1.02 (3H, t, J = 7.49, C*H*$_3$CH$_2$), 2.53 (2H, q, J = 7.49, CH$_3$C*H*$_2$), 6.97 (2H, AA′XX′, J_{AX} = 8.74, $J_{AA'}$ = 2.60, Ar*H* ortho to OH), 6.98 (2H, AA′XX′, J_{AX} = 8.70, $J_{AA'}$ = 2.45, Ar*H* ortho to OH), 7.16 (1H, m, Ar*H* para to furan), 7.19 (2H, AA′XX′, J_{AX} = 8.75, $J_{XX'}$ = 2.48, Ar*H* meta to OH), 7.24 (2H, m, Ar*H* meta to furan), 7.46 (2H, m, Ar*H* ortho to furan), 7.64 (2H, AA′XX′, J_{AX} = 8.66, $J_{XX'}$ = 2.53, Ar*H* meta to OH), 8.55 (2H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ14.9, 17.9, 116.5(2), 116.7(2), 124.2, 124.6, 125.6(2), 125.7, 126.5, 127.5, 127.9(2), 129.2(2), 132.1(2), 132.3, 147.0, 148.4, 157.8, 157.9; MS (EI, 70 eV) *m*/*z* 356.1 (M^+); HRMS calcd for $C_{24}H_{20}O_3$ 356.141 25, found 328.141 29.

2,4-Bis(4-hydroxyphenyl)-5-phenyl-3-propylfuran (15g). Furan **14g** (30.0 mg, 0.075 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15g**. The crude material was purified by flash column chromatography (2:1 hexane:EtOAc) and recrystallized from EtOAc:hexanes to give **15g** (23.2 mg, 86% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 0.80 (3H, t, J = 7.39, C*H*$_3$CH$_2$), 1.44 (2H,

m, $CH_3CH_2CH_2$), 2.49 (2H, m, CH_2-furan), 6.969 (2H, AA′XX′, $J_{AX} = 8.87$, $J_{AA'} = 2.55$, Ar*H* ortho to OH), 6.972 (2H, AA′XX′, $J_{AX} = 8.55$, $J_{AA'} = 2.41$, Ar*H* ortho to OH), 7.16 (1H, m, Ar*H* para to furan), 7.18 (2H, AA′XX′, $J_{AX} = 8.78$, $J_{XX'} = 2.44$, Ar*H* meta to OH), 7.24 (2H, m, Ar*H* meta to furan), 7.45 (2H, m, Ar*H* ortho to furan), 7.64 (2H, AA′XX′, $J_{AX} = 8.68$, $J_{XX'} = 2.62$, Ar*H* meta to OH), 8.52 (1H, bs, O*H*), 8.57 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 14.1, 23.6, 26.6, 116.3(2), 116.5(2), 123.0, 124.0, 125.4(2), 125.5, 126.5, 127.3, 127.7(2), 128.9(2), 131.9(2), 132.1, 146.7, 148.5, 157.6, 157.7; MS (EI, 70 eV) *m*/*z* 370.2 (M^+); HRMS calcd for $C_{25}H_{22}O_3$ 370.156 890, found 370.156 61.

3-Ethyl-2,5-bis(4-hydroxyphenyl)-4-phenylfuran (15h). Furan **14h** (30.0 mg, 0.08 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15h**. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) to provide **15h** (25.8 mg, 93% yield) as a white powder: mp 127−132 °C (dec); ^{1}H NMR (500 MHz, acetone-d_6) δ 1.00 (3H, t, $J = 7.47$, CH_3CH_2), 2.52 (2H, q, $J = 7.50$, CH_3CH_2), 6.72 (2H, AA′XX′, $J_{AX} = 8.86$, $J_{AA'} = 2.48$, Ar*H* ortho to OH), 6.96 (2H, AA′XX′, $J_{AX} = 8.75$, $J_{AA'} = 2.56$, Ar*H* ortho to OH), 7.27 (2H, AA′XX′, $J_{AX} = 8.91$, $J_{XX'} = 2.47$, Ar*H* meta to OH), 7.36 (2H, m, Ar*H* ortho to furan), 7.41 (1H, tt, $J = 7.51$, 1.34, Ar*H* para to furan), 7.48 (2H, m, Ar*H* meta to furan), 7.62 (2H, AA′XX′, $J_{AX} = 8.84$, $J_{XX'} = 2.46$, Ar*H* meta to OH), 8.44 (1H, bs, O*H*), 8.54 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 14.9, 17.9, 116.1(2), 116.5(2), 123.8, 123.9, 124.0, 124.3, 127.5(2), 127.8(2), 128.3, 129.7(2), 131.1(2), 135.4, 147.6, 147.7, 157.5, 157.6; MS (EI, 70 eV) *m*/*z* 356.2 (M^+); HRMS calcd for $C_{24}H_{20}O_3$ 356.141 25, found 356.141 68.

3-Ethyl-4,5-bis(4-hydroxyphenyl)-2-phenylfuran (15i). Furan **14i** (40.0 mg, 0.10 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15i**. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) and recrystallized from EtOAc:hexanes to give **15i** (31.3 mg, 84% yield): mp 204−206 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 1.04 (3H, t, $J = 7.53$, CH_3CH_2), 2.57 (2H, q, $J = 7.50$, CH_3CH_2), 6.75 (2H, AA′XX′, $J_{AX} = 9.14$, $J_{AA'} = 2.46$, Ar*H* ortho to OH), 6.97 (2H, AA′XX′, $J_{AX} = 8.59$, $J_{AA'} = 2.40$, Ar*H* ortho to OH), 7.18 (2H, AA′XX′, $J_{AX} = 8.79$, $J_{XX'} = 2.32$, Ar*H* meta to OH), 7.30 (1H, m, Ar*H* para to furan), 7.34 (2H, AA′XX′, $J_{AX} = 8.86$, $J_{XX'} = 2.47$, Ar*H* meta to OH), 7.47 (2H, m, Ar*H* meta to furan), 7.77 (2H, m, Ar*H* ortho to furan), 8.52 (1H, bs, O*H*), 8.54 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 14.8, 18.0, 116.1(2), 116.6(2), 123.8, 124.4, 125.7, 125.9(2), 126.6, 127.5(2), 127.6, 129.6(2), 132.2(2), 132.7, 146.8, 148.5, 157.7, 157.8; MS (EI, 70 eV) *m*/*z* 356.2 (M^+); MS (CI, 130 eV) *m*/*z* 357.2 ($M^+ + H$); HRMS calcd for $C_{24}H_{20}O_3$ 356.141 25, found 356.140 45.

3-Ethyl-2-(4-hydroxyphenyl)-(4,5)-bisphenylfuran (15j). Furan **14j** (40 mg, 0.11 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15j**. The crude material was purified by flash column chromatography (75:25 hexane:EtOAc) and recrystallized from hexane:EtOAc to give **15j** (21 mg, 55% yield) as a white crystalline solid: mp 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, $J = 7.57$, CH_3), 2.53 (2H, q, $J = 7.51$, CH_2), 4.76 (1H, s, O*H*), 6.93 (2H, d, $J = 8.34$, Ar*H* ortho to OH), 7.13−7.47 (10H, m, Ar*H*), 7.65 (2H, d, $J = 8.75$, Ar*H* meta to OH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.6, 17.3, 115.6(2), 124.1, 124.8, 125.1(2), 126.7, 127.2(2), 127.4, 128.2(2), 128.8(2), 130.2(2), 131.1, 134.2, 146.6, 147.2, 154.6, 164.5; MS (EI, 70 EV) *m*/*z* 340.2 (M^+); HRMS calcd for $C_{24}H_{20}O_2$ 340.146 33, found 340.146 11.

3-Ethyl-4-(4-hydroxyphenyl)-(2,5)-bisphenylfuran (15k). Furan **14k** (42 mg, 0.12 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15k**. The crude material was purified by flash column chromatography (75:25 hexane:EtOAc) and recrystallized from hexane:EtOAc to give **15k** (28 mg, 70% yield) as a white powder: mp 144−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, t, $J = 7.45$, CH_3), 2.62 (2H, q, $J = 7.36$, CH_2), 4.92 (1H, s O*H*), 6.97 (2H, d, $J = 8.21$, Ar*H* ortho to OH), 7.28−7.49 (10H, m, Ar*H*), 7.8 (2H, d, $J = 7.87$, Ar*H* meta to OH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.6, 17.4, 115.8, 125.1, 125.2(2), 125.4(2), 125.8, 126.4, 126.8, 126.9, 128.3(2), 128.6(2), 131.1, 131.5(2), 131.6, 147.1, 147.2, 154.9; MS (EI, 70 EV) *m*/*z* 340.2 (M^+); HRMS calcd for $C_{24}H_{20}O_2$ 340.146 33, found 340.146 49.

3-Ethyl-5-(4-hydroxyphenyl)-(2,4)-bisphenylfuran (15l). Furan **14l** (13.4 mg, 0.04 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15l**. The crude product was purified by flash column chromatography (95:5 hexane:EtOAc) and recrystallized from hexane:EtOAc to give furan **15l** (10 mg, 78% yield) as a light yellow powder: mp 133−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, t, $J = 7.35$, CH_3), 2.57 (2H, q, $J = 7.48$, CH_2), 4.65 (1H, s, O*H*), 6.69 (2H, d, $J = 8.47$, Ar*H* ortho to OH), 7.26−7.46 (10H, m, Ar*H*), 7.74 (2H, d, $J = 7.26$, Ar*H* meta to OH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.6, 17.4, 115.2(2), 124.7, 124.3, 125.4(2), 125.5, 126.8, 127.0(2), 127.4, 128.5, 128.6(2), 128.8(2), 130.3(2), 131.7, 134.2, 146.6, 154.6; MS (EI, 70 eV) *m*/*z* 340.2 (M^+); HRMS calcd for $C_{24}H_{20}O_2$ 340.146 33, found 340.146 59.

2,5-Bis(4-hydroxyphenyl)-3-phenylfuran (15m). Furan **14m** (22.0 mg, 0.06 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15m**. The crude material was purified by flash column chromatography (1:1 EtOAc:hexane) followed by recrystallization from CH_2Cl_2:hexanes to give **15m** as a solid (18.7 mg, 92% yield): mp 167−170 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 6.82 (2H, AA′XX′, $J_{AX} = 8.77$, $J_{AA'} = 2.32$, Ar*H* ortho to OH), 6.83 (1H, s, furan*H*), 6.92 (2H, AA′XX′, $J_{AX} = 8.90$, $J_{AA'} = 2.52$, Ar*H* ortho to OH), 7.31 (1H, m, Ar*H* para to furan), 7.39 (2H, m, Ar*H* meta to furan), 7.43 (2H, AA′XX′, $J_{AX} = 8.817$, $J_{XX'} = 2.45$, Ar*H* meta to OH), 7.46 (2H, m, Ar*H* ortho to furan), 7.67 (2H, AA′XX′, $J_{AX} = 8.93$, $J_{XX'} = 2.44$, Ar*H* meta to OH), 8.56 (2H, bs, OH); ^{13}C NMR (100 MHz, acetone-d_6) δ 107.3, 115.6(2), 115.9(2), 122.78, 122.81, 123.1, 125.4(2), 127.2, 127.8(2), 128.6(2), 128.8(2), 134.9, 147.5, 152.5, 157.36, 158.38; MS (FAB) *m*/*z* 328.2 (M^+); HRMS calcd for $C_{22}H_{16}O_3$ 328.109 95, found 328.109 80.

3,5-Bis(4-hydroxyphenyl)-2-phenylfuran (15n). Furan **14n** (65.0 mg, 0.18 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **15n**. The crude material was purified by flash column chromatography (1:1 EtOAc:hexane) followed by recrystallization from CH_2Cl_2:hexanes to give **15n** as a solid (46.0 mg, 77% yield): mp 160−163 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 6.79 (1H, s, furan*H*), 6.89 (2H, AA′XX′, $J_{AX} = 8.65$, $J_{AA'} = 2.47$, Ar*H* ortho to OH), 6.93 (2H, AA′XX′, $J_{AX} = 8.82$, $J_{AA'} = 2.45$, Ar*H* ortho to OH), 7.23 (1H, m, Ar*H* para to furan), 7.30 (2H, AA′XX′, $J_{AX} = 8.67$, $J_{XX'} = 2.53$, Ar*H* meta to OH), 7.32 (2H, m, Ar*H* meta to furan), 7.66 (2H, m, Ar*H* ortho to furan), 7.69 (2H, AA′XX′, $J_{AX} = 8.81$, $J_{XX'} = 2.45$, Ar*H* meta to OH), 8.58 (2H, bs, OH); ^{13}C NMR (100 MHz, acetone-d_6) δ108.7, 116.5(2), 116.6(2), 123.4, 125.63, 126.3(2), 126.5(2), 128.0, 129.3(2), 130.7(2), 132.4, 147.0, 153.7, 157.9, 158.36 (2); MS (EI, 70 eV) *m*/*z* 328.2 (M^+); HRMS calcd for $C_{22}H_{16}O_3$ 328.109 95, found 328.109 55.

General Procedure for Thiophenes. The 1,4-dione and Lawesson's Reagent were stirred in CH_2Cl_2 at 40 °C until all 1,4-dione had been consumed, as shown by TLC (2−3 h). The reaction mixture was then poured into a separatory funnel, washed with H_2O, 10% sodium bicarbonate, and saturated NaCl, and dried over sodium sulfate. Solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography and recrystallization to afford cyclized thiophenes.

2,5-Bis(4-hydroxyphenyl)-3-phenylthiophene (17a). Thiophene **16a** (22.6 mg, 0.06 mmol) was reacted according to the general demethylation procedure using BBr_3 to afford crude **17a**. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) to give **17a** as a solid (18.3 mg, 88% yield): mp 125−130 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 6.78 (2H, AA′XX′, $J_{AX} = 8.73$, $J_{AA'} = 2.47$, Ar*H* ortho to OH), 6.90 (2H, AA′XX′, $J_{AX} = 8.78$, $J_{AA'} = 2.60$, Ar*H* ortho to OH), 7.14 (2H, AA′XX′, $J_{AX} = 8.52$, $J_{XX'} = 2.47$, Ar*H* meta to OH), 7.26 (1H, m, Ar*H* para to thiophene), 7.32 (4H, m, Ar*H*

meta and ortho to thiophene), 7.34 (1H, s, thiophene*H*), 7.56 (2H, AA′XX′, J_{AX} = 8.79, $J_{XX'}$ = 2.52, Ar*H* meta to OH), 8.54 (1H, bs, O*H*), 8.57 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 115.5(2), 115.8(2), 124.9, 125.5, 125.8, 126.7(2), 126.8, 128.3(2), 128.9(2), 130.3(2), 136.6, 136.9, 138.0, 141.9, 157.2, 157.4; MS (EI, 70 eV) *m*/*z* 344.1 (M^+); HRMS calcd for $C_{22}H_{16}SO_2$ 344.087 10, found 344.086 21.

3,5-Bis(4-hydroxyphenyl)-2-phenylthiophene (17b). Thiophene **16b** (108.0 mg, 0.29 mmol) was reacted according to the general demethylation procedure using BF_3·SMe_2 to afford crude **17b**. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) followed by recrystallization from CH_2Cl_2:hexanes to give **17b** as a solid (85.1 mg, 85% yield): mp 198−200 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 6.79 (2H, AA′XX′, J_{AX} = 8.66, $J_{AA'}$ = 2.47, Ar*H* ortho to OH), 6.90 (2H, AA′XX′, J_{AX} = 8.80, $J_{AA'}$ = 2.60, Ar*H* ortho to OH), 7.17 (2H, AA′XX′, J_{AX} = 8.69, $J_{XX'}$ = 2.47, Ar*H* meta to OH), 7.24−7.34 (5H, m, Ar*H* phenyl), 7.32 (1H, s, thiophene*H*), 7.57 (2H, AA′XX′, J_{AX} = 8.72, $J_{XX'}$ = 2.52, Ar*H* meta to OH), 8.50 (2H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 115.3(2), 115.8(2), 125.3, 125.7, 126.8(2), 127.2, 127.9, 128.5(2), 128.8(2), 130.1(2), 134.7, 134.9, 139.1, 142.6, 156.7, 157.5; MS (EI, 70 eV) *m*/*z* 344.1 (M^+); HRMS calcd for $C_{22}H_{16}SO_2$ 344.087 10, found 344.086 20.

General Procedure for N-Substituted Pyrroles. In toluene, the 1,4-dione, amine, and *p*-toluenesulfonic acid monohydrate were heated to reflux for 24 h, using a Dean−Stark trap. The reaction was cooled and filtered and solvent removed in vacuo. Crude product was purified by flash column chromatography and recrystallization to afford N-substituted pyrroles.

2-Ethyl-1,3-bis(4-hydroxyphenyl)-5-phenylpyrrole (19). Methyl ether protected pyrrole **18** (38.8 mg, 0.10 mmol) and boron tribromide (0.6 mL, 0.6 mmol) were reacted as outlined in the general procedure for demethylation to give 29.0 mg of brownish solid. Trituration with hexane gave product as off-white solid (21.8 mg, 60.8% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 0.90 (3H, t, *J* = 7.42, CH_3), 2.62 (2H, q, *J* = 7.42, CH_2), 6.43 (1, s, pyrrole*H*), 6.88 (2H, AA′XX′, J_{AX} = 8.84, $J_{AA'}$ = 2.63, Ar*H* ortho to OH), 6.90 (2H, AA′XX′, J_{AX} = 8.80, $J_{AA'}$ = 2.76, Ar*H* ortho to OH), 7.07 (1H, m, Ar*H* para to pyrrole), 7.11 (2H, AA′XX′, J_{AX} = 8.70, $J_{XX'}$ = 2.73, Ar*H* meta to OH), 7.15 (4H, m, Ar*H* ortho and meta to pyrrole), 7.32 (2H, AA′XX′, J_{AX} = 8.63, $J_{XX'}$ = 2.51, Ar*H* meta to OH), 8.18 (1H, s, ArO*H*), 8.67 (1H, s, ArO*H*); MS (EI, 70 eV) *m*/*z* 355.2 (M^+); HRMS calcd for $C_{24}H_{21}NO_2$ 355.1572, found 355.1567.

Molecular Modeling. The protein structure used in the docking simulations was based on the X-ray crystallographic structure of the human estrogen receptor ligand binding domain bound to estradiol (entry 1ere in the Protein Data Bank). The crystal structure contains three homodimers with 244 residues each. For modeling purposes only one monomer (chain A) was chosen. The monomer contains several residues with missing atoms and five residues with alternate conformations. Missing atoms were added using InsightII, and one conformation was selected for each of the five residues. Several residues that are part of two loops were completely missing. These two loops were modeled on the basis of the crystal structure of the wild-type estrogen receptor ligand binding domain complexed to estradiol (entry 1qku) using InsightII. To eliminate bad contacts and constraints due to crystal packing and loop reconstruction, the protein was energy minimized for 1000 steps using the Powell algorithm in the presence of strong harmonic constraints on the backbone, followed by an additional 1000 steps without constraints. Minimization was done with the program SYBYL 6.6 and the MMFF94 force field. Furan **15b** was docked into the minimized receptor using the FlexiDock routine and the receptor−ligand complex put through a minimization protocol as previously described.[24]

Biological Procedures. Relative Binding Affinities. Ligand binding affinities (RBAs) using lamb uterine cytosol as a receptor source were determined by a competitive radiometric binding assay using 10 nM [^{3}H]estradiol as tracer and dextran-coated charcoal as an adsorbant for free ligand.[38] Purified ERα and ERβ binding affinities were determined using a competitive radiometric binding assay using 10 nM [^{3}H]estradiol as tracer, commercially available ERα and ERβ preparations (PanVera Inc. Madison, WI), and hydroxylapatite (HAP) to adsorb bound receptor−ligand complex.[39] HAP was prepared following the recommendations of Williams and Gorski.[46] All incubations were done at 0 °C for 18−24 h. Unlabeled competitors were prepared in 1:1 DMF:TEA to ensure solubility. Binding affinities are expressed relative to estradiol on a percent scale (i.e., for estradiol, RBA = 100%). All essays were run in separate, duplicate experiments, which were reproducible with a coefficient of variation of less than 0.3.

Transcriptional Activation Studies. Transactivation by ligands on ERα and ERβ was tested in transfected human endometrial cancer (HEC-1) cells. HEC-1 cells, maintained in MEM containing 5% CS and 5% FCS, were seeded into 24-well plates in transfection media (IMEM containing 5% FCS and transfected at about 50% confluency, using lipofectin−transferrin. For each well, 1 μg of 4ERE-TATA-LUC, 2.5 μg of pCMVβGal as internal control, and 50−100 ng of pCMV5-ERα or pCMV5-ERβ were mixed with 5 μL of lipofectin (GIBCO, BRL) and 1.6 μL of 1 mg/mL transferrin in 150 μL of HBSS. The mixture was applied to the cell with 350 μL of serum-free IMEM media for each well. The cell was incubated at 37 °C in the 5% CO_2 containing incubator for 6 h. Compounds were prepared as solutions in ethanol and were added to medium to give a final ethanol concentration of 0.1%. The cell culture media was replaced by transfection media containing different concentration of ligands. Cell were incubated for 24 h in the presence of ligand. The luciferase reporter assay system (Promega) was used for the luciferase activity assay. The activity of E_2 (10^{-8} M) on ERα or ERβ was set as 100%, and the relative activity was adjusted on the basis of the transfection efficiency, which was monitored by the internal control β-galactosidase activity, as previously described.[16,47]

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Supporting Information Available: Experimental details for all precursors is available.This material is available free of charge via the Internet at http/::pubs.acs.org.

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