3-(Cyanomethyl)-2-methyl-8-((*E*)-3-phenyl-2-propenyl)-imidazo[1,2-*a*]pyridine (34), $C_{19}H_{17}N_3$, M_r 287.37, monoclinic, a = 8.667 (1) Å, b = 11.814 (3) Å, c = 15.184 (4) Å, β = 91.19 (1)°, V = 1554.4 Å^3, Z = 4, d_{calcd} = 1.228 g cm^{-3}, μ(Cu Kα radiation) = 5.4 cm^{-1}. Space group $P2_1/c(C^5_{2h})$ as for 11·HCl·2H$_2$O. Sample dimensions: 0.10 × 0.15 × 0.42 mm.

Acknowledgment. We thank the following individuals for skilled technical assistance: A. Brown, C. Gerhart, P. Mauser, M. Policelli, M. Rivelli, S. Sehring, G. Tetzloff, and Dr. S. Vemulapalli. The efforts of Dr. T. M. Chan in conducting the carbon-13 spin lattice relaxation (T_1) studies are gratefully acknowledged. We are deeply indebted to Drs. E. H. Gold and A. J. Hopfinger for many valuable discussions throughout the course of this work.

Supplementary Material Available: Details of the crystallographic measurements and structure analysis; tables (S1–S15) of atomic positional and thermal parameters, interatomic distances, and angles for 11·HCl·2H$_2$O, 12·HCl·4H$_2$O, **33**, and **34**; and corresponding Figures 1–4; tables (S16 and S17) of the estimated lattice energies calculated for the two conformations of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, **1a** and **1d**, and Figure 7 illustrating the packing arrangement of **1d** in the unit cell; SYBYL 5.1 mol files for the conformations of 1 depicted in Figures 5 and 6 and of **1d**, 11, and **40** shown in Figure 8 (58 pages). Ordering information is given on any current masthead page.

Structure-Activity Relationship of Antiestrogens: A Study Using Triarylbutenone, Benzofuran, and Triarylfuran Analogues as Models for Triarylethylenes and Triarylpropenones†

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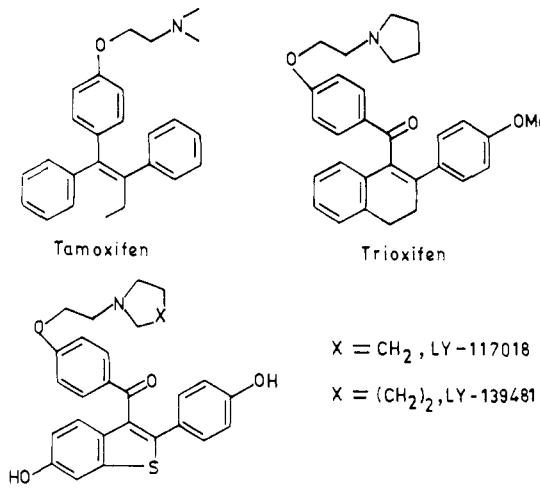
In a study of the structure–activity relationship (SAR) of antiestrogens use has been made of certain 1,2,3-triarylbutenones, of 2-arylbenzofurans carrying aryl or aroyl substituents at C_3, and of 2,3,4-triarylfurans as conformationally constrained models for triarylethylene (TAE) and triarylpropenone (TAP) prototypes. The position-specific contributions of substituents to receptor affinity and to agonist–antagonist profiles were used as aids in characterizing the relative binding orientation of the prototypes. Although most compounds were found to be weak receptor ligands and poorly active in vivo, the following conclusions could be drawn about their SAR: (i) (*Z*)-TAPs and TAEs interact with the receptor in an analogous manner using the *trans*-stilbene core, with their agonist–antagonist profiles depending on the nature of other substructures. (ii) Incorporation into the benzofuran framework introduces a stereoelectronic constraint that compromises the normal binding interactions of TAE, as well as TAP, prototypes, resulting in their poor affinities and weak biological activities. (iii) (*E*)-TAPs can interact with the receptor through their *S*-cis conformation, but such a binding mode is unlikely to account for their behavior as antagonists.

1,2,3-Triarylpropenones (TAPs) have aroused considerable interest as possible leads in the design of newer antiestrogens better than those hitherto known. The motivation for this interest has been the realization that triarylethylenes (TAEs), the best known group of antiestrogens, represented by tamoxifen (Chart I), are associated with partial agonist character, which compromises their effectiveness as antagonist and hence the scope and range of application in research as well as medicine. Certain simple acyclic TAPs were first reported to show antifertility activity with *Z* isomers more effective than (*E*)-TAPs.[1-3] Following this lead, Jones et al. synthesized trioxifen (Chart I) and found it to be a better antiestrogen than tamoxifen, in possessing diminished agonist character.[4] LY-117018[5] and LY-139481,[6] developed later, were found to be progressively better antiestrogens than trioxifen—the latter emerging as a particularly effective antiestrogen with only marginal agonist character. These discoveries have aroused considerable interest in exploring the reasons for improved antagonist activity in (*Z*)-TAPs over TAEs. Since the presence of the intervening carbonyl changes the stereochemical relationship of the aryl bearing the side chain with the *trans*-stilbene core in (*Z*)-TAPs, the analysis of their receptor binding mode in relation to that of the TAEs becomes of interest.

A study on structure–activity relationship (SAR) of acyclic TAPs was thus undertaken by Garg et al.[7] While

Chart I



confirming estrogen antagonist activity in (*Z*)-TAPs, this study also revealed the ability of (*E*)-TAPs to act as an-

† CDRI Communication No. 4223.

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(1) Iyer, R. N.; Gopalachari, R. *Indian J. Pharmacol.* **1969**, *31*, 49.
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(3) Gopalachari, R.; Iyer, R. N.; Kamboj, V. P.; Kar, A. B. *Contraception* **1970**, *2*, 199.
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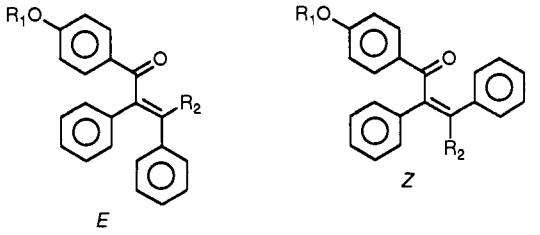
Table I. Physical Data of the (*E*)- and (*Z*)-1,2,3-Triarylpropenones and 1,2,3-Triarylbutenones



no.	R_1	R_2	geometry	mp, °C	solvent[a]	formula	anal. or ref
1	H	H	*E*	96.5–97.5	A	$C_{21}H_{16}O_2$	7
2	H	H	*Z*	82.5–83.5	B	$C_{21}H_{16}O_2$	7
6	H	Me	*E*	134	A	$C_{22}H_{18}O_2$	C, H
7	H	Me	*Z*	144	A	$C_{22}H_{18}O_2$	C, H
8	Py[b]	Me	*E*	oil		$C_{28}H_{30}O_2N$	
9	Py[b]	Me	*Z*	oil		$C_{28}H_{30}O_2N$	

[a] Solvent of crystallization: A = benzene–hexane and B = hexane. [b] Py = pyrrolidinoethyl.

tiestrogens. The position-specific contributions of substituents to the relative binding affinity (RBA) did not permit any definitive conclusions regarding relative positioning of the prototypes on the binding site. (*E*)-TAPs, however, were found to be somewhat better receptor ligands than *Z* isomers and emerged as promising candidates on which design of newer antiestrogens could be based.

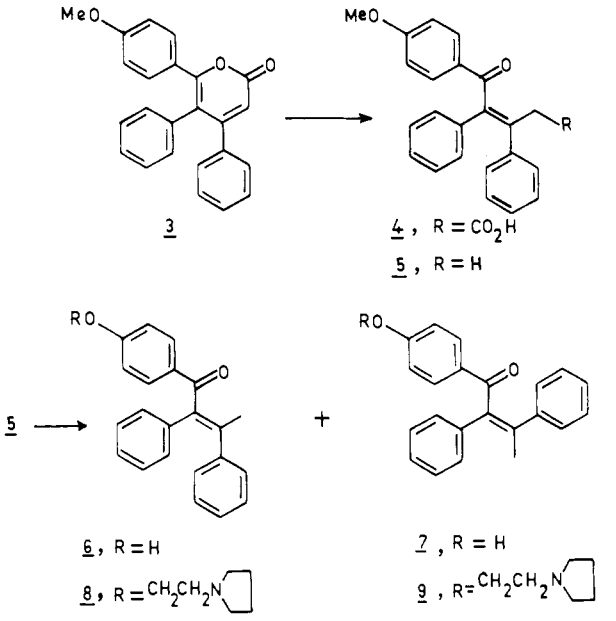
This study was prompted by the need for better understanding of the receptor binding mode of TAPs in relation to that of the TAEs. A reasonably good picture exists regarding binding mode of TAEs in relation to that of other agonists.[8,9] Since the results involving acyclic TAPs were clouded by the geometrical uncertainty inherent to the prototypes, use has been made of model compounds incorporating (*E*)- and (*Z*)-TAPs in a conformationally constrained molecular framework. In this paper we present findings with three series of compounds chosen as possible models for analyzing the binding mode of TAPs. These are (i) 1,2,3-triaryl-2-buten-1-ones, as acyclic TAPs less prone to geometrical isomerization than the propenones and with closer structural correspondence to trioxifen on account of the presence of the additional methyl, (ii) 2-aryl-1-benzofurans, suitably substituted at C_3, as conformationally constrained models for (*Z*)-TAPs and TAEs, and (iii) 2,3,4-triarylfurans, as models for (*E*)-TAPs constrained in the *S*-cis conformation.

Chemistry

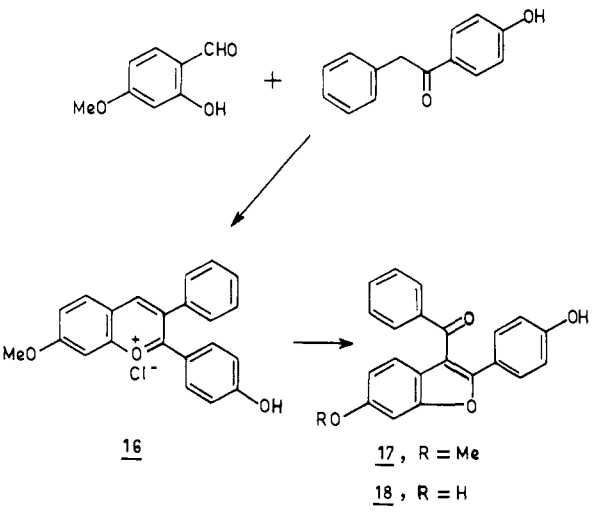
1,2,3-Triaryl-2-buten-1-ones. The phenolic propenones **1** and **2** (Table I), reported earlier,[7] were included in this study as reference compounds.

1-(4-Methoxyphenyl)-2,3-diphenyl-2-buten-1-one (**5**) was synthesized according to the procedure of Ibrahim et al.[10,11] (Scheme I). Thus the triarylpyrone **3** upon hydrolysis with methanolic KOH furnished the vinylogous keto acid **4**, which on pyrolytic decarboxylation furnished the butenone **5** as a single isomer in pure form. This compound was demethylated with piperidine water[12] to a mixture of isomeric phenols **6** and **7**, which were separated by fractional crystallization and converted to the pyrrolidinoethyl ethers **8** and **9**. Geometrical identities of all the isomeric propenones were inferred from their ^1H NMR data. On the basis of the spatial proximity between the carbonyl group and C-4 (methyl) of the butenone moiety, the isomers showing lower field absorption due to the methyl were assigned *E* geometry.

Scheme I



Scheme II



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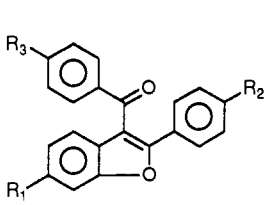
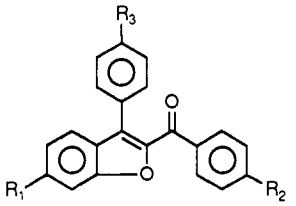
(12) Jackson, B.; Locksley, H. D. (late); Moore, I.; Scheinmann, F. *J. Chem. Soc.* **1968**, 2579.

Table II. Physical Data of the Benzofurans



I



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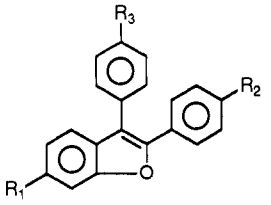


III

no.	type	R_1	R_2	R_3	mp, °C	solvent[a]	formula	anal. or ref
10	I	H	OMe	H	80	A	$C_{22}H_{16}O_3$	13
11	I	H	OH	H	174–175	B	$C_{21}H_{14}O_3$	13
12	I	H	OPy,[b] HCl	H	140–141	C	$C_{27}H_{27}ClO_2N$	C, H, N
13	I	H	H	OMe	70	A	$C_{22}H_{16}O_3$	13
14	I	H	H	OH	164	D	$C_{21}H_{14}O_3$	13
15	I	H	H	OPy[c]	170	E	$C_{27}H_{25}O_3N \cdot CO_2H^1/_2H_2O$	13
17	I	OMe	OH	H	224–225	B	$C_{22}H_{16}O_4$	C, H
18	I	OH	OH	H	120–123	F	$C_{21}H_{14}O_4$	C, H
19	I	H	OMe	OMe	80–83	G	$C_{23}H_{18}O_4$	C, H
20	I	H	OH	OH	208	F	$C_{21}H_{14}O_4$	C, H
21	I	OMe	H	OMe	105	A	$C_{23}H_{18}O_4$	C, H
22	I	OH	H	OH	183	F	$C_{21}H_{14}O_4$	C, H
26	II	OMe	OMe	OMe	112	A	$C_{24}H_{20}O_5$	C, H
27	II	OH	OH	OH	230	F	$C_{21}H_{14}O_5$	C, H
28	III	OH	H	OMe	135–137	D	$C_{21}H_{16}O_3$	29
29	III	OH	H	OH	200–202	F	$C_{20}H_{14}O_3$	C, H
30	III	OMe	H	OH	162	D	$C_{21}H_{16}O_3$	16
31	III	OMe	H	OPy[b]	209	C	$C_{27}H_{28}ClO_3N$	16
32	III	OMe	OMe	OMe	92	A	$C_{23}H_{20}O_4$	29
33	III	OH	OH	OH	234	F	$C_{20}H_{14}O_4$	C, H

[a] Solvent of crystallization: A = hexane, B = methanol, C = EtOH–Et_2O, D = benzene–hexane, E = EtOH, F = EtOAc–hexane, and G = *n*-Heptane. [b] Py = pyrrolidinoethyl. [c] Crystallized and analyzed as the oxalate salt.

Scheme III

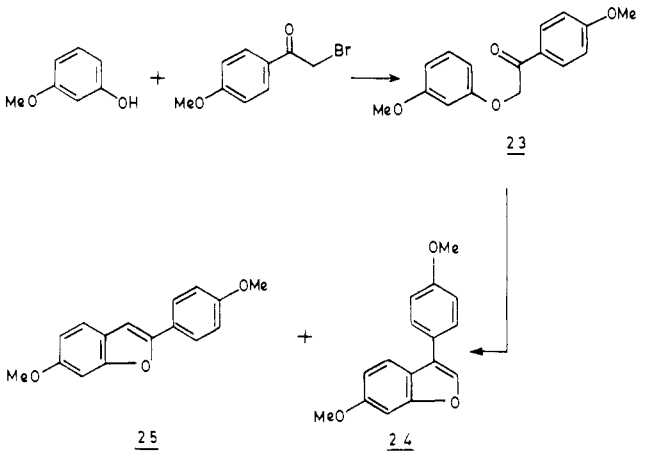
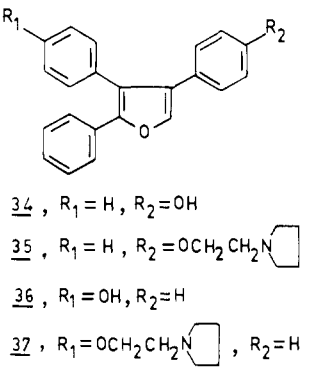


Chart II



34, $R_1 = H$, $R_2 = OH$

35, $R_1 = H$, $R_2 = OCH_2CH_2N$

36, $R_1 = OH$, $R_2 = H$

37, $R_1 = OCH_2CH_2N$, $R_2 = H$

2-Aryl-3-aroyl-1-benzofurans. Synthesis of the benzofurans **10**, **11**, and **13–15** (Table II) has been reported previously.[13] The pyrrolidinoethyl ether **12** was prepared by starting from the phenol **11**.

The benzofurans **17** and **18** were prepared according to the previously described rearrangement of benzopyrylium salts.[14] Thus condensation of 4-methoxysalicylaldehyde with 4′-hydroxy-2-phenylacetophenone, in the presence of anhydrous HCl, furnished the corresponding 1-benzopyrylium chloride **16** (Scheme II) as an amorphous red material. The latter, on acid-catalyzed rearrangement in the presence of H_2O_2, furnished the benzofuran **17**, though in modest yield, which on demethylation furnished the requisite diphenol **18**.

The benzofurans **19** and **21** were synthesized by Friedel–Crafts reaction of 2-(4-methoxyphenyl)-1-benzofuran and 6-methoxy-2-phenyl-1-benzofuran, respectively, with anisoyl chloride and were demethylated to the phenols **20** and **22**.

The dimethoxy-2-phenylbenzofuran **25** (Scheme III), required as an intermediate, was approached according to the procedure of Carter et al.,[15] by heating under reflux a solution of ω-(3-methoxyphenoxy)-4-methoxyacetophenone (**23**) in xylene in the presence of polyphosphoric acid. In our hands, the reaction furnished 3-(4-methoxyphenyl)-6-methoxybenzofuran (**24**) as the major product while **25** was obtained in minor amounts. The benzofuran **24**, characterized on the basis of its ^1H NMR and other physical data, was subjected to Friedel–Crafts reaction with anisoyl chloride to obtain the 2-benzoylbenzofuran analogue **26**, which was demethylated to the triphenol **27**.

2,3-Diaryl-1-benzofurans and 2,3,4-Triarylfurans. The 2,3-diaryl-1-benzofurans **28** and **30–32** were synthesized according to the procedure of Grover et al.,[16,29] by

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(15) Carter, G. A.; Chamberlain, K.; Wain, R. L. *Ann. Appl. Biol.* **1978**, *88*, 57.

Table III. Receptor Affinity and Biological Activity Data of Indicated Triarylpropenone, Triarylbutenone, Benzofuran, and Triarylfuran Derivatives

no.	RBA[a]	dose, mg/rat	uterotrophic act.[b]	antiuterotrophic act.[b]	% estrogenicity[c]	% inhibn[d]
1	1.8 ± 0.3	0.1	49.4 ± 3.6	78.1 ± 6.1	68	0
2	0.06 ± 0.02	0.1	22.2 ± 2.1	70.4 ± 5.7	33	0
6	0.54 ± 0.4	0.1	19.8 ± 1.1	47.3 ± 6.2	0	14
7	3.6 ± 1.1	0.1	46.4 ± 3.3	44.7 ± 6.3	83	21
8	0.24 ± 0.04	0.1	18.0 ± 2.7	46.6 ± 8.1	0	16
9	0.008 ± 0.003	0.1	30.6 ± 6.6	43.1 ± 8.7	38	26
11	0.12 ± 0.02	1.0	13.7 ± 2.4	47.4 ± 3.8	0	0
12	0.30 ± 0.07	1.0	27.7 ± 6.5	29.6 ± 3.5	38	58
14	5.3 ± 0.3	1.0	16.3 ± 1.9	50.7 ± 8.6	10	0
15	0.01 ± 0.001	1.0	16.7 ± 3.8	56.1 ± 8.2	0	0
18	0.72 ± 0.08	1.0	26.6 ± 4.4	43.2 ± 2.3	35	0
20	1.7 ± 0.1	1.0	13.1 ± 1.6	59.3 ± 6.9	0	0
22	2.1 ± 0.1	1.0	22.4 ± 3.1	38.0 ± 2.4	25	37
27	2.7 ± 0.5	1.0	26.3 ± 5.2	48.3 ± 11.3	31	23
28	0.01					
29	1.6 ± 0.9	1.0	14.6 ± 0.8	46.5 ± 2.0	0	0
30	0.01					
31	0.01	1.0	35.4 ± 6.1	61.4 ± 8.6	57	0
33	7.8 ± 2.0	1.0	21.2 ± 1.7	39.6 ± 5.9	22	30
34	3.0 ± 0.5	0.1	48.9 ± 5.7	57.6 ± 5.0	100	0
35	ND[e]	0.1	35.6 ± 6.4	52.1 ± 7.9	61	0
36	4.5 ± 0.5	0.1	16.7 ± 5.5	42.8 ± 6.3	0	0
37	0.84 ± 0.28	0.1	26.4 ± 2.6	53.9 ± 3.2	31	0

[a] The values represent the mean ± SD from at least three independent determinations in each case and are expressed in relation to E_2 taken as 100. [b] The values represent mean uterine weight ± SD in mg for from six to nine animals. Indicated doses of each compound were administered on 3 consecutive days. For antiesterogenic activity 0.001 mg/animal dose of E_2 was coadministered. Control values are 53.0 ± 10.8 mg in the case of animals receiving 0.001 mg of E_2 plus vehicle and 12.3 ± 2.2 mg in the case of those receiving the vehicle alone. [c] Computed as $(C_0 - V)(100)/(E - V)$. [d] Computed as $(E - C_e)(100)/(E - V)$. In these two equations, V, E, C_o, and C_e refer to the mean uterine weight from animals treated with vehicle alone, with E_2 alone, with a given test compound alone, and with a given test compound along with E_2, respectively. [e] ND = no detectable affinity at 100 μM concentration.

acid-catalyzed condensation of suitably substituted benzoins with phenols, in dioxane heating under reflux. The phenols **29** and **33** were obtained by demethylation of the corresponding methyl esters **28** and **32**.

Synthesis of the 2,3,4-triarylfurans **34–37** (Chart II) has been reported earlier.[17]

Results

Receptor Affinities. Receptor affinity studies were carried out with rat uterine cytosol, according to the procedure published previously.[18] The relative binding affinity (RBA) values of different series of compounds evaluated are shown in Table III.

The RBAs of triarylpropenones and triarylbutenones reveal a marked albeit complex influence of molecular geometry as well as substitution pattern on receptor affinity of the prototypes. Between the phenolic propenones **1** and **2** the *E* isomer is the more effective receptor ligand. Upon conversion to the homologous butenones **6** and **7**, there is some decrease in receptor affinity in the *E* series (**1** vs **6**), while in the *Z* series a marked increase in receptor affinity is noticed (**2** vs **7**). Further modification of the phenolic butenones to the pyrrolidinoethyl ethers has little effect on RBA in the *E* series (**6** vs **8**) but causes a marked decrease in receptor affinity in the *Z* series (**7** vs **9**).

The benzofuran analogues by and large are modest receptor ligands with the exception of phenols, some of which have reasonably good RBAs. Among phenols, those bearing an OH for R_3, viz., **14**, **20**, and **22**, are somewhat better ligands than those in which R_3 is an H, viz., **11** and **18**. The marked decrease in receptor affinity of the monophenol **14** upon its conversion to the pyrrolidinoethyl ether **15** is particularly noteworthy, in view of the structural analogy of **15** with the LY antiestrogens. The presence of OH in R_2 not only produces a less effective receptor ligand, viz., the phenol **11**, but also has detrimental effect on RBA of the monophenol **14** substituted in R_3, as is evident from the relatively lower RBA of the diphenol **20**. In contrast to the effect in R_3, replacement of OH by a pyrrolidinoethoxy residue in R_2 has only a marginal effect on RBA of the prototype (**11** vs **12**). From the marginal difference in RBA of the monophenol **11** and the diphenol **18** it appears that an OH when at R_1 makes only a modest contribution to receptor affinity of the prototype.

Though the only compound in the unusual 2-aroyl-3-arylbenzofuran series, viz., the triphenol **27**, is also a weak receptor ligand, it is of note that its RBA is comparable to that of the phenols in other series of compounds studied.

In the 2,3-diarylbenzofuran series, only the diphenol **29** and the triphenol **33** show reasonable receptor affinity. The free OH groups apparently are critical for receptor affinity of the prototypes, since removal of one OH from **33** leads to the less effective diphenol **29**. Furthermore, conversion of either of the OH groups in this diphenol (**29**) into methyl ethers (**28** and **30**) results in analogues showing vanishingly low receptor affinities. It is of note that the phenol **30** and the corresponding pyrrolidinoethyl ether **31** show almost no differences in their RBAs.

In the 2,3,4-triarylfuran series, the phenols **34** and **36** are found to be modest receptor ligands with comparable affinities. The pyrrolidinoethyl ether **37** substituted in R_1 is a less effective ligand than both these while the analogous ether **35**, substituted in R_2, has no detectable receptor affinity.

Estrogen Agonist and Antagonist Activities. Estrogen agonist and antagonist activities of the test compounds, evaluated according to the immature rat uterotrophic assays, are shown in Table III.

(16) Grover, P. K.; Chawla, H. P. S.; Anand, N.; Kamboj, V. P.; Kar, A. B. *J. Med. Chem.* **1965**, *8*, 720.
(17) Dixit, D. K.; Kapil, R. S.; Kamboj, V. P.; Anand, N. *Indian J. Chem.* **1974**, *12B*, 1144.
(18) Garg, S.; Bindal, R. D.; Durani, S.; Kapil, R. S. *J. Steroid Biochem.* **1983**, *18*, 89.

The isomeric propenones 1 and 2 are both effective as agonists while being inactive as antagonists. Upon its conversion to the homologous butenone 6 followed by conversion to the pyrrolidinoethyl ether 8, the (*E*)-propenone 1 loses its agonist activity but the analogues show marginal antagonist activities. Similar changes produce a somewhat different effect in the *Z* series, with the butenone phenol 7 showing greater agonist activity than the parent propenone 2, while showing some antagonist activity as well. The ether 9 likewise shows weak antagonist activity while retaining marginal agonist activity.

The benzofuran analogues were found to be inactive in both the assays at a 100-μg dose (data not shown). When analyzed at the 10-fold higher dose, only some showed activity (Table III). In the 2-aryl-3-aroylbenzofuran series the only compounds showing a reasonable degree of effectiveness as agonists are the pyrrolidinoethyl ether 12, substituted in R_2, and the diphenols 18 and 22, substituted in R_1, R_2 and R_1, R_3, respectively. Of these, the ether 12 and the diphenol 22 are the only ones in the series also showing antagonist activity, with the former somewhat more effective of the two. It is of note that the benzofuran 15, bearing a pyrrolidinoethoxy residue for R_3 and thus analogous to the LY compounds, is devoid of activity in both the assays.

In the 2,3-diarylbenzofuran series the diphenol 29, substituted in R_1 and R_3, is completely inactive while the analogous 31, bearing a methoxy for R_1 and a pyrrolidinoethoxy for R_3, is partially effective as an agonist but not as an antagonist. The triphenol 33 is the only compound in this series showing partial agonist–antagonist activity. The 2-aroyl-3-arylbenzofuran analogue 27 with OH groups for R_1, R_2, and R_3 is a partial agonist–antagonist.

In the 2,3,4-triarylfuran series none of the compounds show any antagonist activity at 100 μg nor at a 1-mg dose (data not shown). The analogues substituted in R_2 (34 and 35) act as potent estrogens, with the phenol the more effective of the two. The phenol was found to be active at 10 μg as well but inactive at a 1-μg dose (data not shown). In the series substituted in R_1 the ether 37 shows marginal agonist activity while the phenol 36 is inactive.

Discussion

The study of position-specific contributions of substituents to receptor affinity and antagonist–agonist profiles has been quite rewarding in rationalizing SAR among TAEs.[8,19-21] The same strategy can be extended to TAPs in order to analyze their receptor binding mode in relation to that of the TAEs. This is a requirement for better understanding of the factors that influence antagonist–agonist balance of the prototypes. In analyzing the present results in terms of binding mode of TAPs, we will make use of the binding model presented earlier for receptor interaction of TAEs.[8] The model, visualizing the binding site as a collection of five subsites designated A–E (Figure 1), is of particular value in diagnosing as well as expressing binding orientation of receptor ligands on the basis of the known preference of subsite A for 4-hydroxyphenyl, of subsite E for 4′-(*tert*-aminoalkoxy)phenyl, and of subsites D and B for aryl and alkyl residues as in tamoxifen. Since agonist–antagonist behavior is likely to correlate with binding mode of a ligand, the model also provides a framework in which such correlations may afford mechanistically significant interpretations.

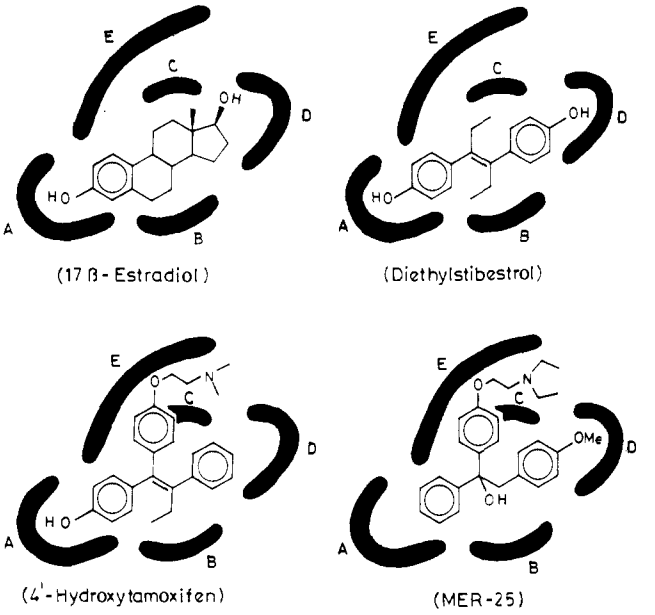

Figure 1. Binding site model for estrogen receptor showing five constituent subsites in interaction with the complementary substructures of the agonist and antagonist prototypes shown.

Our earlier results with acyclic propenones[7] were in accord with the possibility that (*Z*)-TAPs interact with subsites A and D through the aryl groups in their *trans*-stilbene core. The (*Z*)-butenones now investigated were used in order to diagnose possible interaction of TAPs, such as trioxifen, with subsite B and to establish if this interaction will explain their partial agonist character. Increased receptor affinity as well as agonist potency of (*Z*)-butenone 7 compared to that of the propenone 2 appears to support this reasoning as the difference in their activity is attributable to the extra methyl in the butenone. (*Z*)-TAPs would thus appear to resemble TAEs in their interaction with subsites A, B, and D. A possible role of subsite B in modulating agonist activity may be significant since it could explain why LY-117018 is a weaker agonist than trioxifen and why MER-25 is devoid of agonist activity while tamoxifen is not. However, an element of caution is necessary in stretching this argument because butenone phenol 7 is an antagonist even while lacking the characteristic side chain while provision of the chain does not cause any significant improvement in its antagonist potency. In contrast, involvement of subsite E in the antagonist activity of tamoxifen, trioxifen, and LY-117018 appears not to be in question since all are known to become poorer receptor ligands and to loose antagonist activity upon deletion of the side chain.[21-25]

The present findings confirm the emergence of (*E*)-TAPs as a new group of receptor ligands but fail to provide any definite clues regarding their binding mode. Of the two extreme conformations possible in (*E*)-TAPs, 2,3,4-triarylfurans model the *S*-cis conformation. The triarylfurans, known previously to act as antifertility agents,[17] have been found to possess modest receptor affinity and good agonist activity. This reveals the possibility that (*E*)-TAPs may interact with the receptor through their

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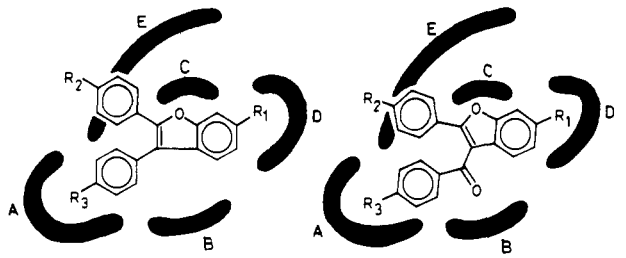
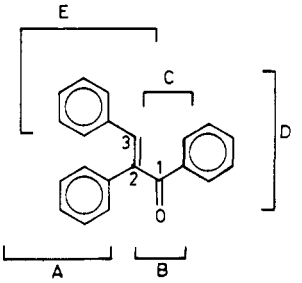


Figure 2. Possible binding mode of benzofuran prototypes in the framework of the proposed binding site model for estrogen receptor.

S-cis conformation but that such an interaction is unlikely to account for their action as antiestrogens. In the absence of any diagnostic trends in substituent contributions among triarylfurans the binding mode of (*E*)-TAPs in relation to that of the TAEs remains obscure. The triarylfuran **35** has been found to be a modest estrogen even while showing no detectable receptor affinity. While the reason for this discrepancy is unclear, the possibility remains that the ether **35** undergoes metabolism to a receptor ligand, possibly the phenol **34**, in vivo, prior to its action as an estrogen.

There is the alternate possibility that (*E*)-TAPs interact with the receptor through the *S*-trans conformational mode, with their C_1, C_2, and C_3 aryls interacting with subsites D, A, and E, respectively:



Such a binding mode seems to be in conformity with the previous data on acyclic TAPs, in which OH groups were found to contribute more effectively to the RBA of the prototype when in C_1 and/or C_2 aryl than when in C_3 aryl.[7] The present findings with (*E*)-butenones are in accord with this possibility but do not confirm it.

The benzofuran analogues (Table II), when analyzed in accordance with the conventional notions about binding orientation of TAEs and (*Z*)-TAPs, reveal many inconsistencies in substituent contributions. The result can be better rationalized if an atypical binding mode, illustrated in Figure 2, is assumed for the prototypes. Thus, in the 2,3-diaryl-1-benzofuran series (type III), high affinity of diphenol **29** is in accord with possible interaction of its OH groups with subsites A and D while decreased receptor affinity and lack of antagonist activity of the corresponding diether **31** suggests possible orientation of its side chain (R_3) toward subsite A. Similarly, among 3-aroyl-2-arylbenzofurans (type I) higher affinity of the ether **12** than that of the phenol **11** and the action of the former as an antagonist is in accord with possible orientation of their 2-aryl toward subsite E. Likewise, higher affinity of the monophenol **14** than that of the ether **15** and lack of their antagonist activity support the suggested orientation of R_3 toward subsite A. In the absence of any comparative data, the possible binding orientation of 2-aroyl-3-arylbenzofuran (type II) remains unknown.

The results with benzofurans are in contrast to the action of the LY benzothiophenes as good ER ligands as well as potent antiestrogens. Possibly the LY compounds, trioxifen, and other (*Z*)-TAPs can interact with the receptor through the normal binding mode with their *trans*-stilbene core interacting with subsites A and D and the side chain with subsite E. Replacement of sulfur by oxygen and the stereoelectronic consequence clearly prevents such a binding mode in benzofurans. Interaction of O, with its higher electronegativity and smaller size than S, with the region that accepts the carbonyl group in trioxifen may be a factor influencing atypical binding of benzofurans.

In conclusion, benzofurans have emerged as poor models for TAEs and TAPs, and this seems to be the consequence of their atypical binding with the receptor. The binding model proposed earlier for TAEs does however seem to provide a satisfactory framework for rationalization of SAR of TAPs as well. (*Z*)-TAPs appear to resemble TAEs in their overall binding mode, with the nature of interactions in subsites E and B influencing their intrinsic activities. The binding orientation of (*E*)-TAPs in relation to that of the TAEs however remains obscure. Although the prototypes may interact with the receptor through the *S*-cis conformational mode, this is unlikely to account for their antagonist behavior. The possibility that (*E*)-TAPs interact with the receptor through the *S*-trans conformational mode is an appealing one but remains to be further explored with suitable models.

Experimental Section

General. The melting points were determined on a Townson Mercer's apparatus and are uncorrected. The ^1H NMR spectra were recorded on Perkin-Elmer R-32 or Varian EM-360 L instruments using tetramethylsilane as the internal reference. The mass spectra were carried out on Jeol JMS-D300 instrument fitted with a direct inlet system. The IR spectra were recorded as KBr wafers or as neat films on Perkin-Elmer 157 or 557 infracord instruments. Thin-layer chromatography was performed on silica gel or alumina plates.

Synthetic Procedures. Demethylations of **17**, **19**, **21**, **26**, **28**, and **32**, to their respective phenols **18**, **20**, **22**, **27**, **29**, and **33**, were carried out according to the following general procedure. A mixture of the respective ethers and pyridine hydrochloride (1:3 w/w) were heated at 200 °C for 2 h, cooled, diluted with water, and extracted with EtOAc. The organic layers were washed once with an equal volume of 1 N HCl followed by water, dried (Na_2SO_4), and concentrated to obtain the products invariably in better than 80% yield. The products were purified directly by crystallization or after elution through a short column of silica gel. Structural data of the phenols thus prepared are given below.

[6-Hydroxy-2-(4-hydroxyphenyl)-1-benzofuran-3-yl]phenylmethanone (18): IR 3200 (OH) and 1600 (CO) cm^{-1}; ^1H NMR (acetone-d_6) δ 6.65–7.55 (m, 10 H, Ar-*H*) and 7.6–7.8 (m, 2 H, Ar-*H*, ortho to CO).

[2-(4-Hydroxyphenyl)-1-benzofuran-3-yl](4-hydroxyphenyl)methanone (20): IR 3250 (OH) and 1600 (CO) cm^{-1}; ^1H NMR (acetone-d_6) δ 6.0–6.66 (m, 4 H, Ar-*H*, ortho to OH), 7.1–7.56 (m, 6 H, Ar-*H*), and 7.7 (d, 2 H, J = 9.0 Hz, Ar-*H*, ortho to CO); MS, m/z 330 (M^+).

(6-Hydroxy-2-phenyl-1-benzofuran-3-yl)(4-hydroxyphenyl)methanone (22): IR 3200 (OH) and 1600 (CO) cm^{-1}; ^1H NMR (acetone-d_6) δ 6.65–6.95 (m, 4 H, Ar-*H*, ortho to OH), 6.95–7.6 (m, 6 H, Ar-*H*), and 7.7 (d, 2 H, J = 9.0 Hz, Ar-*H*, ortho to CO); MS, m/z 330 (M^+).

[6-Hydroxy-3-(4-hydroxyphenyl)-1-benzofuran-2-yl](4-hydroxyphenyl)methanone (27): IR 3300 (OH) and 1600 (CO) cm^{-1}; ^1H NMR (acetone-d_6) δ 6.7–7.03 (m, 6 H, Ar-*H*, ortho to OH), 7.23–7.54 (m, 3 H, Ar-*H*), and 7.75 (d, 2 H, J = 9.0 Hz, Ar-*H*, ortho to CO).

2-Phenyl-3-(4-hydroxyphenyl)-6-hydroxy-1-benzofuran (29): IR 3300 (OH) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 6.53–7.6 (m, 12 H, Ar-*H*).

2,3-Bis(4-hydroxyphenyl)-6-hydroxy-1-benzofuran (33): IR 3350 (OH) cm^{-1}; ^1H NMR (acetone-d_6) δ 6.58–6.98 (m, 6 H, Ar-*H*, ortho to OH) and 6.58–7.06 (m, 5 H, Ar-*H*).

4,5-Diphenyl-6-(4-methoxyphenyl)-2-pyrone (3). 4'-Methoxy-2-phenylacetophenone (4.8 g) and methyl phenylpropiolate (3.5 g) were added successively to an ice-cold ethereal suspension of sodium methoxide (1.1 g), and the mixture was kept at 0 °C for 2 days. It was then poured into water and the yellow precipitate filtered and crystallized from dichloromethane–methanol to afford **3** (6.4 g), mp 196 °C (lit.[10,11] mp 200 °C).

5-Oxo-5-(4-methoxyphenyl)-3,4-diphenylpent-3-enoic Acid (4). A solution of pyrone **3** (2.5 g) in 10% methanolic KOH (50 mL) was heated under reflux for 1 h. The solvent was then removed in vacuo and the residue taken up in water (50 mL) and washed with ether (2 × 100 mL), acidified by 1 N HCl, and extracted with ether (3 × 100 mL). The ethereal layer was dried (Na_2SO_4) and concentrated. The residue (2.4 g) was first triturated with hot water (50 mL) to remove 4-methoxybenzoic acid (200 mg) and then crystallized from dichloromethane-methanol to furnish **4** (2.2 g) mp 168 °C (lit.[10,11] mp 163 °C).

1-Oxo-2,3-diphenyl-1-(4-methoxyphenyl)but-2-ene (5). The foregoing acid **4** was pyrolyzed at 180 °C in vacuo for 2 h and the resultant oil chromatographed over a column of silica gel, eluting with hexane–benzene (1:1) to furnish **5** (1.5 g), which was crystallized from hexane–benzene; mp 86 °C; IR 1668 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 6.85 (d, 2 H, ortho to OCH_3), 6.95–7.19 (m, 10 H, Ar-*H*), and 7.95 (d, 2 H, Ar-*H*, meta to OCH_3); MS, *m/z* 328 (M^+).

1-Oxo-2,3-diphenyl-1-(4-hydroxyphenyl)but-2-ene (6 and 7). A mixture of **5** (1 g), piperidine (100 mL), and water (100 mL) was heated under reflux for 48 h with stirring. The mixture was cooled, acidified (aqueous HCl), and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated to obtain an oil, which was filtered through a column of silica gel, eluting with hexane–benzene (1:1) to obtain a mixture of **6** and **7** (200 mg), which were resolved by fractional crystallization from hexane–benzene (1:9) to furnish **6** and **7**. For **6**: mp 134 °C; IR 1635 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3 H, CH_3), 6.64 (d, 2 H, Ar-*H*, ortho to OH), 7.05–7.19 (m, 10 H, Ar-*H*), 7.44 (d, 2 H, Ar-*H*, meta to OH); MS, *m/z* 314 (M^+). For **7**: mp 144 °C; IR 1635 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, 3 H, CH_3), 6.75 (d, 2 H, Ar-*H*, ortho to OH), 6.95–7.15 (m, 10 H, Ar-*H*), and 7.89 (d, 2 H, Ar-*H*, meta to OH); MS, *m/z* 314 (M^+).

1-Oxo-2,3-diphenyl-1-[4-(2-pyrrolidinoethoxy)phenyl]but-2-ene (8 and 9). These were prepared individually starting with the phenols **6** and **7** as follows: A mixture of respective phenols (100 mg) with 2-pyrrolidinoethyl chloride hydrochloride (60 mg), anhydrous acetone (10 mL), and anhydrous K_2CO_3 (100 mg) was heated under reflux overnight, cooled, and filtered. The filtrates were concentrated in vacuo and subjected to chromatography over a column of basic alumina to furnish **8** (80 mg) and **9** (85 mg). For **8**: IR (neat) 1660 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.55–1.8 [m, 4 H, $-CH_2(CH_2)_2CH_2-$], 2.10 (s, 3 H, CH_3), 2.3–2.6 (m, 4 H, CH_2NCH_2-), 2.7 (t, 2 H, $-OCH_2CH_2N$), 3.89 (t, 2 H, OCH_2), 6.55 (d, 2 H, Ar-*H*, ortho to OCH_2), 6.89–7.25 (m, 10 H, Ar-*H*), and 7.55 (d, 2 H, Ar-*H*, meta to OCH_2); MS, *m/z* 411 (M^+). For **9**: IR (neat) 1664 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.55–1.80 (m, 4 H, $-CH_2(CH_2)_2CH_2-$), 1.99 (s, 3 H, CH_3), 2.3–2.6 (m, 4 H, $-CH_2NCH_2$), 2.7 (t, 2 H, $-OCH_2CH_2N-$), 3.89 (t, 2 H, OCH_2), 6.72 (d, 2 H, Ar-*H*, ortho to OCH_2), 6.82–7.10 (m, 10 H, Ar-*H*), and 7.78 (d, 2 H, Ar-*H*, meta to OCH_2); MS, *m/z* 411 (M^+).

[2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-1-benzofuran-3-yl]phenylmethanone (12). A mixture of [2-(4-hydroxyphenyl)-1-benzofuran-3-yl]phenylmethanone[13] (**11**; 1 g), 2-pyrrolidinoethyl chloride hydrochloride (800 mg), anhydrous acetone (40 mL), and anhydrous K_2CO_3 (2.5 g) was heated under reflux for 40 h. It was then cooled and filtered, and the filtrate was concentrated. The residual oil was extracted with EtOAc (2 × 100 mL). The organic layer was washed with water (2 × 100 mL), dried (Na_2SO_4), and concentrated and the residual oil passed through a column of basic alumina, eluting with benzene to furnish **12** (900 mg): IR (neat) 1630 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59–1.9 [m, 4 H, $-CH_2(CH_2)_2CH_2-$], 2.38–2.66 (m, 4 H, $-CH_2NCH_2-$), 2.67 (t, 2 H, *J* = 6.0 Hz, $-OCH_2CH_2N-$), 6.65 (d, 2 H, *J* = 9.0 Hz, Ar-*H*), and 7.65 (m, 2 H, Ar-*H*, ortho to CO); MS, *m/z* 411 (M^+).

2-(4-Hydroxyphenyl)-3-phenyl-7-methoxy-1-benzopyrylium Chloride (16). Dry HCl gas was bubbled through a mixture of 2-hydroxy-4-methoxybenzaldehyde (2.3 g) and 4'-hydroxy-2-phenylacetophenone (3.2 g) in EtOAc (30 mL) and absolute EtOH (10 mL) at 0 °C for 15 min and the resulting cherry red solution allowed to stand overnight at room temperature. A red-colored pyrylium salt separated out, which was filtered. Addition of dry ether to the mother liquor furnished an additional amount of the pyrylium salt **16** (5.4 g): IR 3000–3400 (OH) cm^{-1}; ^1H NMR (TFA) δ 3.75 (s, 3 H, OCH_3), 6.4–7.7 (m, 12 H, Ar-*H*), and 8.5 (s, 1 H, C_4-*H*).

[6-Methoxy-2-(4-hydroxyphenyl)-1-benzofuran-3-yl]phenylmethanone (17). To a solution of the foregoing pyrylium salt **16** (1.6 g) in EtOH (50 mL), cooled in ice, was added concentrated HCl (1.5 mL) followed by 30% H_2O_2 (2.3 mL) with continuous stirring. The reaction mixture was then allowed to stand at room temperature. A yellow-colored solid material separated out, which was filtered and recrystallized from methanol to obtain the methanone **17** (200 mg): IR 3300 (OH) and 1600 (CO) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.66 (s, 3 H, OCH_3), 6.55–6.85 (m, 4 H, Ar-*H*, ortho to OMe and OH), 7.15–7.48 (m, 6 H, Ar-*H*), and 7.54–7.69 (m, 2 H, Ar-*H*, ortho to CO); MS, *m/z* 344 (M^+).

[2-(4-Methoxyphenyl)-1-benzofuran-3-yl](4-methoxyphenyl)methanone (19). To a solution of 2-(4-methoxyphenyl)-1-benzofuran[26] (1.5 g) in chlorobenzene (50 mL), cooled in ice, was added $SnCl_4$ (5.2 g) followed by anisoyl chloride (1.4 g) portionwise under stirring. The reaction mixture was stirred at room temperature for 5 h. It was then poured over crushed ice and extracted with dichloromethane (2 × 100 mL). The organic layer was washed with water (2 × 100 mL), dried (Na_2SO_4), and concentrated to obtain an oil, which was chromatographed over a column of silica gel, eluting with hexane to obtain **19** (1.7 g): IR 1600 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6 and 3.8 (2 s, 6 H, OCH_3), 6.7 (d, 4 H, *J* = 9.0 Hz, Ar-*H*, ortho to OCH_3), 7.1–7.5 (m, 4 H, Ar-*H*), 7.55 (d, 2 H, Ar-*H*), and 7.75 (d, 2 H, *J* = 9.0 Hz, Ar-*H*, ortho to CO); MS, *m/z* 358 (M^+).

[6-Methoxy-2-phenyl-1-benzofuran-3-yl](4-methoxyphenyl)methanone (21). To a solution of 6-methoxy-2-phenyl-1-benzofuran[15] (1 g) in dry dichloromethane (20 mL), cooled in ice, was added $SnCl_4$ (1.5 mL) with stirring, followed by anisoyl chloride (1.8 g) portionwise. The reaction mixture was stirred to room temperature for 2 h. It was then poured over crushed ice and extracted with dichloromethane (2 × 100 mL). The extract was washed with water (2 × 75 mL), dried (Na_2SO_4), and concentrated to obtain an oil, which was chromatographed over a column of silica gel, eluting with benzene–hexane (1:1) to obtain **21** (1.1 g): IR 1600 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66–3.90 (m, 6 H, OCH_3), 6.6–6.9 (m, 4 H, Ar-*H*, ortho to OMe), 6.95–7.4 (m, 6 H, Ar-*H*), and 7.76 (d, 2 H, *J* = 9.0 Hz, Ar-*H*, ortho to CO); MS, *m/z* 358 (M^+).

ω-(3-Methoxyphenoxy)-4-methoxyacetophenone (23). A mixture of 2-bromo-4'-methoxyacetophenone[27] (40 g), *m*-methoxyphenol (20 g), and dry acetone (200 mL) was heated under reflux with anhydrous K_2CO_3 (30 g) for 6 h. The reaction mixture was cooled and filtered and the filtrate concentrated to obtain an oil, which was extracted with ether (2 × 250 mL). The organic layer was washed with aqueous 2 N NaOH (2 × 100 mL) and then with water (2 × 200 mL), dried (Na_2SO_4), and concentrated to obtain an oil, which was chromatographed over a column of silica gel, eluting with benzene to obtain **23**, which was crystallized from benzene–hexane (26 g): mp 67–70 °C; IR 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.5–3.8 (m, 6 H, OCH_3), 5.3 (s, 2 H, $-CH_2-$), 6.26–7.2 (m, 6 H, Ar-*H*), and 7.7 (d, 2 H, *J* = 9.0 Hz, Ar-*H*, ortho to CO); MS, *m/z* 272 (M^+).

3-(4-Methoxyphenyl)-6-methoxy-1-benzofuran (24) and 2-(4-Methoxyphenyl)-6-methoxy-1-benzofuran (25). A mixture of **23** (10 g), PPA (40 g), and xylene (200 mL) was heated under reflux for 8 h. Xylene was decanted from the viscous lower layer, washed with water, dried, and concentrated to obtain an oil, which was found to be a mixture of **24** and **25** on the basis of GLC and ^1H NMR. Fractional crystallization afforded **24** (1.5 g), mp 60 °C (lit.[28] mp 60 °C), and **25** (0.1 g), mp 156 °C (lit.[15] mp 159 °C).

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[6-Methoxy-3-(4-methoxyphenyl)-1-benzofuran-2-yl](4-methoxyphenyl)methanone (26). To a solution of 3-(4-methoxyphenyl)-6-methoxy-1-benzofuran (**24**; 300 mg) in dry dichloromethane (5 mL) was added $SnCl_4$ (0.4 mL) under stirring, followed by addition of anisoyl chloride (230 mg) portionwise. The reaction mixture was stirred at room temperature for 4 h. It was then poured into crushed ice and extracted with dichloromethane (2 × 75 mL). The organic layer was washed with water (2 × 60 mL), dried (Na_2SO_4), and concentrated to obtain an oil, which was passed through a bed of silica gel, eluting with benzene to obtain **26** (300 g): IR 1600 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.7–3.9 (m, 9 H, OCH_3), 6.7–7.05 (m, 6 H, Ar-*H*, ortho to OCH_3), 7.3–7.54 (m, 3 H, Ar-*H*), and 7.85 (d, 2 H, J = 9.0 Hz, Ar-*H*, ortho to CO); MS, m/z 388 (M^+).

2-Phenyl-3-(4-methoxyphenyl)-6-hydroxy-1-benzofuran (28). A mixture of 4-methoxybenzoin (1.2 g) and resorcinol (1.1 g) in peroxide-free dioxane (30 mL) and concentrated HCl (10 mL) was heated under reflux for 2 h. The reaction mixture was poured into water and extracted with ether (2 × 100 mL). The organic layer was separated, washed with aqueous 1 N NaOH (50 mL) and water (2 × 100 mL), dried (Na_2SO_4), and concentrated to afford an oil, which was chromatographed over a column of silica gel, eluting with benzene to obtain **28** (700 mg), recrystallized from benzene–hexane, mp 135–137 °C (lit.[29] mp 137–138 °C).

2-Phenyl-3-(4-hydroxyphenyl)-6-methoxy-1-benzofuran (30). A mixture of 4-(benzyloxy)benzoin (3.1 g), *m*-methoxyphenol (1.24 g) in peroxide-free dioxane (90 mL), and concentrated HCl (30 mL) was heated under reflux for 24 h. Another aliquot of concentrated HCl (30 mL) was added to the reaction mixture, which was heated under reflux for another 48 h. It was cooled, concentrated in vacuo to remove dioxane, poured into water (100 mL), and then extracted with EtOAc (2 × 100 mL). The organic layer was washed with aqueous 1 N NaOH (50 mL) and water (2 × 100 mL), dried (Na_2SO_4), and concentrated to obtain an oil, which was chromatographed over a column of silica gel, eluting with benzene to obtain **30** (1.5 g), which was crystallized from benzene–hexane, mp 162 °C (lit.[16] mp 167 °C).

2-Phenyl-3-[4-(2-pyrrolidinoethoxy)phenyl]-6-methoxy-1-benzofuran (31). A mixture of the benzofuran **30** (1.9 g), 2-pyrrolidinoethyl chloride hydrochloride (2 g), anhydrous K_2CO_3 (4 g), and anhydrous acetone (60 mL) was heated under reflux for 24 h. The reaction mixture was cooled and filtered and the filtrate concentrated to obtain an oily residue, which was poured into water (100 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was dried (Na_2SO_4) and concentrated to obtain an oil, which was chromatographed over a column of basic alumina, eluting with benzene–hexane (1:1) to obtain **31** (1.8 g), which was crystallized as its hydrochloride salt from ethanol–water, mp 209 °C (lit.[16] mp 209–210 °C).

2,3-Bis(4-methoxyphenyl)-6-methoxy-1-benzofuran (32). Anisoin (5.4 g), resorcinol (2.2 g) in peroxide-free dioxane (90 mL), and concentrated HCl (30 mL) were heated under reflux for 12 h. The reaction mixture was concentrated in vacuo to remove most of the dioxane and the residue poured in water (100 mL) and extracted with EtOAc (2 × 150 mL). The organic layer was washed with aqueous 1 N NaOH (100 mL) and then with water (2 × 100 mL), dried (Na_2SO_4), and concentrated to obtain an oil, which was chromatographed over a column of silica gel, eluting with benzene–hexane to furnish 2,3-bis(4-methoxyphenyl)-6-hydroxy-1-benzofuran (3.5 g), crystallized from benzene, mp 135 °C (lit.[29] mp 136 °C), which was solubilized in methanol (35 mL). To this solution was added aqueous 1 N NaOH (7 mL) and dimethyl sulfate (7 mL). The reaction mixture was heated under reflux for 1 h, cooled, and concentrated in vacuo. The residue poured into water (200 mL) was extracted with EtOAc (3 × 100 mL). The organic layer was washed with water (2 × 100 mL), dried (Na_2SO_4), and concentrated to obtain an oil, which was subjected to chromatography over a column of silica gel, eluting with benzene–hexane to obtain **32** (2.1 g), crystallized from hexane, mp 92 °C (lit.[29] mp 90–91 °C).

(29) Chawla, H. P. S.; Grover, P. K.; Anand, N.; Kamboj, V. P.; Kar, A. B. *J. Med. Chem.* **1970**, *13*, 454.

Biology. Materials. [2,4-^{3}H]Estradiol ([^{3}H]E_2; 55 Ci $mmol^{-1}$) was purchased from New England Nuclear Corp. and was assessed as 95% radiochemically pure by using a Panax Radio TLC scanner. Unlabeled estradiol was purchased from Steraloids Inc., activated charcoal and Norit A were from Sigma Chemicals, and dextran T-70 was from Pharmacia Fine Chemicals. All other chemicals and reagents were of analytical or scintillation grade.

Female rats, 21–23 days old, of Sprague-Dawley strain were taken from the CDRI rodent colony. For receptor binding experiments the rats were primed subcutaneously with 1 μg of E_2 for 3 consecutive days, in order to increase the yield of the receptor in their uteri. The animals were autopsied 24 h after the last injection.

Preparation of Test Solution. The stock solutions for RBA experiments were prepared in DMF–TEA buffer (1:1 v/v) and for bioassay in propylene glycol–0.9% saline (1:1 v/v) designated as the vehicle.

Receptor Binding Experiments. Receptor binding experiments were performed on microtiter plates by minor modification of the procedure reported earlier.[18] Briefly, 50-μL aliquots of cytosol (1 uterine equiv/mL) were incubated at 4 °C for 18 h with increasing concentrations of the test compounds (10^{-4}–10^{-9} M) in triplicate and fixed concentration of [^{3}H]E_2 (5×10^{-9} M) dissolved in 20 μL of DMF–TEA buffer. Each incubate (70 μL) in TEA buffer (Tris-HCl, 10 mmol; EDTA, 165 mmol; NaN_3, 0.02%; pH 7.4) was 7% in DMF. For separation of free from bound [^{3}H]E_2, each incubate was treated with 10 μL of charcoal–dextran slurry (2.5 and 0.25% w/v, respectively) in TEA buffer for 20 min. Radioactivity of a 50-μL aliquot of each incubate was measured in a Packard Tricarb liquid scintillation spectrometer in minivials containing 5 mL of scintillation fluid (1.5:2.5:2.5 v/v mixture of methanol, dioxane, and toluene containing 0.5% PPO, 0.01% POPOP, and 9% naphthalene).

Bioassay. For utertrophic assays the indicated doses of the test compounds, suspended in 0.2 mL of propylene glycol–1 N saline (1:1 v/v), were injected subcutaneously into the animals, in groups of seven to nine, on 3 consecutive days. The control group received similar injections of the vehicle alone. Twenty-four hours after the last injection the animals were autopsied and their uterine wet weights were recorded.

Antiuterotrophic assays were performed similarly, with the difference that the animals were coadministered 1 μg of E_2 each in the same vehicle but at a different site. The control group in this case received 1 μg of E_2 plus the vehicle alone at two different sites.

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Registry No. **1**, 63645-39-6; **2**, 94348-28-4; **3**, 65714-05-8; **4**, 120990-39-8; **5**, 111022-32-3; **6**, 120990-40-1; **7**, 120990-41-2; **8**, 120990-42-3; **9**, 120990-43-4; **10**, 57664-47-8; **11**, 57664-48-9; **12**·HCl, 120990-44-5; **12**, 120990-54-7; **13**, 55877-35-5; **14**, 55877-36-6; **15**·oxalate, 120990-45-6; **15**, 87444-83-5; **16**, 121011-56-1; **17**, 120990-46-7; **18**, 120990-47-8; **19**, 102593-72-6; **20**, 102184-07-6; **21**, 120990-48-9; **22**, 120990-49-0; **23**, 52814-89-8; **24**, 52814-52-5; **25**, 1838-44-4; **26**, 120990-50-3; **27**, 120990-51-4; **28**, 25433-74-3; **29**, 120990-52-5; **30**, 3333-88-8; **31**·HCl, 3333-85-5; **31**, 26049-62-7; **32**, 25439-60-5; **33**, 120990-53-6; **34**, 54756-51-3; **35**, 54756-56-8; **36**, 54756-50-2; **37**, 54756-54-6; 4-methoxysalicylaldehyde, 673-22-3; 4′-hydroxy-2-phenylacetophenone, 2491-32-9; 2-(4-methoxyphenyl)-1-benzofuran, 19234-04-9; 6-methoxy-2-phenyl-1-benzofuran, 33973-14-7; anisoyl chloride, 100-07-2; *m*-methoxyphenol, 150-19-6; 2-bromo-4-methoxyacetophenone, 2632-13-5; 4′-methoxy-2-phenylacetophenone, 1023-17-2; methyl phenylpropiolate, 4891-38-7; 2-pyrrolidinoethyl chloride hydrochloride, 7250-67-1; 4-methoxybenzoin, 4254-17-5; resorcinol, 108-46-3; 4-(benzyloxy)benzoin, 52600-66-5; anisoin, 30587-18-9; 2-phenyl-3-[(4-benzyloxy)phenyl]-6-methoxy-1-benzofuran, 3333-86-6; 2,3-bis(4-methoxyphenyl)-6-hydroxy-1-benzofuran, 87220-26-6.