(10^{-10}–10^{-6} mol). Stock solutions of compound **6L** and nitrendipine (0.01 mol) were prepared in DMSO and then diluted in Krebs-Henseleit buffer. Final concentration of DMSO in organ bath was always <0.1%. The isometric contraction was measured continuously by using a LETICA force displacement transducer and recorded on a GRAPHIC 1002 (LLOYD Instrument) recorder. The values of rate and contractile force were expressed as percent of variation with respect to control values.

Statistical Methods. Paired Student's *t* test was used to show any significant difference.

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Structure–Activity Relationship of Antiestrogens. Studies on 2,3-Diaryl-1-benzopyrans†

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A series of 2,3-diaryl-1-benzopyran analogues substituted at position 4 of 2-phenyl with a hydroxy or pyrrolidinoethoxy residue were synthesized as models for (*E*)-triarylpropenones constrained in the s-trans conformation. The prototypes, belonging to five chemical series, were evaluated for their estrogen receptor affinity and for estrogen agonist–antagonist activities. The 4*H*-1-benzopyran-4-one, the 2,3-dihydro-4*H*-1-benzopyran-4-one, the 4*H*-1-benzopyran, and the 2,3-dihydro-1-benzopyran derivatives were found to be inactive or only marginally activate as receptor ligands or estrogen agonists–antagonists. In the 2*H*-1-benzopyran category the parent phenol was also inactive whereas the basic ethers **16** and **26** were modest receptor ligands while being quite active as antiestrogens. In a comparative study the benzopyran **16** was found to be more effective antiestrogen than tamoxifen while being as effective as LY-117018. The benzopyrans have thus emerged as a new class of potent antiestrogens.

Introduction

The triarylethylene (TAE) antiestrogens represented by tamoxifen (Chart I) are well known for being associated with marked agonist activity.[1-6] The (*Z*)-triarylpropenones (*Z*-TAPs), such as trioxifen, LY-117018, and LY-139481 (Chart I), though better antiestrogens than TAEs, are also associated with some residual agonist character.[7-10] Although Wakeling and Bowler reported recently the development of 7α-substituted estradiols as "pure" antiestrogens,[11,12] the link between molecular structure of antiestrogens and their residual agonist character has remained an obscure one. Our efforts in this area have thus focused on structure–activity relationship (SAR) among TAEs and TAPs so as to better understand this link.

In a recent study on SAR of *Z*-TAPs, using acyclic propenones as models, we discovered that *E*-TAPs were also associated with significant receptor affinity with some of the compounds more effective ligands than the *Z* isomers.[13] A follow-up study based on conformationally constrained models suggested that *E*-TAPs could interact with the receptor through their s-cis conformation but that such a binding mode was unlikely to account for their action as antagonists.[14]

Upon careful reappraisal the previously published data on relative binding affinity (RBA) of *E*-TAPs[14] suggested the alternate possibility that the prototype may interact with the receptor through s-trans conformation such that its C-1 and C-2 aryls simulate the Ph and Ph′ residues of

Chart I

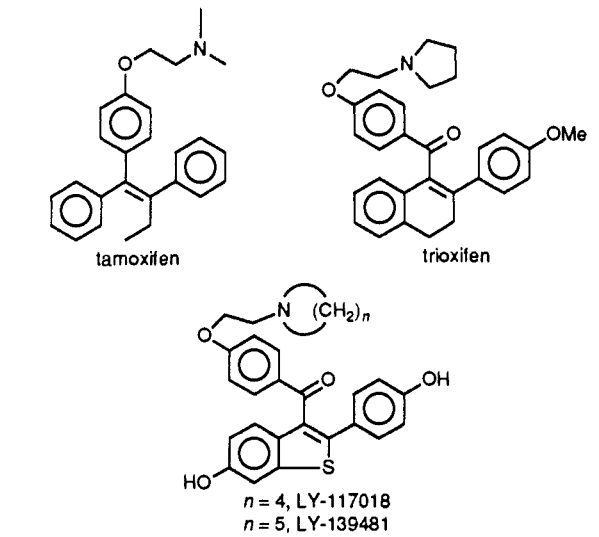
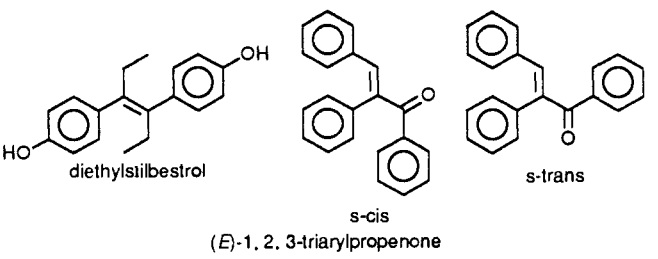


Chart II



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(1) Harper, M. J. K.; Walpole, A. L. *J. Reprod. Fertil.* **1967**, *13*, 101.

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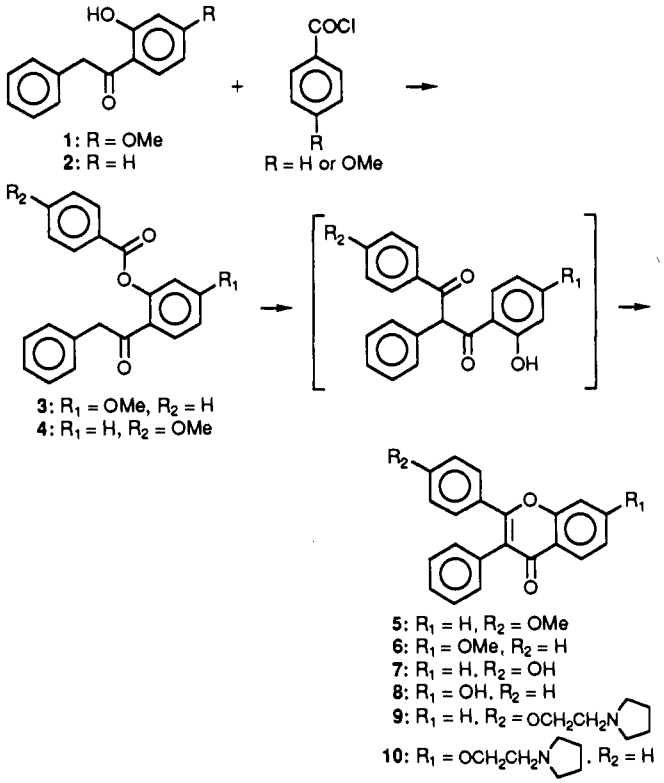
Scheme I

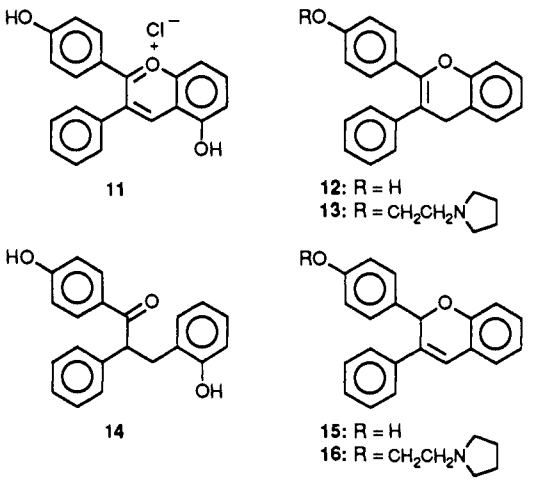


diethylstilbestrol (Chart **II**). If this was the case we reasoned that incorporation of basic ether chain at 4′ position of 4-phenyl in *E*-TAPs could lead to better antiestrogens. Following this rationale we have synthesized a series of 2,3-diaryl-1-benzopyran analogues as models for *E*-TAPs constrained in the s-trans conformation. The compounds were subjected to SAR study and the results are presented in this paper.

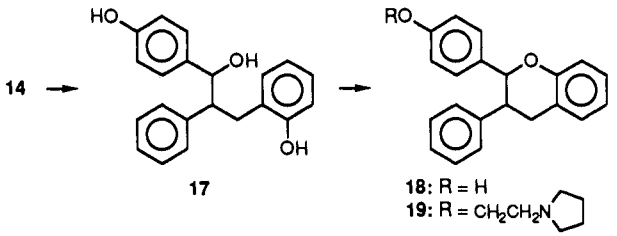
Chemistry

The five categories of benzopyran analogues synthesized are shown in Table I. The benzopyranones (type I) were synthesized by slight modification of a reported procedure,[15] starting from the desoxybenzoins **1**[16] and **2**[17]

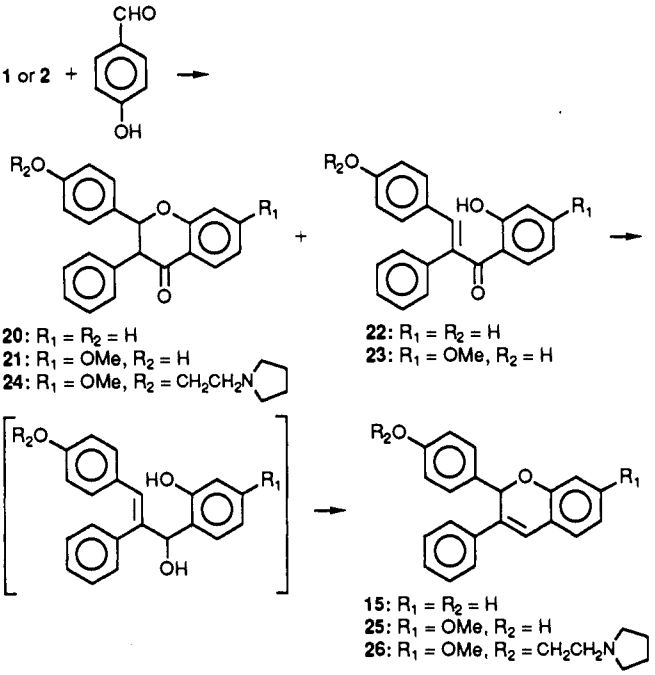
Chart III



Scheme II



Scheme III



(Scheme I). Esterification of the desoxybenzoin **1** with anisoyl chloride and of the desoxybenzoin **2** with benzoyl chloride furnished the corresponding benzoate esters **3** and **4**, which on heating in glycerol at 260 °C, under inert atmosphere, furnished the desired benzopyranones **5** and **6**. The latter were first demethylated to the phenols **7** and **8** and then alkylated with 2-pyrrolidinoethyl chloride to

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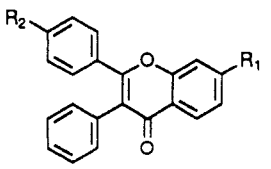
Table I. Physical Data of the Indicated Benzopyranone and Benzopyran Derivatives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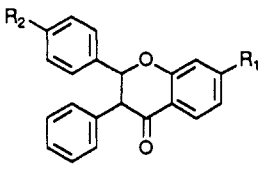
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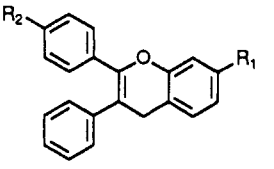
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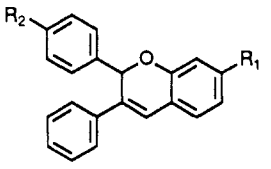
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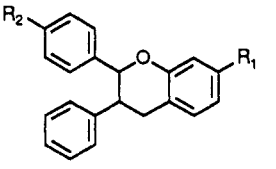
V

compd	type	R_1	R_2	mp, °C	solvent[a]	mol formula	anal.
9	I	H	OPy[b]	115–118	A	$C_{27}H_{25}O_3N$	C,H,N
10	I	OPy	H	98	B	$C_{27}H_{25}O_3N$	C,H,N
12	III	H	OH	132–134	A	$C_{21}H_{16}O_2$	C,H
13	III	H	OPy[c]	193–193	C	$C_{27}H_{27}O_2N$ $CO_2H \cdot {}^1/_2H_2O$	C,H,N
15	IV	H	OH	144	A	$C_{21}H_{16}O_2$	C,H
16	IV	H	OPy	78	B	$C_{27}H_{27}O_2N$	C,H,N
18	V	H	OH	179–180	A	$C_{21}H_{18}O_2$	C,H
19	V	H	OPy	75	B	$C_{27}H_{29}O_2N$	C,H,N
24	II	OMe	OPy	131	A	$C_{28}H_{29}O_4N$	C,H,N
26	IV	OMe	OPy	99	B	$C_{28}H_{29}O_3N$	C,H,N

[a] Solvent of crystallization: A = benzene–hexane; B = hexane; C = ethanol. [b] Py = pyrrolidinoethyl. [c] Crystallized and analyzed as the oxalate salt.

furnish the requisite ethers **9** and **10**.

Synthesis of the benzopyran analogues (type III and type IV) and of the dihydrobenzopyran analogues (type V) was first approached via reduction of the corresponding benzopyrillium salt. Thus the benzopyrillium salt **11** (Chart III) reported previously,[18] on reduction with sodium borohydride in dimethylformamide (DMF) furnished a mixture of the 4*H*-benzopyran **12**, the propanone **14**, and the 2*H*-benzopyran **15**, with their relative yields depending upon the method of workup. Use of mildly acidic ammonium chloride as the proton source furnished the 4*H*-benzopyran **12** in major amount while the use of sulfuric acid furnished the propanone **14** as the major product. The phenols **12** and **15** were further converted to the requisite ethers **13** and **16**. The propanone **14** was reduced with sodium borohydride to the propanol **17** (Scheme II) which on treatment with ethanolic HCl furnished the dihydrobenzopyran as a mixture of cis and trans isomers. The latter was converted to the ether **19**, also a mixture of isomers.

The dihydrobenzopyran-4-one analogues (type II) were prepared as outlined in Scheme III. The route also gave access to the benzopyran **15** in much higher yield. Thus, base-catalyzed condensation of 4-hydroxybenzaldehyde with the desoxybenzoin **1** gave a mixture of the dihydro-4*H*-1-benzopyran-4-one **20** and the 2-phenychalcone **22**. Similar reaction of 4-hydroxybenzaldehyde with the desoxybenzoin **2** furnished **21** and **22**. On the basis of the characteristic doublets in their NMR spectra, with $J = 12$ Hz, assignable to 2 H and 3 H, the dihydrobenzopyran-4-ones **20** and **21** were assigned the trans geometry. The 2-phenylchalcones **22** and **23** when reduced with sodium borohydride furnished the 2*H*-benzopyran phenols **15** and **25**, respectively, in high yield, following thermal cyclodehydration of the alcohols initially formed. The phenols **21** and **25** were then alkylated to obtain the ethers **24** and **26**.

Table II. Receptor Affinity and Biological Activity Data of the Indicated Benzopyranone and Benzopyran Derivatives

compd	RBA[a]	dose, mg/rat	estrogenic activity[b]	antiestrogenic activity[b]
9	ND[b]	0.01	13.2 ± 2.2	40.3 ± 5.6
10	ND[d]	0.01	11.1 ± 1.6	40.7 ± 2.0
12	0.5 ± 0.1	1.0	26.2 ± 7.1	46.7 u 5.1
13	0.02 ± 0.002	1.0	24.0 ± 1.6	29.4 ± 2.8
15	0.05 ± 0.01	1.0	13.8 ± 2.1	48.8 ± 3.6
16	0.5 ± 0.1	1.0	25.5 ± 1.1	26.3 ± 1.1
18	0.04 ± 0.01	1.0	14.9 ± 1.1	59.0 ± 3.0
19	0.004	1.0	12.3 ± 1.2	57.2 ± 4.2
24	ND[d]	0.01	12.0 ± 1.4	46.5 ± 2.8
26	0.4 ± 0.2	0.01	27.6 ± 1.7	28.3 ± 3.5
estradiol	100	0.001	53.0 ± 10.8	-
control[c]	-	-	12.3 ± 2.2	-

[a] The values represent the mean ± SD from at least three independent determinations in each case. [b] Indicated doses of each compound were administered on three consecutive days. For antiestrogenic activity 0.001 mg/animal dose of E_2 was coadministered. [c] Control group of animals received the vehicle alone. The values represent, in milligrams, mean uterine weight ± SD from six to nine animals. [d] ND = no detectable affinity at 100 μM concentration.

Results

RBA of the test compounds for estrogen receptor (ER) were evaluated as reported previously[19] and their estrogen agonist and antagonist activities were evaluated in immature rats by using the uterotrophic assays. The data are presented in Table II.

The benzopyranones **9** and **10** and the dihydrobenzopyranone **24** do not show any detectable ER affinity. The rest of the compounds do interact with the receptor, but their RBAs are less than 1% that of estradiol (E_2). Significant variation in RBA results from absence or presence of the side chain in these molecules. Among 4*H*-benzopyrans and dihydrobenzopyrans, the phenols **12** and **18** are

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(19) Garg, S.; Bindal, R. D.; Durani, S.; Kapil, R. S. *J. Steroid Biochem.* **1983**, *18*, 89.

Table III. Estrogen Agonist and Antagonist Activities of the Selected Benzopyrans at Indicated Doses

compd	dose, μg/rat	estrogenic activity[a]	antiestrogenic activity[c]	% inhibition[b]
16	0	11.2 ± 1.6	45.1 ± 2.2	0
	1	22.5 ± 0.4	39.9 ± 3.8	12
	10	24.6 ± 2.6	26.2 ± 1.0	66
	30	23.6 ± 2.8	22.2 ± 2.6	70
26	0	10.6 ± 2.6	44.7 ± 2.4	0
	1	23.8 ± 1.2	38.3 ± 4.8	9
	10	26.9 ± 1.3	27.5 ± 2.5	50
	30	25.0 ± 1.3	23.6 ± 1.4	65

[a] The values are in milligrams, mean uterine weight ± SD from 6–9 animals. For antiestrogenic activity 0.3 μg/animal dose of E_2 was coadministered along with indicated doses of test compound. [b] Computed as $(E - C_e)100/(E - V)$, where V, E, and C_e refer to the mean uterine weight from animals treated with vehicle alone, with E_2 alone, and with a given compound along with E_2, respectively.

1 order of magnitude more effective ER ligands than the ethers **13** and **19**. In the 2*H*-benzopyran series, the ethers **16** and **26** are more effective ligands than the phenol **15**. The 4*H*-benzopyran phenol **12** and the 2*H*-benzopyran ethers **16** and **26** thus have comparable receptor affinities about 200-fold less than that of E_2.

From the biological activity data it is noticed that at the dose level employed the benzopyranones **9** and **10**, the dihydrobenzopyranone **24** and the dihydrobenzopyrans **18** and **19** are all inactive, as agonists as well as antagonists. The 4*H*-benzopyran and the 2*H*-benzopyran analogues however, do show some activity in both the assays. Among 4*H*-benzopyrans, the phenol **12** is a weak agonist but devoid of antagonist activity whereas the ether **13** is active in both these assays. Both compounds were found inactive when assayed at the 100 μg dose level (data not shown). In the 2*H*-benzopyran series the parent phenol **15** is inactive in both the assays whereas the ethers **16** and **26** show weak uterotrophic and marked antiuterotrophic activities of comparable order.

The 2*H*-benzopyran ethers **16** and **26** were next evaluated for their activity as a function of dose. From these data, presented in Table III, the compounds are found to evoke near maximal uterotrophic response at the 1-μg dose level, causing 2-fold increase in uterine weight. Both are antiestrogenic, showing comparable potency, with their activity increasing progressively in going from 1 to 30 μg dose.

The activity of the 2*H*-benzopyran **16** was next compared with that of tamoxifen and LY-117018. From the data (Figure 1) it is noticed that the compound compares quite well with the standard antiestrogens both as an agonist as well as antagonist. All show comparable activity profiles in the lower dose range but characteristic differences become apparent at the 10-μg dose. Whereas the benzopyran **16** and LY-117018 show comparable activities as agonists as well as antagonists, tamoxifen is more agonistic and less antagonistic than both these.

Discussion

These studies, focused on SAR of *E*-TAPs, were prompted by the possibility that the prototypes may interact with the receptor through their s-trans conformation. Accordingly, a series of 2,3-diphenyl-1-benzopyran analogues substituted on 2-phenyl with an OH or pyrrolidinoethoxy residue were synthesized as possible models and evaluated for receptor affinity and estrogen agonist–antagonist activity. An important structural variable in the models was the oxidation state of the pyran ring and, consequently, the molecular conformation of the prototypes. The prototypes, ranging from the planar 4*H*-1-benzopyran-4-one (type I) to the fully saturated nonplanar

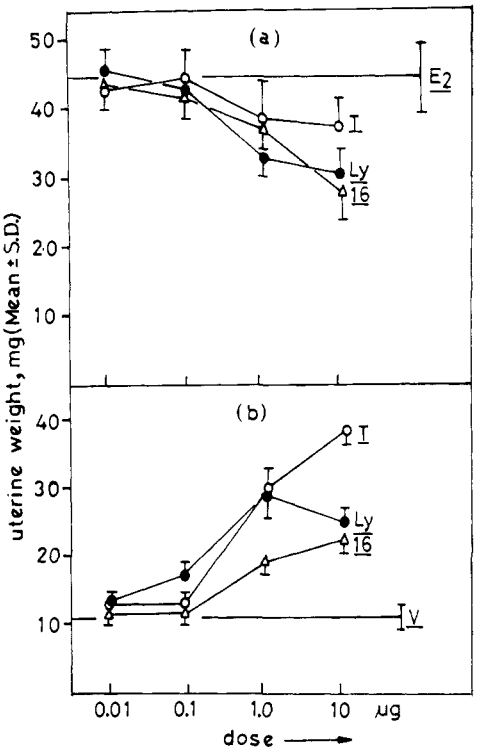

Figure 1. Uterotrophic (panel a) and antiuterotrophic (panel b) activities of 2,3-diaryl-2*H*-1-benzopyran **16** and that of tamoxifen (T) and LY-117018 (Ly) at indicated doses in immature female rats. Control group of animals received either the vehicle alone (V) or 1 μg of estradiol along with the vehicle (E_2). The values represent mean uterine weight ± SD in milligrams from at least seven animals in each case.

dihydro-1-benzopyran (type V), gave access to several conformational modes possible in an acyclic *E*-TAP.

From the data presented (Table II) it is obvious that all the series of compounds except one are either inactive or only marginally active. The ether derivatives in the 2,3-diphenyl-2*H*-1-benzopyran series (type IV), viz. **16** and **26**, are associated with marked estrogen antagonist activity.

Compound **16** is as potent an antiestrogen as LY-117018 but superior to it in possessing a lower degree of estrogen agonist character (Figure 1). The molecule however has rather poor receptor affinity which makes it likely that a hydroxylated metabolite may be responsible for its activity in vivo as reported in the case of tamoxifen.[8]

Although conceived as conformationally constrained models for *E*-TAPs the 2,3-diaryl-2*H*-1-benzopyrans are much more effective antiestrogens than *E*-TAPs and possess many distinctive features which may be responsible for their superior activity. First, the prototypes actually are derivatives of *trans*-stilbene and therefore possess closer correspondence in molecular terms to *Z*-TAPs and TAEs than to *E*-TAPs. Secondly, the substituted phenyl, crucial for antagonist activity, being linked to an sp^3 carbon, is out of plane with respect to benzopyran nucleus as well as stilbene core. The phenyl thus exists in a conformational mode which is precluded in the 4*H*-1-benzopyranone **9**, but which the equivalent phenyls in acyclic *E*-TAP (3-phenyl) as well as in *Z*-TAP (1-phenyl) may assume. The phenol **15**, from which the benzopyran ether **16** is derived, is a relatively weak receptor ligand and inactive as an agonist as well as antagonist. This is in sharp contrast to the behavior of TAEs in which case the parent phenols usually are full agonists,[20] but in consonance with

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the lack of activity of unsubstituted phenols of *Z*-TAPs. In their SAR, therefore, the benzopyrans seem to resemble *Z*-TAPs more closely than TAEs.

In conclusion, these efforts focused on SAR of TAPs have resulted in the development of 2,3-diaryl-2*H*-1-benzopyran as a promising new lead in antiestrogen design. Our forthcoming papers will focus on further elaboration of this lead.

Experimental Section

The melting points were determined on a Towson and Mercer's (U.K.) melting point apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 157 or 177 instruments or on Beckman Acculab-1 or Acculab-10 instruments as KBr wafers and values are reported in the cm^{-1} scale. The ^1H NMR spectra were recorded either on a Varian CFT-20, on a Perkin-Elmer R-32, or on a Varian EM-360 spectrometers, with tetramethylsilane as the internal standard and $CDCl_3$ as the solvent, unless indicated otherwise. The values are given in the δ scale. The mass spectra were run on a JEOL-JMS-D 300 instrument fitted with a direct inlet system. The homogeneity of compounds was routinely checked on silica gel or neutral alumina plates.

Synthesis of the desoxybenzoins **1**[16] and **2**[17] and of the benzopyrilium salt **11**[18] has been reported earlier. The following general procedure was used for converting the phenols **7**, **8**, **12**, **15**, **18**, **20**, and **25** in the requisite basic ethers. A mixture of the phenol (1 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (1.6 mmol), anhydrous potassium carbonate (1.6 mmol), and dry acetone (20 mL) was stirred and heated under reflux for 30 h. It was then cooled, and the solid material was filtered off and washed with acetone. The combined filtrate was concentrated and the residue chromatographed over a column of basic alumina with ethyl acetate–hexane (1:50, v/v) as eluant to afford the requisite ethers as oils (yield 80%) which were crystallized as such or as oxalate salts. Their melting points and solvents of crystallization are given in Table I. The IR, ^1H NMR, and mass data of the basic ethers **9**, **10**, **13**, **16**, **19**, **24**, and **26** are given below.

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-4*H*-1-benzopyran-4-one (9): IR 1620 (CO); ^1H NMR 1.65–1.85 (m, 4 H, $-CH_2(CH_2)_2CH_2-$), 2.40–2.70 (m, 4 H, CH_2NCH_2), 2.80 (t, 2 H, OCH_2CH_2N), 4.00 (t, 2 H, $-OCH_2-$), 6.75 (d, 2 H, J = 9.0 Hz, Ar-*H*, *o* to OCH_2), 7.15–7.75 (m, 10 H, Ar-*H*), 8.20 (dd, 2 H, J = 8.5 and 2.5 Hz, Ar-*H*, *o* to CO); MS m/z 411 (M^+).

2,3-Diphenyl-7-(2-pyrrolidinoethoxy)-4*H*-1-benzopyran-4-one (10): IR 1630 (CO); ^1H NMR (CCl_4) 1.65–1.85 (m, 4 H, $-CH_2(CH_2)_2$ CH_2-), 2.40–2.70 (m, 4 H, $-CH_2NCH_2-$), 2.80 (*t*, 2 H, $-OCH_2CH_2N-$), 4.10 (*t*, 2 H, $-OCH_2-$), 6.75–6.95 (m, 2 H, Ar-*H*), *o* to $-OCH_2$), 7.00–7.3 (m, 10 H, Ar-*H*), 8.05 (d, 1 H, J = 9.0 Hz, Ar-*H*, *o* to CO); MS m/z 411 (M^+).

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-4*H*-1-benzopyran (13): ^1H NMR 1.62–1.84 (m, 4 H, $-CH_2(CH_2)_2CH_2-$), 2.33–2.86 (m, 6 H, $-CH_2N(CH_2-)_2$, 3.7 (s, 2 H, $-CH_2-$), 3.95 (t, 2 H, J = 6.0 H_2, $-OCH_2-$), 6.62 (d, 2 H, J = 9.0 Hz, Ar-*H*, *o* to OCH_2), 6.96–7.23 (m, 11 H, Ar-*H*); MS m/z 397 (M^+).

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-2*H*-1-benzopyran (16): ^1H NMR 1.6–1.9 (m, 4 H, $CH_2(C_{H2})_2$), 2.43–2.66 (m, 4 H, $-CH_2NCH_2-$), 2.78 (t, 2 H, J = 6.0 Hz, $-OCH_2CH_2N-$), 3.96 (t, 2 H, J = 6.0 Hz, OCH_2) 6.13 (s, 1 H, *CH*Ph), 6.6–7.4 (m, 14 H, Ar-*H* and olefinic *H*); MS m/z 397 (M^+).

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-2,3-dihydro-4*H*-1-benzopyran (19): ^1H NMR 1.68–2.0 (*m*, 4 H, $CH_2-(CH_2)_2CH_2$), 2.4–2.7 (m, 4 H, $-CH_2NCH_2-$) 2.7–3.0 (m, 2 H, OCH_2CH_2N), 3.07–3.36 (m, 3 H, $-CHCH_2-$), 3.9–4.1 (m, 2 H, $-OCH_2-$), 4.9–5.1 (m, 1 H, $-OCH-$), 6.6–7.33 (m, 13 H, Ar-*H*); MS m/z 399 (M^+).

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-one (24): IR 1680 (CO); ^1H NMR 1.6–1.9 (m, 4 H, $-CH_2(CH_2)_2CH_2-$), 2.4–2.7 (m, 4 H, $-CH_2NCH_2-$), 2.8 (t, 2 H, J = 6.0 Hz, OCH_2CH_2), 4.1 (**d**, 1 H, J = 12.0 Hz, $-COCH-$), 5.5 (d, 1 H, J = 12.0 Hz, $-OCH-$), 6.4–7.3 (m, 11 H, Ar-*H*), 7.9 (d, 1 H, J = 8.0 Hz, Ar-*H*, *o* to OH); MS m/z 443 (M^+).

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-7-methoxy-2*H*-1-benzopyran (26): ^1H NMR 1.65–2.0 (m, 4 H, $CH_2-(CH_2)_2CH_2$), 2.4–2.75 (m, 4 H, $-CH_2NCH_2-$), 2.8 (t, 2 H, J = 6.0 Hz, $-OCH_2CH_2-$), 3.65 (s, 3 H, OCH_3), 4.0 (*t*, 2 H, J = 6.0 Hz, OCH_2CH_2), 6.15 (s, 1 H, $-OCH-$), 6.2–6.45 (m, 2 H, Ar-H, *o* to OCH_3), 6.7 (d, 2 H, J = 8.0 Hz, Ar-*H*, *o* to $-OCH_2CH_2-$), 6.9–7.4 (m, 11 H, Ar-*H* and olefinic *H*); MS m/z 427 (M^+).

1-[2-(Benzoyloxy)-4-methoxyphenyl]-2-phenylethanone (3). A solution of 1-(2-hydroxy-4-methoxyphenyl)-2-phenylethanone (**1**)[16] (448 mg) and benzoyl chloride (0.56 mL) in dry pyridine (5 mL) was stirred at room temperature for 5 h. The residue obtained after concentrating the reaction mixture in vacuo was then poured into water (25 mL) and extracted with ether (2 × 10 mL). The organic layer was first washed with 5% aqueous HCl (10 mL) and then with water (3 × 10 mL), dried (Na_2SO_4), and concentrated to yield an oily residue which was chromatographed over a column of silica gel with benzene–hexane (1:1, v/v) as eluant, to obtain **3**, which was crystallized from benzene–hexane (500 mg): mp 80 °C; IR 1750 ($-CO_2Ar$), 1710 (CO); ^1H NMR 3.78 (s, 3 H, OCH_3), 3.95 (s, 2 H, $-CH_2-$), 6.5–7.0 (m, 2 H, Ar-*H*, *o* to OCH_3), 7.15 (s, 5 H, Ar-*H*), 7.30–7.45 (m, 3 H, Ar-*H*, *m* and *p* to CO of CO_2Ar), 7.7 (d, 1 H, J = 9.0 Hz, Ar-*H*, *o* to CO), 8.05 (dd, 2 H, J = 9.0 Hz and 2.5 Hz, Ar-*H*, *o* to CO_2Ar); MS m/z 346 (M^+). Anal. ($C_{22}H_{18}O_4$) C and H.

1-[2-[(4-Methoxybenzoyl)oxy]phenyl]-2-phenylethanone (4). This was prepared according to the procedure detailed for **3**. Thus, stirring a solution of 1-(2-hydroxyphenyl)-2-phenylethanone (**2**)[17] (500 mg) and anisoyl chloride (800 mg) in dry pyridine (6 mL) at room temperature for 24 h, furnished a colorless oil after workup. Elution of the crude reaction mixture over a column of silica gel with benzene furnished **4**, which was crystallized from benzene–hexane (350 mg): mp 86 °C; IR 1750 (CO_2Ar), 1710 (CO); ^1H NMR (CCl_4) 3.69 (s, 3 H, OCH_3), 3.95 (s, 2 H, $-CH_2$), 6.75 (d, 2 H, J = 9.0 Hz, Ar-*H*, *o* to OCH_3), 7.0–7.5 (m, 9 H, Ar-*H*), 7.95 (dd, 2 H, J = 9.0 and 2.5 Hz, Ar-*H*, *o* to CO_2Ar); MS m/z 346 (M^+). Anal. ($C_{22}H_{18}O_4$) C and H.

2-(4-Methoxyphenyl)-3-phenyl-4*H*-1-benzopyran-4-one (5). A stirred solution of the ester **3** (200 mg) in freshly distilled anhydrous glycerol (2 mL) was heated at 260 °C for 2 h under nitrogen atmosphere. The reaction mixture, after cooling, was poured into water (20 mL) and the solution rendered alkaline with 4 N NaOH. The resulting mixture was stirred at room temperature for 15 min and allowed to stand at 0–4 °C for 24 h. The white precipitate which appeared was filtered and dissolved in dichloromethane (10 mL). The organic layer was washed with water (2 × 5 mL), dried (Na_2SO_4), and concentrated to furnish **5** which was crystallized from benzene–hexane (95 mg): mp 160 °C; IR 1620 (CO); ^1H NMR 3.80 (s, 3 H, OCH_3), 6.75 (d, 2 H, J = 9.0 Hz, Ar-*H*, *o* to OCH_3), 7.25–7.8 (m, 10 H, Ar-*H*), 8.25 (dd, 1 H, J = 8.5 Hz and 2.5 Hz, Ar-*H*, *o* to CO); MS m/z 328 (M^+). Anal. ($C_{22}H_{16}O_3$) C and H.

2,3-Diphenyl-7-methoxy-4*H*-1-benzopyran-4-one (6). This was prepared by heating a solution of the benzoate ester **4** (200 mg) in anhydrous glycerol (2 mL) at 260 °C under nitrogen atmosphere, followed by workup similarly described for **5**, and crystallized from benzene–hexane (120 mg): mp 215 °C; IR 1640 (CO); ^1H NMR; 3.85 (s, 3 H, OCH_3), 6.80–7.00 (m, Ar-*H*, *o* to OCH_3), 7.10–7.40 (m, 10 H, Ar-*H*), 8.15 (d 1 H, J = 9.0 Hz, Ar-H, *o* to CO); MS m/z 328 (M^+). Anal. ($C_{22}H_{16}O_3$) C and H.

2-(4-Hydroxyphenyl)-3-phenyl-4*H*-1-benzopyran-4-one (7). To a stirred solution of the benzopyranone **5** (100 mg) in dry dichloromethane (10 mL) under nitrogen atmosphere at −78 °C was added boron tribromide. After stirring for 15 min at this temperature, the solution was allowed to warm up to 0 °C and stirred for an additional 2 h. The reaction mixture was again cooled to −78 °C and absolute alcohol (2 mL) added to it. After warming to ambient temperature the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 10 mL). The organic extract was washed with water (3 × 5 mL), dried (Na_2SO_4), and concentrated to furnish a pale yellow solid, which was crystallized from benzene–acetone (72 mg): mp 260 °C; IR 3250 (OH), 1615 (CO); ^1H NMR (DMSO-d_6) 6.5 (d, 2 H, J = 9.0 Hz, Ar-*H*, *o* to OH), 7.1–7.5 (m, 10 H, Ar-*H*), 8.0 (dd, 1 H, J = 9.0 and 2.5 Hz, Ar-*H*, *o* to CO); MS m/z 314 (M^+). Anal. ($C_{21}H_{14}O_3$) C and H.

2,3-Diphenyl-7-hydroxy-4*H*-benzopyran-4-one (8). A mixture of the benzopyranone **6** (100 mg) and pyridine hydrochloride (400 mg) was heated at 200 °C for 2 h. It was then cooled and diluted with water (20 mL) to furnish **8** as a white solid which was filtered, washed with aqueous HCl, dried over P_2O_5 in vacuo,

and crystallized from benzene–acetone: mp 270–271 °C; IR 3300 (OH), 1625 (CO); ^{1}H NMR (acetone-d_6 + DMSO-d_6) 6.8–7.0 (m, 2 H, Ar-*H*, *o* to OH), 7.1–7.40 (m, 10 H, Ar-*H*), 7.95 (d, 1 H, *J* = 9.0 Hz, Ar-*H*, *o* to CO); MS *m*/*z* 314 (M^+). Anal. ($C_{21}H_{14}O_3$) C and H.

Sodium Borohydride Reduction of 1-Benzopyrylium Salt 11. To a cooled solution of 1-benzopyrylium salt **11**[18] (10.9 g) in dry DMF (200 mL) was added sodium borohydride (2.5 g) and the mixture stirred till the red color of the solution disappeared. The reaction mixture was neutralized with saturated ammonium chloride solution and extracted with ethyl acetate (2 × 200 mL). The organic layer was washed with water (2 × 150 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed over a column of silica gel, eluting first with hexane, to afford 2-(4-hydroxyphenyl)-3-phenyl-4*H*-1-benzopyran (**12**) (10.9 g), which was crystallized from benzene–hexane: mp 132–134 °C IR 3330 (OH); ^{1}H NMR 3.73 (s, 2 H, CH_2), 6.55 (d, 2 H, *J* = 9.0 Hz, Ar-*H*, *o* to OH), 6.85–7.26 (m, 11 H, Ar-*H*); MS *m*/*z* 300 (M^+). Anal. ($C_{21}H_{16}O_2$) C and H.

Further elution with 10% EtOAc–hexane furnished 1-(4-hydroxyphenyl)-2-phenyl-3-(2-hydroxyphenyl)propan-1-one (**14**) (1.6 g), which was crystallized from EtOAc–hexane: mp 189 °C; IR 1620 (CO), 3300–3500 (OH); ^{1}H NMR (acetone-d_6) 2.99 (dd, 1 H, *J* = 14.0 and 8.0 Hz, COC*H*CH$_2$), 3.4 (dd, 1 H, *J* = 14.0 and 8.0 Hz, COCHCH_2), 5.0 (t, 1 H, *J* = 8.0 Hz, –COC*H*–), 6.6–7.4 (m, 11 H, Ar-*H*), 7.73 (d, 2 H, *J* = 8.0 Hz, Ar-*H*, *o* to CO); MS *m*/*z* 318 (M^+). Anal. ($C_{21}H_{18}O_3$) C and H.

1-(4-Hydroxyphenyl)-2-phenyl-3-(2-hydroxyphenyl)-propan-1-ol (17). To a solution of the propanone **14** (100 mg) in methanol (10 mL), cooled in an ice bath, was added sodium borohydride (600 mg) and stirred for 12 h. The reaction mixture was concentrated in vacuo and the residue neutralized with a saturated NH_4Cl solution and the resulting precipitate filtered to obtain **17** (80 mg) which was crystallized from EtOAc–hexane: mp 216–218 °C; IR 3200–3510 (OH); ^{1}H NMR (acetone-d_6) 2.67–3.33 (m, 3 H, CHCH_2), 4.74 (d, 1 H, *J* = 5.0 Hz, C*H*OH), 5.01 (s, 1 H, O*H*, exchangeable H^+), 6.45–7.2 (m, 13 H, Ar-*H*); MS *m*/*z* 302 (M^+). Anal. ($C_{21}H_{20}O_3$) C and H.

2-(4-Hydroxyphenyl)-3-phenyl-2,3-dihydro-4*H*-1-benzopyran (18). To a solution of the alcohol **17** (500 mg) in ethanol (10 mL) was added ethanolic HCl (1 mL) and the mixture left at 4 °C for 12 h. A white crystalline material separated out which was filtered and crystallized from benzene–hexane to furnish **18** (350 mg): mp 179–80 °C; IR 3500 (OH); ^{1}H NMR 3.0–3.22 (m, 3 H, CHCH_2), 4.8–5.0 (m, 1 H, –OC*H*–), 6.49 (d, 2 H, *J* = 9.0 Hz, Ar-*H*, *o* to OH), 6.7–7.28 (m, 12 H, Ar-*H*); MS *m*/*z* 302 (M^+). Anal. ($C_{21}H_{18}O_2$) C and H.

2-(4-Hydroxyphenyl)-3-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-one (20) and 1-(2-Hydroxyphenyl)-2-phenyl-3-(4-hydroxyphenyl)prop-2-en-1-one (22). To a mixture of the desoxybenzoic **2** (53 g), 4-hydroxybenzaldehyde (30.5 g), and dry benzene (1 L) was added dry piperidine (1.5 mL). The mixture was heated under reflux for 30 h, removing water azeotropically, then cooled and washed with water (2 × 250 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was allowed to stand for 24 h. The solidified material was filtered off and washed with chloroform to afford the pyranone **20** (33 g) which was crystallized from EtOAc–hexane: mp 207 °C; IR 1680 (CO), 3400 (OH); ^{1}H NMR (acetone-d_6): 4.30 (d, 1 H, *J* = 12.0 Hz, –COC*H*–), 5.65 (d, 1 H, *J* = 12.0 Hz, –OC*H*–), 6.65 (d, 2 H, *J* = 8.0 Hz, Ar-*H*, *o* to OH), 6.90–7.30 (m, 9 H, Ar-*H*), 7.50 (td, 1 H, *J* = 8.0 and 2.0 Hz, Ar-*H*, *p* to CO), 7.80 (dd, 1 H *J* = 8.0 and 2.0 Hz, Ar-*H*, *o* to CO); MS *m*/*z* 316 (M^+). Anal. ($C_{21}H_{16}O_3$) C and H.

The combined filtrate left after removal of **20** was concentrated and the residue was chromatographed over a column of silica gel, with EtOAc–hexane (1:50, v/v) as eluant, to afford first the unreacted desoxybenzoin **1** then, on increasing the solvent polarity (1:10, v/v), the phenylchalcone **22** (26.5 g). It was crystallized from benzene–hexane, mp 146 °C; IR 1620 (CO), 3300 (OH); ^{1}H NMR 5.70 (br, 1 H, exchangeable H^+), 6.60 (d, 2 H, *J* = 8.0 Hz, Ar-*H*, *o* to OH), 6.70–7.50 (m, 1 H, Ar-*H* and olefinic H), 7.60 (dd, 1 H, *J* = 8.0 and 2.0 Hz, Ar-*H*, *o* to CO), 13.0 (*s*, 1 H, O*H*, *o* to CO); MS *m*/*z* 316 (M^+). Anal. ($C_{21}H_{16}O_3$) C and H.

2-(4-Hydroxyphenyl)-3-phenyl-7-methoxy-2,3-dihydro-4*H*-1-benzopyran-4-one (21) and 1-(2-Hydroxy-4-methoxyphenyl)-2-phenyl-3-(4-hydroxyphenyl)prop-2-en-1-one (23). These were obtained in about 30% overall yield by heating under reflux a mixture of 4-methoxybenzoin **1** (56 g) and 4-hydroxybenzaldehyde (30.5 g) in dry benzene (1 L) in the presence of dry piperidine (1.5 mL) followed by workup and purification as described for **20** and **22**. **21** (crystallized from EtOAc–hexane): mp 195 °C; IR 1680 (CO), 3450 (OH); ^{1}H NMR 3.80 (*s*, 3 H, OCH_3), 4.10 (d, 1 H, *J* = 12.0 Hz, –COC*H*–), 5.50 (d, 1 H, *J* = 12.0 Hz, –COC*H*–), 5.50 (d, 1 H, *J* = 12.0 Hz, –OC*H*–), 6.40–7.20 (m, 11 H, Ar-*H*), and 7.9 (d, 1 H, *J* = 8.0 Hz, Ar-*H*, *o* to CO); MS *m*/*z* 346 (M^+). Anal. ($C_{22}H_{18}O_4$) C and H.

23 (crystallized from benzene–hexane): mp 150 °C; IR 1620 (CO), 3400 (OH); ^{1}H NMR 3.70 (s, 3 H, OCH_3), 5.60 (br, 1 H, exchangeable H^+), 6.20 (dd, 1 H, *J* = 8.0 and 2.0 Hz, Ar-*H*, *p* to OH), 6.40 (d, 1 H, *J* = 2.0 Hz, Ar-*H*, *o* to OH), 6.60 (d, 2 H, *J* = 8.0 Hz, Ar-*H*, *o* to OH), 7.00–7.35 (m, 8 H, Ar-*H* and olefinic H), 7.50 (d, 1 H, *J* = 8.0 Hz, Ar-*H*, *o* to CO), 14.0 (s, 1 H, O*H*, *o* to CO); MS *m*/*z* 346 (M^+). Anal. ($C_{22}H_{18}O_4$) C and H.

2-(4-Hydroxyphenyl)-3-phenyl-2*H*-1-benzopyran (15). To a stirred solution of the 2-phenylchalcone **22** (31.6 g) in ethanol (150 mL), cooled to an ice bath, was added sodium borohydride in three portions at 15-min intervals and the stirring continued for 12 h. Ethanol was removed in vacuo and the residue adjusted to pH 8 with saturated ammonium chloride solution. It was extracted with EtOAc (2 × 200 mL), and the organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue upon chromatography over a column of silica gel eluting with EtOAc–hexane (1:10, v/v) furnished the 2*H*-1-benzopyran **15** (18 g), which was crystallized from benzene–hexane.

2-(4-Hydroxyphenyl)-3-phenyl-7-methoxy-2*H*-1-benzopyran (25). This was prepared in 60% overall yield starting from the 2-phenylchalcone **23** (34.6 g), according to the procedure detailed for **15**: mp 162 °C; IR 3350 (OH); ^{1}H NMR; 3.70 (s, 3 H, OCH_3), 5.50 (br, 1 H, exchangeable H^+), 6.20 (s, 1 H, –OC*H*–), 6.30–6.55 (m, 2 H, *J* = 8.0 Hz, Ar-*H*, *o* to OH), 6.90–7.40 (m, 11 H, Ar-*H* and olefinic *H*); MS *m*/*z* 330 (M^+). Anal. ($C_{22}H_{18}O_3$) C and H.

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 (E_2) was purchased from Steraloids Inc., activated charcoal, Norit A, from Sigma Chemicals, and Dextran T-70, from Pharamacia 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 microtiterplates by minor modification of the procedure reported earlier.[19] Briefly, 50-μL aliquots of cytosol (1 uterine equivalent/mL) were incubated at 4 °C for 18 h with increasing concentrations of the test compounds (10^{-4}–10^{-8} 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; ethylenediaminetetraacetic acid (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% v/v, respectively) in TEA buffer for 20 min. Radioactivity of 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, v/v mixture of methanol–dioxane and toluene containing 0.5% PPO (2,5-diphenyloxazole) 0.01% POPOP [1,4-bis(5-phenyloxazol-2-yl)benzene] and 9% naphthalene).

Bioassay. For uterotrophic assays indicated doses of the test compounds, suspended in 0.2 mL of propylene glycol–*N*-saline

(1:1, v/v) were injected subcutaneously to the animals, in groups of 6-9, on three consecutive days. The control group received similar injections of the vehicle alone. 24 h 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 different site. The control groups in this case received 1 μg of E_2 plus the vehicle alone at two different sites.

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Structure-Activity Relationship of Antiestrogens. Effect of the Side Chain and Its Position on the Activity of 2,3-Diaryl-2*H*-1-benzopyrans†

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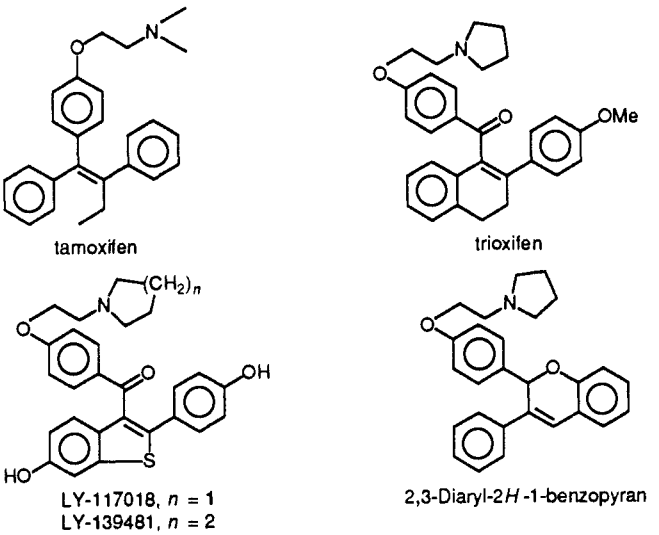
A series of 2,3-diaryl-2*H*-1-benzopyrans carrying a tertiary aminoethoxy chain at the ortho, meta, or para position of 2-phenyl or an alkyl at position 4 of the pyran ring were synthesized and evaluated for their affinity for estrogen receptor (ER) and for microsomal antiestrogen specific binding site and for their uterotrophic-antiuterotrophic activities in rodents. The analogues bearing the side chain at the para position of 2-phenyl were found to be active while those substituted at the meta and ortho positions were inactive as ER ligands as well as estrogen agonists-antagonists. Among para-substituted ethers, the 2-piperidinoethoxy analogue **5** was found to be a more effective antiestrogen than the corresponding pyrrolidino, dimethylamino, and related analogues. Incorporation of a methyl or an ethyl at C_4 in the pyran nucleus was found to increase receptor affinity of the prototypes. The ethyl was also found to potentiate agonist activity of the prototype while abolishing its antagonist activity. The piperidino analogue **5** was found to be a better antiestrogen than tamoxifen as well as LY-117018 in rats as well as mice. The prototypes were also found to have high affinity for the microsomal antiestrogen specific binding sites. The benzopyrans have thus emerged as a new group of potent antiestrogens.

Introduction

Our continuing efforts to extend the structure-activity relationship (SAR) among antiestrogens, so as to provide the guideline for design of potentially better antiestrogens, led us to undertake detailed explorations, first among triarylethylenes (TAEs) and then among (Z)-triarylpropenones (*Z*-TAPs). The latter, represented by trioxifen, LY-117018, and LY-139481 on the I) are known to possess a lesser degree of intrinsic agonist character than TAEs.[1-3] Though 7α-substituted estradiols have recently been reported to act as "pure" estrogen antagonists devoid of agonist activity,[4,5] the essential link between molecular structure and residual agonist activity in antiestrogens has remained an obscure one. Careful comparison between TAE and TAP antiestrogens promised to offer critical clues regarding this link. With this objective our initial studies among TAEs led first to the proposal of a working model for binding site on estrogen receptor (ER).[6] Following this, a study on TAPs, using certain acyclic analogues as models, led to the discovery of antiestrogenic activity in *E*-TAPs[7,8] and then, following this lead, in 2,3-diaryl-2*H*-1-benzopyrans (Chart I).[9] The 2,3-diaryl-2*H*-1-benzo-pyrans, in particular, were found to be comparable to TAP antiestrogens and better than TAEs in being associated with diminished agonist activity. The prototypes emerged as attractive models for further explorations on SAR of estrogen antagonists.

Chart I



The basic ether side chain is well recognized for its modulating influence on antagonist efficacy among TAE

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