(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.

Acknowledgment. We acknowledge Dr. Nitya Anand for his keen interest in this study. We are grateful to Dr. A. H. Todd of ICI Ltd., U.K., for providing a gift sample of tamoxifen, and to Dr. William R. Fields of Eli Lilly, for providing a gift sample of LY-117018.

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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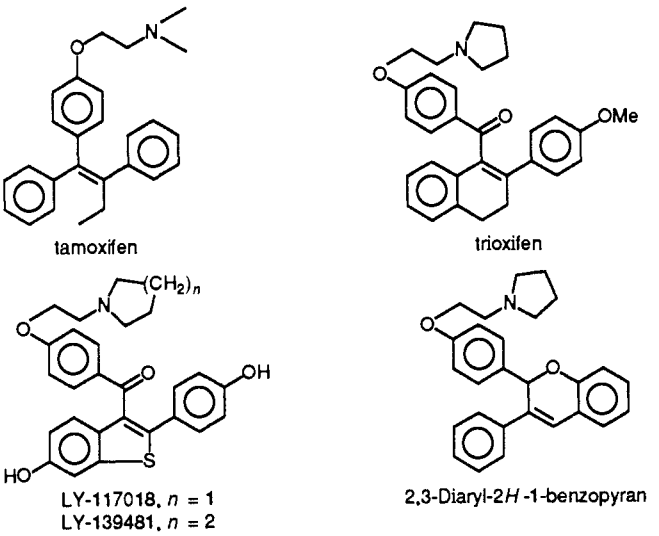
A series of 2,3-diaryl-2*H*-1-benzopyrans carrying a tertiary aminoethoxy chain at the ortho, meta, or para position of 2-phenyl or an alkyl at position 4 of the pyran ring were synthesized and evaluated for their affinity for estrogen receptor (ER) and for microsomal antiestrogen specific binding site 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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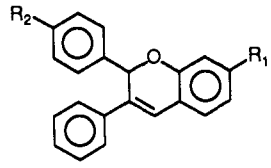
Chart II



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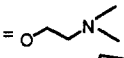
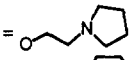
2: R_1 = OMe, R_2 = OH
3: R_1 = H, R_2 = 
4: R_1 = H, R_2 = 
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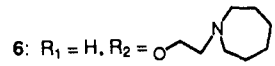
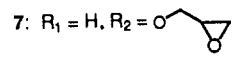
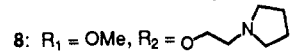
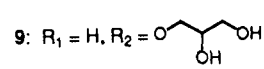
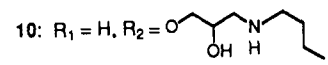
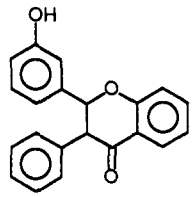
6: R_1 = H, R_2 = 
7: R_1 = H, R_2 = 
8: R_1 = OMe, R_2 = 
9: R_1 = H, R_2 = 
10: R_1 = H, R_2 = 

Chart III



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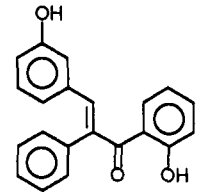
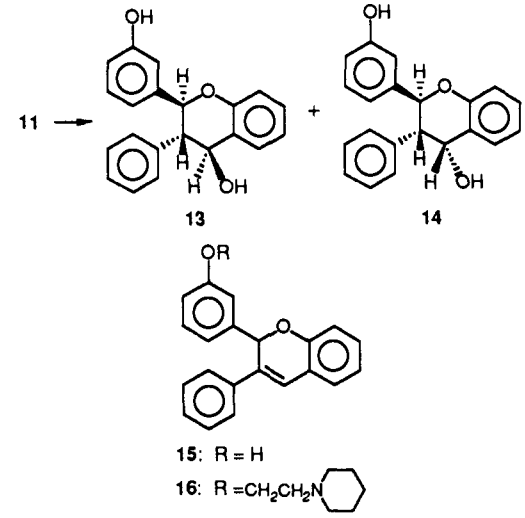


12

as well as TAP prototypes.[10-14] In this paper we report the effect of the side chain on antagonist activity of the benzopyrans. In addition, the effect of an alkyl at position 4 of pyran nucleus on receptor affinity and agonist-antagonist profile of the prototype has also been explored. This was of interest on account of the possibility that this alkyl may be congruent with the ethyl in tamoxifen and with the equivalent methylenes in trioxifen.

The discovery of an estrogen noncompetable site commonly termed as antiestrogen binding site (AEBS) in many estrogen target and nontarget organs[15-18] with which TAE antiestrogens interact has been the subject of considerable interest. Though the initial speculation about its involvement in estrogen antagonist activity of TAEs has been discounted,[19-20] the possibility remains that AEBS may have some role, even if indirect, in antitumor activity of the prototypes.[21-23] Accordingly we have undertaken an AEBS affinity study with the benzopyran antiestrogens so as to better define their possible potential as anticancer agents.

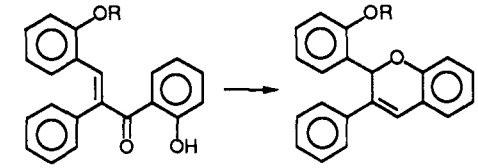
Scheme I



11 → 13 + 14

15: R = H
16: R = CH_2CH_2N

Scheme II



17: R = CH_2Ph
18: R = H

19: R = H
20: R = CH_2Ph
21: R = CH_2CH_2N 

Chemistry

Synthesis of the 2*H*-1-benzopyran phenols **1** and **2** and that of their ether derivatives **4** and **8** has been reported earlier.[9] The basic ethers **3**, **5**, and **6** and the oxirane ether **7** (Chart II) were prepared in the usual manner by alkylation of the phenol **1**. Solvolysis of the oxirane ether **7** in aqueous tetrahydrofuran using catalytic amount of perchloric acid furnished the glyceryl ether **9** while its reaction with *n*-butylamine in ethanol furnished the *n*-butylamine ether **10**.

The dihydrobenzopyranone phenol **11** and the 2-phenylchalcone phenol **12** (Chart III) were obtained as a separable mixture by base-catalyzed condensation of *m*-hydroxybenzaldehyde with 2′-hydroxydesoxybenzoin. In the pyranone **11** the phenyl residues were found to be trans on the basis of ^{1}H NMR spectrum as the doublets for 3-H and 2-H at δ 4.25 and 5.65, respectively, showed J values of 12.0 Hz.

The dihydrobenzopyran phenol **11** was subjected to sodium borohydride reduction in ethanol to afford a mixture of the diastereomeric alcohols **13** and **14** (Scheme I) which were separated by fractional crystallization. The characteristic feature in the ^{1}H NMR spectrum of **13** was a one proton triplet for 3-H at δ 3.15 (J = 12.0 Hz) and a two proton doublet at δ 5.5 (J = 12.0 Hz) for 2-H and 4-H, with the J values indicating trans axial relationship between all the protons. In the case of isomeric alcohol

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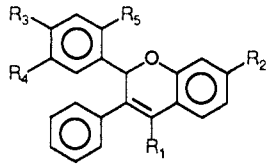
Table I. Melting Point, Receptor Affinity, and Estrogen Agonist-Antagonist Activities of the Indicated Benzopyran Derivatives



compd	R_1	R_2	R_3	R_4	R_5	mp, °C	RBA-ER[a]	RBA-AEBS[a]	estrogenic activity[b]	antiestrogenic activity[b]	% inhibition[c]
1	H	H	OH	H	H	ref 13	0.05 ± 0.01	ND[j]	12.6 ± 0.9	45.5 ± 2.1	0
3	H	H	ODa[d]	H	H	98	0.11 ± 0.06	98 ± 24	33.9 ± 2.2	36.5 ± 1.9	30
4	H	H	OPy[e]	H	H	ref 13	0.5 ± 0.1	134 ± 17	24.6 ± 2.6	26.2 ± 1.0	56
5	H	H	OPi[f]	H	H	87	0.3 ± 0.1	225 ± 26	14.8 ± 1.4	18.8 ± 2.1	75
6	H	H	OHp[g]	H	H	69–73	0.24 ± 0.02	153 ± 23	19.3 ± 2.3	23.1 ± 4.4	61
8	H	OMe	OPy[e]	H	H	ref 13	0.4 ± 0.2	66 ± 13	27.6 ± 1.7	28.3 ± 3.5	48
9	H	H	OGl[h]	H	H	oil	-	-	20.7 ± 3.4	38.8 ± 5.1	-
10	H	H	OnB[i]	H	H	oil	ND[j]	ND[j]	8.7 ± 0.5	45.9 ± 3.0	0
16	H	H	H	OPi[f]	H	200	<0.001	-	17.4 ± 1.7	42.2 ± 4.3	0
21	H	H	H	H	OPi[f]	118	<0.001	-	11.1 ± 2.6	43.1 ± 3.8	0
24	Me	H	OPy[e]	H	H	160	9.9 ± 1.9	150 ± 34	27.2 ± 1.9	27.0 ± 1.3	56
25	Et	OMe	OPy[e]	H	H	120–125	2.1 ± 0.4	51 ± 21	34.5 ± 2.8	40.6 ± 5.6	0

[a] The values represent the mean ± SD from at least three independent determinations in each case. Binding affinities for ER and AEBS are expressed in relation to that of E_2 and tamoxifen, respectively, taken as 100. [b] A 10 μg/rat dose of each compound was administered on three consecutive days. The values represent mean uterine weight ± SD in milligrams from six to nine animals. For antiestrogenic activity a 0.3 μg/rat dose of E_2 was coadministered. Control values are 45.1 ± 3.2 in case of animals receiving 0.3 μg of E_2 plus vehicle and 11.5 ± 0.9 in case of those receiving the vehicle alone. [c] 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. [d] Da = (Dimethylamino)ethyl. [e] Py = Pyrrolidinoethyl. [f] Pi = Piperidinoethyl. [g] Hp = Homopiperidinoethyl. [h] Gl = Glyceryl. [i] nB = (*n*-Butylamino)-2-hydroxypropyl. [j] ND = not detectable.

14, a one proton double doublet at δ 3.55 (J = 9.0 and 2.0 Hz), assignable to 3-H and a two proton multiplet between 5.4 to 5.6, assignable to 2-H and 4-H, revealed the cis relationship between 3-H and 4-H and equatorial orientation of 4-H. Both the alcohols were dehydrated by using piperidine–thionyl chloride to the common phenol **15** which was converted via alkylation to the ether **16**.

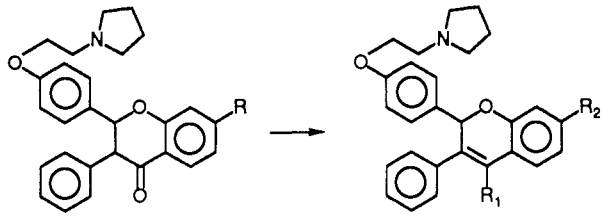
The 2*H*-benzopyran analogues featuring phenolic group at ortho position in 2-phenyl were approached as shown in Scheme II. The (benzyloxy)-2-phenylchalcone **17**, prepared by base-catalyzed condensation of *o*-(benzoyloxy)benzaldehyde with 2′-hydroxydesoxybenzoin, was debenzylated to the corresponding phenol **18** by using $BF_3{\cdot}Et_2O/Me_2S$. The phenol was then reduced with sodium borohydride and the resultant alcohol, when treated with concentrated HCl in ethanol, furnished the requisite benzopyran phenol **19**. Since the yield was rather poor, the (benzyloxy)-2-phenylchalcone **17** was reduced and cyclodehydrated similarly. The resultant (benzyloxy)-benzopyran **20**, obtained in good yield, was then debenzylated with $BF_3{\cdot}Et_2O/Me_2S$ to afford the benzopyran phenol **19**, which was then converted to the requisite ether **21** in good overall yield.

The benzopyran analogues **24** and **25**, featuring alkyl groups at position 4, were prepared by reacting the dihydrobenzopyranone ethers **22** and **23** with alkylmagnesium halides (Scheme III), followed by acid catalyzed dehydration of the alcohols thus obtained.

Results

Relative binding affinities (RBAs) of the test compounds for the cytosolic ER, obtained from rat uterus, were evaluated as reported previously.[24] Their estrogen agonist and antagonist activities were evaluated as detailedin experimental section. The compounds were also analyzed for their AEBS affinity according to the procedure reported earlier.[25]

Scheme III



22: R = H
23: R = OMe

24: R_1 = Me, R_2 = H
25: R_1 = Et, R_2 = OMe

ER and AEBS Affinities. RBA values of the benzopyran derivatives for ER are found to vary in a broad range not exceeding 10% that of E_2 (Table I). The benzopyran phenol **1** is a modest receptor ligand. Most of its ether derivatives have an order of magnitude better receptor affinity. The *n*-butylamine ether **10** is, however, devoid of receptor affinity while RBA of the glyceryl ether **9** was not evaluated. Among other ethers the progression of affinities follows the order: dimethylamino **3** < homopiperidino **6** < piperidino **5** < pyrrolidino ethyl ether **4**. The affinity of the pyrrolidinoethyl ether **4** remains almost unchanged upon incorporation of a methoxy at its 7 position (**4** vs **8**) while subsequent incorporation of an ethyl at position 4 causes marked increase in receptor affinity of the molecule (**8** vs **25**). Even more marked increase in affinity occurs in the pyrrolidinoethyl ether **4** upon incorporation of a methyl at position 4 (viz. compound **24**). Comparison of RBA of the ether **5** with that of the analogs **16** and **21** reveals that transposition of the side chain from para to meta or to ortho is detrimental to receptor affinity of the prototype.

The phenolic benzopyran **1** does not show any affinity for AEBS. All its ether derivatives, with the exception of the *n*-butylamine analogue **9**, however, show marked affinity of almost comparable magnitude for this site. The

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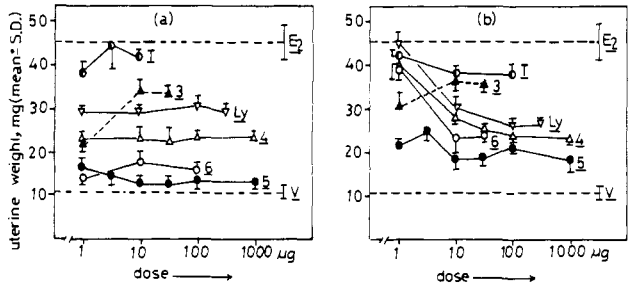

Figure 1. Uterotrophic (panel a) and antiuterotrophic (panel b) activities of dimethylamino- (**3**, ▲–▲), pyrrolidino- (**4**, Δ–Δ), piperidino- (**5**, ●–●), and homopiperidino- (**6**, O–O) benzopyrans and that of tamoxifen (T, ◐–◐) and LY-117018 (LY, ▽–▽) at the indicated doses in immature rats. Control group of animals received either the vehicle alone (V) or 0.3 μg of estradiol along with vehicle (E_2). The values represent mean uterine weight ± SD in milligrams from at least six animals in each case.

RBA of the methoxy analogues **8** and **25** however are on the lower side while the piperidino analogue **5** is a better ligand than other ether derivatives.

Estrogen Agonist and Antagonist Activities. As reported earlier[9] the benzopyran phenol **1** has been found to be inactive as agonist as well as antagonist. All its derivatives with the exception of the butylamino ether **10**, however, are active. The ethers **3–6** are mixed agonists antagonists, with their agonist and antagonist potencies showing a reciprocal relationship. Agonist potencies of the analogues decrease while antagonist potencies correspondingly increase in going from the dimethylamino ether **3** to the pyrrolidino ether **4**, to the homopiperidino ether **6** and to the piperidino ether **5**. The glyceryl ether **9** also shows weak agonist-antagonist activity. From a comparison of the data of compounds **5**, **16**, and **21** it is apparent that transposition of the side chain from para to meta or from para to ortho position is detrimental to agonist as well as antagonist activity of the prototype.

The incorporation of methoxy at position 7 does not cause any marked changes in activity of the pyrrolidino analogue (compound **4** vs **8**). Presence of an ethyl at position 4 on the other hand results in marked increase in agonist activity of compound **4** together with near loss of its antagonist activity (c.f. compound **25**). The activities of the ether **4** and its 4-methyl derivative **24**, however, are comparable.

The estrogen agonist and antagonist activities of the benzopyran analogues **3–6** were next compared with that of tamoxifen and LY-117018, in rats as well as mice. The results from this dose dependent study are shown in Figures 1 and 2. From the data it is noticed that the activity profiles of the analogues are comparable in the animal species used and follow trends that are similar to those noticed in the single dose study. Thus, the agonist activity of the analogues in rats follows the order **3** > **4** > **5** ≥ **6**, while their effectiveness as antagonist are in the order **3** < **4** ≤ **6** < **5**. When compared with tamoxifen, all the compounds are found to be weaker agonists and stronger antagonists in rats. In mice the activities of **3–5** follow a similar trend; all are much weaker agonists than tamoxifen and effective as antagonists while tamoxifen is not. In confirmation of the literature reports,[2] LY-117018 has been found to be a more effective antagonist than tamoxifen in both the animal species, while the benzopyran **5**, on the other hand, emerges as an even more effective antagonist in rats as well as mice. The activities of other benzopyran analogues are nearly comparable to that of LY-117018. A dose for dose comparison reveals that in both the species the benzopyran **5** evokes lower degree of

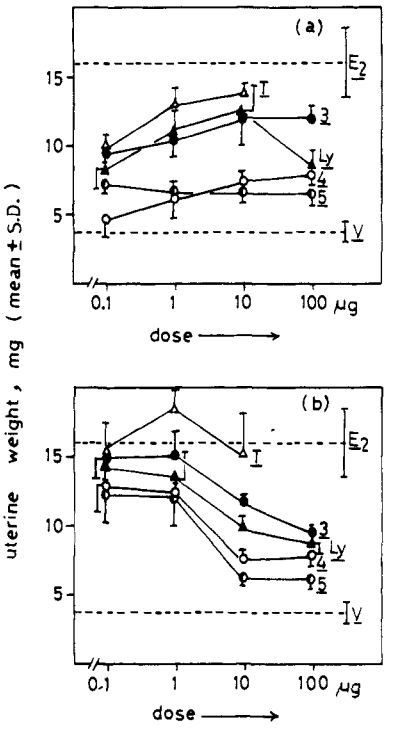

Figure 2. Uterotrophic (panel a) and antiuterophic (panel b) activities of the indicated benzopyran analogues and that of tamoxifen (T) and LY-117018 (LY) at indicated doses in immature mice. Control group of animals received either the vehicle alone (V) or 0.1 μg of estradiol along with vehicle (E_2). The values represent mean uterine weight ± SD in milligrams from at least seven animals in each case.

uterine weight gain than LY-117018 while it causes suppression of E_2-stimulated uterine growth to a significantly greater extent. Thus the piperidino analogue **5** is the most active antiestrogen in the benzopyran series causing nearly 75% inhibition in E_2-stimulated uterine growth in rats as well as mice. LY-117018, among the more effective antiestrogen hitherto known, is a comparatively poorer antagonist in both the animal species.

Discussion

These findings confirm the 2,3-diaryl-2*H*-1-benzopyrans as a new group of potent antiestrogens. The prototypes clearly are superior to TAEs in possessing diminished agonist activity and increased effectiveness as antagonist in rats as well as mice. The more potent members of the class are even superior to LY-117018 in both these respects.

The basic ether chain, known to be critical for TAE and TAP antiestrogens,[13,14] is an important determinant of antiestrogenic activity of the benzopyrans as well. As pointed out earlier, there seems to be a fundamental difference in the influence of the chain on the activity of the benzopyran as against that on the TAE antiestrogens. While the parent TAEs lacking in the side chain are well known to act as potent agonists, the benzopyran phenol **1** is inactive, both as agonist and antagonist. Only on provision of the chain does it become active as an antiestrogen. Apparently, the benzopyrans and the *Z*-TAPs resemble each other in this respect.

The contribution of the basic ether chain to ER affinity and estrogen-antagonist activity of the benzopyrans is structure as well as position specific. The prototype is active with the chain at para position and inactive with the chain at ortho or meta position in its 2-phenyl. The piperidino and homopiperidino groups in the side chain impart better antagonist activity to benzopyran than the pyrrolidino, the dimethylamino, the glyceryl, or the *n*-

butylamino groups. The progression of activity appears to be similar to that reported in the LY series of antiestrogens.[14] Among TAEs, on the other hand, pyrrolidino residue is commonly recognized as the optimum for antagonist activity.[13,26]

The study of the effect of an alkyl at C_4 in benzopyrans was an important objective, in view of the possibility that these alkyls may be congruent to those at the corresponding position in tamoxifen and trioxifen. The results indicate that indeed the alkyls impart increased receptor affinity to the benzopyrans. The presence of ethyl, though not of methyl, also potentiates agonist activity of the prototype while decreasing its antagonist activity to an almost imperceptible level. The relationship thus perceived between presence of ethyl and increased agonist activity in benzopyrans is significant and may explain why trioxifen (bearing a sulfur) and tamoxifen (bearing an ethyl) are partial agonists while MER-25 (bearing an H) is a full antagonist devoid of agonist activity.

The benzopyran antiestrogens have also been found to be good AEBS ligands some of them more potent than tamoxifen. However, as established by others in TAE and related series of compounds, this appears only to be incidental to the action of benzopyrans as estrogen antagonists. It remains to be seen if benzopyrans would have any activity in the MCF-7 cell line or against mammary tumors, and if they do, whether high AEBS affinity might confer them any advantage over tamoxifen.

Experimental Section

The melting points were determned on a Towson and Mercer's (U.K.) apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 157 and 177 or on Beckman Acculab-1 or Acculab-10 instruments as KBr wafers or as neat films and the values are given in the cm^{-1} scale. The ^1H NMR spectra were recorded either on Varian CFT-20 or on Perkin-Elmer R-32 or on Varian EM-360 L spectrometers with tetramethylsilane as internal standard and $CDCl_3$ as solvent, unless indicated otherwise. The values are given in the δ scale. The mass spectra were recorded 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.

General Method for Synthesis of Ethers. The basic ethers **3**, **5**, **6**, **16**, and **21** and the oxirane ether **7** were synthesized by using the following general procedure.

A mixture of phenol 1[9] (1 mmol), 1-(2-chloroethyl)alkylamine hydrochloride or epichlorohydrin (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 was chromatographed over a column of basic alumina (for basic ethers) or silica gel (for oxirane ether) with EtOAc–hexane (1:50, v/v) as eluant to furnish the requisite ethers (yield 80‰) as oils. The ethers were crystallized as such from hexane or as oxalate salts from EtOAc–ether. The spectral and analytical data of the ethers are given below:

2-[4-[2-(*N*,*N*-Dimethylamino)ethoxy]phenyl]-3-phenyl-2*H*-1-benzopyran (3): ^1H NMR 2.10 (s, 6 H, $N(CH_3)_2$), 2.55 (t, 2 H, J = 6.0 Hz, $-OCH_2CH_2-$), 3.85 (t, 2 H, J = 6.0 Hz, OCH_2CH_2), 6.10 (s, 1 H, $-OCH-$), 6.60–7.30 (m, 14 H, ArH and olefinic H); MS m/z 371 (M^+). Anal. ($C_{25}H_{25}O_2N$) C, H, and N.

2-[4-(2-Piperidino)ethoxy)phenyl]-3-phenyl-2*H*-1-benzopyran (15): ^1H NMR 1.3–1.7 (m, 6 H, $-CH_2(CH_2)_3CH_2-$), 2.15–2.4 (m, 4 H, $-CH_2N\,CH_2-$), 2.5 (t, 2 H, J = 6.0 Hz, $-OCH_2CH_2-$), 3.85 (t, 2 H, J = 6.0 Hz, $-OCH_2CH_2-$), 6.1 (s, 1 H, $-OCH-$), 6.8–7.4 (m, 14 H, Ar-H and olefinic H); MS m/z 411 (M^+). Anal. ($C_{28}H_{29}O_2N$) C, H, and N.

2-[4-(2-Homopiperidinoethoxy)phenyl]-3-phenyl-2*H*-1-benzopyran (6): ^1H NMR 1.5 (br s, 8 H, $-CH_2(CH_2)_4CH_2-$), 2.5–2.75 (m, 4 H, $-CH_2NCH_2-$), 2.8 (t, 2 H, J = 6.0 Hz, $-OCH_2CH_2-$), 3.85 (t, 2 H, J = 6.0 Hz, $-OCH_2CH_2-$), 6.05 (s, 1 H, $-OCH-$), 6.6–7.3 (m, 14 H, Ar-H and olefinic H); MS m/z 425 (M^+). Anal. ($C_{29}H_{31}O_2N$. CO_2H H_2O) C, H, and N.

2-[4-(2,3-Epoxypropoxy)phenyl]-3-phenyl-2H-1-benzopyran (7): ^1H NMR (CCl_4) 2.4–2.6 (m, 2 H, $OCH(O)CH_2$), 2.9–3.1 (m, 1 H, $CH(O)CH_2$), 3.8 (d, 2 H, J = 4.0 Hz, OCH_2CH_2), 6.0 (s, 1 H, $-OCH-$), 6.4–7.3 (m, 14 H and olefinic H); MS m/z 356 (M^+), 299 ($M^+ - 57$).

2-[3-(2-Piperidinoethoxy)phenyl]-3-phenyl-2*H*-1-benzopyran (16): ^1H NMR (CCl_4) 1.3–1.7 (m, 6 H, $-CH_2(CH_2)_3CH_2-$), 2.2–2.4 (m, 4 H, $-CH_2NCH_2-$) 2.5 (t, 2 H, J = 6.0 Hz, $-OCH_2CH_2-$), 3.8 (t, 2 H, J = 6.0 Hz, OCH_2), 6.0 (s, 1 H, $-OCH-$), 6.5–7.3 (m, 14 H, Ar-H and olefinic H); MS m/z 411 (M^+).

2-[2-(2-Piperidinoethoxy)phenyl]-3-phenyl-2*H*-1-benzopyran (21): ^1H NMR 1.3–1.7 (m, 6 H, $-CH_2(CH_2)_3CH_2-$), 2.4–2.7 (m, 4 H, CH_2NCH_2-), 2.8 (t, 2 H, J = 6.0 Hz, OCH_2CH_2), 4.15 (t, 2 H, J = 6.0 Hz, OCH_2CH_2), 6.55–7.35 (m, 15 H, Ar-H, $-OCH$, and olefinic H); MS m/z 411 (M^+).

2-[4-(2,3-Dihydroxypropoxy)phenyl]-3-phenyl-2*H*-1-benzopyran (9). To a solution of epoxide **7** (712 mg) in tetrahydrofuran (50 mL) and water (0.1 mL) was added $HClO_4$ (70%, 0.05 mL). After 24 h the solution ws concentrated, and residue was dissolved in EtOAc (50 mL). The organic layer was washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed over a column of silica gel, with EtOAc–hexane (1:4, v/v) as eluant, to afford glycerylbenzopyran **9** (600 mg) as an oil: IR 3400 (OH); ^1H NMR 3.65 (br s, 3 H, $-OCH_2CH(OH)-$), 6.8 (s, 1 H, $-OCH-$), 6.55–7.4 (m, 14 H, Ar-H and olefinic H): MS m/z 374 (M^+).

2-[4-[2-Hydroxy-3-(*n*-butylamino)propoxy]phenyl]-3-phenyl-2*H*-1-benzopyran (10). A solution of epoxide **7** (1.07 g) and *n*-butylamine (0.3 mL) in ethanol (20 mL) was heated under reflux for 30 min. The solution was concentrated, and the residue was chromatographed over a column of silica gel, with EtOAc–hexane (1:4, v/v) as eluant, to afford **10** (772 mg) as an oil: IR 3400 (OH and NH); ^1H NMR (CCl_4) 0.7–0.9 (m, 3 H, CH_3), 1.2–1.4 (m, 4 H, $NHCH_2(CH_2)_2CH_3$), 1.8 (s, 1 H, NH), 2.4–2.6 (m, 4 H, CH_2NCH_2), 3.5–3.8 (m, 3 H, $-OCH_2CH(OH)-$), 6.0 (s, 1 H, $-OCH-$), 6.4–7.3 (m, 14 H, Ar-H and olefinic H); MS m/z 429 (M^+).

2-(3-Hydroxyphenyl)-3-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-one (11) and 1-(2-Hydroxyphenyl)-2-phenyl-3-(3-hyroxyphenyl)prop-2-en-1-one (12). To a solution of 2′-hydroxydesoxybenzoin[27] (26.5 g) and 3-hydroxybenzaldehyde (15.3 g) in dry benzene (300 mL) was added dry piperidine (0.75 mL). The mixture was heated under reflux for 30 h, while water was removed aziotropically. After the reaction mixture was cooled, it was washed with water (2 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed over a column of silica gel, with EtOAc–hexane (1:20, v/v) as eluant, to furnish first unreacted 2′-hydroxydeoxybenzoin, then on increasing solvent polarity (1:5 v/v), 2-phenylchalcone **12** (11.9 g), which was crystallized from benzene–hexane: mp 143 °C; IR 3400 (OH), 1620 (CO); ^1H NMR (CCl_4 + $CDCl_3$) 5.40 (br s, 1 H, exchangeable H), 6.40–7.35 (m, 13 H, Ar-H and olefinic H), 7.45 (dd, 1 H, J = 8.0and 2.0 Hz, Ar-H, o to CO), 14.00 (s, 1 H, OH, o to CO); MS m/z 316 (M^+). Anal. ($C_{21}H_{16}O_3$) C and H. Further elution with EtOAc–hexane (1:5, v/v) afforded the dihydrobenzopyranone **11** (13.5 g) which was crystallized from EtOAc–hexane: mp 196 °C; IR 3450 (OH), 1680 (CO); ^1H NMR (acetone-d_6) 4.25 (d, 1 H, J = 12.0 Hz, $-COCH-$), 5.65 (d, 1 H, J = 12.0 Hz, $-OCH-$), 6.5–7.1 (m, 11 H, Ar-H), 7.5 (dd, 1 H, J = 8.0 and 2.0 Hz, Ar-H, p to CO), 7.8 (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.

2-(3-Hydroxyphenyl)-3-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-ol (13 and 14). A stirred solution of the dihydrobenzopyranone **11** (3.16 g) in ethanol (15 mL) was cooled in an ice bath. Sodium borohydride (800 mg) was added in three

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portions at 15-min intervals. After 12 h, the solvent was removed in vacuo and residue neutralized with saturated ammonium chloride solution (50 mL). The mixture was then extracted with EtOAc (2 × 100 mL), and the organic layer was washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated. The residue, upon fractional crystallization from chloroform–hexane, furnished the dihydropyranols **13** (1.1 g) and **14** (1.0 g) as homogeneous compounds.

13: mp 188 °C; IR 3400–3200 (OH); ^{1}H NMR (acetone-d_6) 3.15 (t, 1 H, J = 12.0 Hz, –(OH)CHC*H* CHO–), 5.50 (d, 2 H, J = 12.0 Hz, –(OH)C*H*CH C*H*O–), 6.40–7.30 (m, 12 H, Ar-*H*), 7.5 (dd, 1 H, J = 8.0 Hz, Ar-*H*, *o* to –(OH)CH–); MS m/z 318 (M^+). Anal. ($C_{21}H_{18}O_3$) C and H.

14: mp 154 °C; IR 3400–3200 (OH); ^{1}H NMR (acetone-d_6) 3.55 (dd, 1 H, J = 9.0 and 2.0 Hz, –(OH)CHC*H*CHO–), 5.3–5.4 (m, 2 H, –(OH)C*H*CHC*H*O), 6.45–7.25 (m, 12 H, Ar-*H*), 7.5 (dd, 1 H, J = 8.0 Hz, Ar-H, *o* to –(OH)CH–): MS m/z 318 (M^+). Anal. ($C_{21}H_{18}O_3$) C and H.

2-(3-Hydroxyphenyl)-3-phenyl-2*H*-1-benzopyran (15). A solution of the dihydrobenzopyranol **13**/**14** (1.92 g) in dry pryidine was cooled in an ice bath, and freshly distilled thionyl chloride (1 mL) was added dropwise. The reaction mixture was allowed to stand for 3 h at room temperature and then cooled again in an ice bath, and water (5 mL) was added dropwise. The reaction mixture was then extracted with EtOAc (2 × 150 mL), and the organic layer was washed with water (5 × 50 mL), dried (Na_2SO_4), and concentrated. The residue on chromatography over a column of silica gel, with EtOAc–hexane (1:20, v/v) as eluent, furnished **15** (800 mg) as an oil: IR 3500 (OH); ^{1}H NMR 6.10 (s, 1 H, –C*H*O–) and 6.50–7.45 (m, 14 H, Ar-*H* and olefinic H); MS m/z 300 (M^+).

1-(2-Hydroxyphenyl)-2-phenyl-3-[2-(benzyloxy)phenyl]-prop-2-en-1-one (17). To a solution of 2-(benzyloxy)benzaldehyde (6.4 g) and the 2′-hydroxydesoxybenzoin (6.4 g) in dry benzene (100 mL) was added dry piperidine (0.15 mL). The solution was heated under reflux for 10 h while water was removed aziotropically, and then it was cooled and concentrated. The oily residue was crystallized from benzene–hexane to furnish **17** (10 g): mp 90 °C; IR 1630 (CO); ^{1}H NMR 5.00 (s, 2 H, OCH_2Ph), 6.70–7.40 (*m*, 18 H, Ar-*H* and olefinic *H*), 7.75 (dd, 1 H, J = 8.0 Hz, Ar-*H*, *o* to CO), 15.00 (s, 1 H, O*H*, *o* to CO); MS m/z 406 (M^+). Anal. ($C_{28}H_{22}O_3$) C and H.

2-(2-Hydroxyphenyl)-2-phenyl-3-(2-hydroxyphenyl)prop-2-en-1-one (18). To a stirred solution of (benzyloxy)-2-phenylchalcone **17** (406 mg) in dichloromethane (1 mL) were added BF_3·Et_2O (0.3 mL) and Me_2S (1 mL). The stirring was continued for 3 h, and then the reaction mixture was poured into water, and the product was extracted with EtOAc (2 × 50 mL). The organic layer was washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated. The oily residue was crystallized from dichloromethane-hexane to furnish **18** (300 mg): mp 166–170 °C; IR 1630 (CO), 3550 (OH); ^{1}H NMR ($CDCl_3$ + acetone-d_6) 6.50–7.50 (m, 13 H, Ar-*H*), 7.75 (*d*, 1 H, J = 8.0 Hz, Ar-*H*, *o* to CO), 15.00 (s, 1 H, -*OH*, *o* to CO); MS m/z 316 (M^+). Anal. ($C_{21}H_{16}O_3$) C and H.

2-(2-Hydroxyphenyl)-3-phenyl-2*H*-1-benzopyran (19). To a stirred solution of 2-phenylchalcone **18** (316 mg) in ethanol (30 mL) was added sodium borohydride (100 mg), and stirring was continued for 8 h. Ethanol was then removed in vacuo and the residue adjusted to pH 8 with saturated ammonium chloride solution. The mixture was extracted with EtOAc (2 × 50 mL), and the organic layer was washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed over a column of silica gel, with EtOAc–hexane (1:20, v/v) as eluant, to afford **19** (90 mg) as an oil, which was crystallized from benzene–hexane: mp 140 °C; IR 3550 (OH); ^{1}H NMR 6.6 (s, 1 H, –OC*H*–), 6.4–7.4 (m, 14 H, Ar-*H* and olefinic *H*); MS m/z 300 (M^+). Anal. ($C_{21}H_{16}O_2$) C and H.

2-[2-(Benzyloxy)phenyl]-3-phenyl-2*H*-1-benzopyran (20). To a solution of (benzyloxy)-2-phenylchalcone **17** (1.62 g) in ethanol (20 mL) was added sodium borohydride (100 mg), and the reaction mixture was stirred for 24 h. Concentrated HCl (0.1 mL) was then added dropwise to it, and the mixture was heated under reflux for 4 h, and then it was cooled and concentrated in vacuo. The residue was taken up in EtOAc (100 mL) and the solution washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated. The oily residue was crystallized from dichloromethane–hexane to afford **20** (1.25 g): mp 130–132 °C; ^{1}H NMR 5.15 (s, 2 H, OCH_2Ph), 6.55–7.55 (m, 20 H, Ar-*H* and olefinic *H*); MS m/z 390 (M^+). Anal. ($C_{28}H_{22}O_2$) C and H.

A mixture of compound **20** (1 mmol) with dichloromethane (1 mL), BF_3·Et_2O (0.3 mL), and Me_2S (1 mL) when stirred for 3 h and then worked up as described for preparation of **18** furnished the debenzylated compound **19** in good yield.

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-one (22). A mixture of dihydrobenzopyranone phenol[9] (1.9 g) 1-(2-chloroethyl)pyrrolidine hydrochloride (1.7 g), sodium carbonate (1.5 g), and dry acetone was stirred and heated under reflux for 36 h. The mixture was cooled and filtered. The combined filtrate was concentrated, and the residue was chromatographed over a column of neutral alumina, with EtOAc–hexane (1:50, v/v) as eluant, to afford **22** (1.12 g) as an oil: IR 1700 (CO); ^{1}H NMR 1.60–2.00 (m, 4 H, –CH_2-(CH_2)$_2$$CH_2$–), 2.45–2.75 (m, 4 H, –$CH_2NCH_2$–), 2.8 (t, 2 H, J = 6.0 Hz, –OC$H_2$$CH_2$–), 4.00 (t, 2 H, J = 6.0 Hz, –O$CH_2$$CH_2$–), 4.10 (d, 1 H, J = 12.0 Hz, –COC*H*–), 5.50 (d, 1 H, J = 12.0 Hz, –OC*H*–), 6.60–7.30 (m, 12 H, Ar-H), 7.80 (dd, 1 H, J = 8.0 Hz, Ar-H, *o* to CO); MS m/z 413 (M^+).

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-4-methyl-2*H*-1-benzopyran (24). To a stirred suspension of Grignard reagent prepared from magnesium–iodine (200 mg:20 mg, w/w) in dry ether (20 mL) and methyl iodide (75 mL), and cooled in an ice bath, was added dropwise a solution of the dihydrobenzopyranone **22** (826 mg) in dry ether (20 mL). The reaction mixture was then heated under reflux for 6 h, and then it was cooled and treated with saturated ammonium chloride solution (20 mL). The mixture was extracted with ether; the extract was washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was taken up in ethanol (20 mL), mixed with concentrated HCl (0.01 mL), and heated under reflux for 4 h. The resulting mixture was then concentrated in vacuo and the residue treated with saturated sodium carbonate solution (2 × 20 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue upon chromatography over a column of basic alumina, eluting with EtOAc-hexane (1:50, v/v), furnished **24** (210 mg), which was crystallized as an oxalate salt from benzene–hexane: mp 160 °C; ^{1}H NMR 1.50–1.90 (m, 4 H, –CH_2(CH_2)$_2$$CH_2$–), 2.00 (s, 3 H, CH_3), 2.45–2.75 (m, 4 H, –CH_2NCH_2–), 2.80 (t, 2 H, J = 6.0 Hz, –OC$H_2$$CH_2$–), 4.00 (t, 2 H, J = 6.0 Hz, –O$CH_2$$CH_2$–), 5.85 (s, 1 H, –OC*H*–) and 6.50–7.30 (m, 13 H, Ar-H); MS m/z 411 (M^+). Anal [$C_{28}H_{29}NO_2$·$^1/_2$($C_2H_2O_4$·$2H_2O$)] C, H, and N.

2-[4-(2-Pyrrolidinoethoxy)phenyl]-3-phenyl-4-ethyl-7-methoxy-2*H*-1-benzopyran (25). This compound was prepared with the dihydrobenzopyranone ether **23**[9] (443 mg) and ethyl magnesium iodide as starting material according to the procedure described for **24**. The product (352 mg) was crystallized as an oxalate salt from benzene–hexane: mp 120–125 °C; ^{1}H NMR 1.10 (t, 3 H, J = 6.0 Hz, CH_2CH_3), 1.50–1.90 (m, 4 H, –CH_2(CH_2)$_2$$CH_2$–), 2.40–2.70 (m, 6 H, CH_2CH_3 and –CH_2NCH_2–), 2.80 (t, 2 H, J = 6.0 Hz, –OC$H_2$$CH_2$–), 3.65 (s, 3 H, O$CH_3$), 4.00 (t, 2 H, J = 6.0 Hz, –OC$H_2$$CH_2$–) 5,70 (s, 1 H, –OC*H*–), 6.30–6.50 (m, 2 H, Ar-*H*, *o* to OCH_3), 6.70 (d, 2 H, J = 8.0 Hz, Ar-*H*, *o* to –O$CH_2$$CH_2$–), 6.90–7.30 (m, 10 H, Ar-*H*); MS m/z 455 (M^+).

Biology. Materials. [2,3,6,7-^{3}H]Estradiol (^{3}H-E_2, 100 Ci mmol^{-1}) and [*N*-Methyl-^{3}H]tamoxifen (^{3}H-Tam, 76 Ci mmol^{-1}) were purchased from New England Nuclear Corp. and were assessed as 95% radiochemically pure by use of a Panax radio TLC scanner. Unlabeled estradiol (E_2) was obtained from Steraloids Inc., activated charcoal, Norit A, from Sigma Chemicals, and Dextran T-70, from Pharmacia Fine Chemicals. All other chemicals and reagents were of analytical or scintillation grade. Female mice (21–23 days old; 8–12 g body weight) and rats (21–23 days old; 25–40 g body weight) of Swiss and Charles Foster strain, respectively, were obtained from the Central Drug Research Institute, Lucknow rodent colony. For ER binding experiments the rats were primed subcutaneously with 0.1 μg of E_2 each, 24 h prior to sacrifice, to increase yield of the receptor protein in their uteri.

Competition Experiments. ER binding experiments were a minor modifications of the previously reported procedure.[24] Briefly, 50-μL aliquots of cytosol (one uterine equivalent per milliliter of TEA buffer) were incubated at 4 °C for 18–20 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). 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 dimethylformamide (DMF). Free and bound ^{3}H-E_2 were seaprated by treating each incubate 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 minivials containing 5 mL of scintillation fluid (1.5:2.5:2.5, v/v mixture of methanol–dioxane–toluene containing 0.5% PPO (2,5-diphenyloxazole), 0.01% POPOP [1,4-bis(5-phenyloxazol-2-yl)benzene], and 9% naphthalane).

The competition experiments with liver microsomal fraction, using ^{3}H-Tam as the reference ligand, were performed according to previously reported procedure.[25] The liver microsomal fractions were first incubated at 4 °C for 2 h, with 2 μM diethylstibestrol added in a small volume of DMF to saturate ER sites. Aliquots (200 μL) of the fraction were then mixed in a Pyrex glass tube with 20 μL of competitor (1×10^{-9} M to 3×10^{-6} M) and 20 μL of ^{3}H-Tam (1×10^{-9} M) dissolved in 35% DMF–TEA buffer. The tubes were incubated for 18 h at 4 °C and then treated with charcoal–dextran slurry (100 μL) for 15 min at 4 °C to separate bound and free ^{3}H-Tam. The tubes were centrifuged at 1000*g* for 15 min, and the supernatants were counted for radio activity.

Uterotrophic and Antiuterophic Activity. For uterotrophic activity various doses of the test compounds, suspended in 0.1 mL of propylene glycol–0.9% saline (1:1, v/v), were injected subcutaneously to the test animals on three consecutive days, while the control group of animals received the vehicle alone. Antiuterotrophic assay was similarly performed by administering various doses of test compounds and 0.3 μg of E_2 in the case of rats and 0.1 μg of E_2 in the case of mice, each suspended in 0.1 mL of propylene glycol–0.9% saline (1:1, v/v), to the test animals a two different sites, while the control group of animals received the injection of E_2 and the vehicle alone. Animals were autopsied 24 h after last injection and their uterine weights were recorded in the usual manner.

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Structure–Activity Relationship of Antiestrogens. Phenolic Analogues of 2,3-Diaryl-2*H*-1-benzopyrans†

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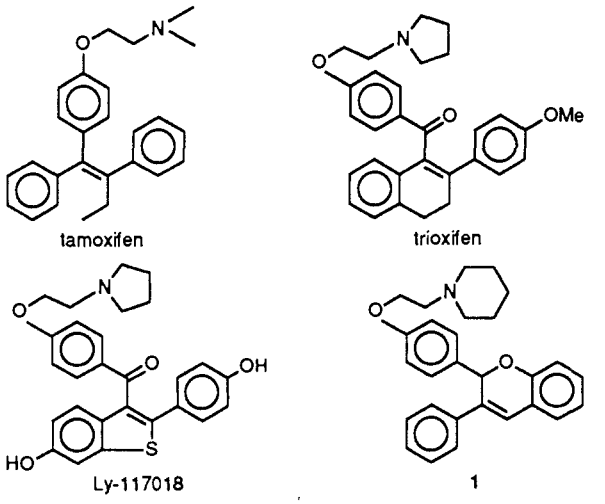
Phenolic analogues of 2-[4-(2-piperidinoethoxy)phenyl]-3-phenyl-2*H*-1-benzopyran (1), a novel antiestrogen, were synthesized and evaluated for their structure–activity relationship. Incorporation of OH at position 7 was found to improve receptor affinity of the benzopyran while having no effect on its action as an antagonist. Similar substitution of 2-phenyl as well potentiated receptor affinity as well as antagonist activity of the prototype. The monophenol **19** and the diphenol **25** were thus found to be good receptor ligands, devoid of estrogen agonist activity and associated with marked antiestrogenic activity of comparable order. Both caused nearly complete inhibition of the estradiol stimulated uterine growth in rats as well as mice and were thus found to be better antiestrogens than tamoxifen, trioxifen, and LY-117018. A binding-site model for estrogen receptor rationalizing the structure–activity relationship of benzopyrans in relation to that of the triarylethylene and the triarylpropenone antiestrogens has been discussed.

Introduction

The triarylethylene (TAE) and (*Z*)-1,2,3-triarylpropen-1-one (TAP) antiestrogens, represented by tamoxifen, trioxifen, and LY-117018 (Chart I), are well recognized as being partial agonists–antagonists.[1-6] Our continuing efforts to study structure–activity relationship (SAR) of antiestrogens,[7-13] so as to unravel the molecular origins of their partial agonist character, resulted recently in the development of 2,3-diaryl-2*H*-1-benzopyran (DABP) as yet another group of potent antiestrogens.[12,13] The ensuing studies on SAR resulted in 2-[4-(2-piperidinoethoxy)-phenyl]-3-phenyl-2*H*-1-benzopyran (1) (Chart I) as a potent antiestrogen possessing weaker agonist character than tamoxifen as well as LY-117018.[13] In this paper we focus on the effect of hydroxyl groups on agonist–antagonist profile of the DABP prototypes. This was of interest on account of the known propensity of OH groups, when at

Chart I



4,4′-position of the *trans*-stilbene core, to impart improved activity to TAE as well as TAP antiestrogens.[2-4,14] The

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