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Preliminary communication

Synthesis and post-coital contraceptive activity of a new series of substituted 2,3-diaryl-2*H*-1-benzopyrans

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Summary — A series of substituted 2,3-diaryl-2*H*-1-benzopyrans have been synthesized and screened for their post-coital contraceptive activity in rats. Most of the compounds showed 100% inhibition in a single day schedule at a dose level of 1.0 mg/kg. Compound **32** was found to be the most active with a minimum effective dose (MED) of 0.2 mg/kg in single day testing. Further, it also showed high antiestrogenic activity and is devoid of any agonistic activity.

benzopyran / antiestrogenic activity / post-coital contraceptive

Introduction

Antiestrogens are compounds that block uterine growth and the growth of estrogen-dependent mammary tumors. They are also effective in the control of diverse neoplastic diseases [1], endocrine disorders and, most importantly, can be used against reproductive hormones to regulate fertility [2].

Several non-steroidal antiestrogens belonging to diverse classes, such as stilbenes [3], ethanes [4], 2-phenylindoles [5], phenylindenes [6], benzofurans [7], benzothiophenes [8], benzocarbazoles [9], triarylethylenes [10–12], have shown estrogen antagonistic activity. Tamoxifen [13], a representative of the triarylethylene (TAE) group, is an established therapeutic agent for estrogen-dependent tumors, principally breast cancers. Centchroman [14], another potent antiestrogen of the same class, has recently been introduced to the Indian market as the first non-steroidal oral contraceptive. Recently, triarylpropenones (TAPs) have emerged as a new class of non-steroidal antiestrogens [15, 16] better than TAEs and some of their acyclic derivatives were shown to possess antifertility activity [17–19]. Encouraged by these findings and continuing our efforts further in the design and synthesis of more atypical estrogens which may possess antifertility activity, our interest was directed towards the synthesis of TAP prototypes. Since acyclic TAPs were conformationally labile, existing as *Z* and *E* isomers with *Z* isomers more effective than *E*, efforts were made to design compounds incorporating *E*- and *Z*-TAPs in a conformationally constrained molecular framework. Suitably substituted 2-aryl-1-benzofurans were synthesized as conformationally constrained models for *Z*-TAPs and TAEs and 2,3,4-triarylfurans as models for *E*-TAPs. These were screened for antiestrogenic and antifertility activities. Neither of the prototypes exhibited any significant antagonistic activity [20]. The results necessitated further modification in the pharmacophore. Armed with a better understanding of receptor binding mode of TAPs, suitable modifications helped in the development of 2,3-diaryl-2*H*-1-benzopyrans as a new class of potent antiestrogens [21, 22] possessing potential antiimplantation activity [23].

In a continuation of our earlier work [21, 22, 24] we have synthesized several new analogues of 2,3-substituted diaryl-2*H*-1-benzopyrans. Thus in the present communication, we report the synthesis and post-coital contraceptive activity of a series of compounds which possess the benzopyran nucleus with various substituents like alkyl/alkoxy/halogen, etc, at the 4'-position of 2-phenyl ring and 7-position of the benzopyran nucleus.

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Chemistry

Variously substituted 2,3-diaryl-2*H*-1-benzopyran analogues were synthesized as follows. Deoxybenzoins **1–10** with alkoxy/alkyl and halogen substituents in the 4 and 4' positions were synthesized by Fries rearrangement of the respective phenyl-(4-substituted phenyl) acetates, which in turn were obtained in almost quantitative yield by reacting 4-methoxyphenylacetyl chlorides with different phenols. The desired 2-hydroxy isomers were isolated from the reaction mixture in a pure form by column chromatography over silica gel. Deoxybenzoins carrying hydroxy groups were prepared by demethylation of methoxy benzoins and subsequently protected as tetrahydropyranyl ethers (table I). Base-catalysed condensation of substituted or protected deoxybenzoins with 4-hydroxybenzaldehyde gave a mixture of the respective dihydro-4*H*-1-benzopyranones and 2-phenylchalcones **11–24**. The compounds were isolated in a pure form by column chromatography. When the substituted chalcones were reduced with sodium borohydride they furnished the desired 2,3-diaryl-2*H*-1-benzopyran phenols **25–31** (table II) in good yields following thermal cyclodehydration of the alcohols initially formed. On alkylation with 1-(2-chloroethyl) piperidine hydrochloride the respective phenols gave the basic ethers **32–38** (table III) in satisfactory yield. Compounds **1–38** synthesized following the above procedure were adequately characterized by spectral data and analyses (scheme 1).

For the preparation of benzopyran analogues **51–53** with alkyl groups at the 3-position instead of a substituted aromatic ring, 2-hydroxyketones **39–41** were condensed with 4-hydroxybenzaldehyde to give chal-

Table I. Physical data of substituted/protected deoxybenzoins.

Compound	*R*	*R'*	*Mp (°C)*	*Molecular formula*
1	H	OMe	85	$C_{15}H_{14}O_3$
2	H	OH	102	$C_{14}H_{12}O_3$
3	H	OTHP	95	$C_{19}H_{20}O_4$
4	OH	OH	186	$C_{14}H_{12}O_4$
5	OTHP	OTHP	118	$C_{24}H_{28}O_6$
6	OH	OMe	155	$C_{15}H_{14}O_4$
7	OTHP	OMe	70	$C_{20}H_{22}O_5$
8	OMe	OMe	136	$C_{16}H_{16}O_4$
9	Me	OMe	124	$C_{16}H_{16}O_3$
10	Cl	OMe	107	$C_{15}H_{13}O_3C$

THP: tetrahydropyranyl.

Table II. Physical data of compounds **26–31**.

Compound	*R*	*R'*	*Mp (°C)*	*Molecular formula*	*MS (M+)*	*^{1}H-NMR*
26	H	OTHP	144	$C_{26}H_{24}O_4$	400	($CDCl_3$) δ: 1.4–1.9 (m, 6H, 3'-H, 4'-H, 5'-H), 3.5–3.8 (m, 2H, 6'-H), 2.3 (bs, 1H, 2-H), 6.1 (s, 1H, OCH), 6.5–7.4 (m, 13H, ArH and olefinic H)
27	OTHP	OTHP	180	$C_{31}H_{32}O_6$	500	(Acetone-d_6) δ: 1.3–1.8 (m, 12H, 3'-H, 4'-H and 5'-H), 3.2–3.9 (m, 4H, 6'-H), 5.2 and 5.3 (bs, 2H, 2'-H), 6.1 (s, 1H, OCH) and 6.2–7.3 (m, 12H, ArH)
28	OTHP	OMe	132	$C_{27}H_{26}O_5$	430	($CDCl_3$) δ: 1.4–1.8 (m, 6H, 3'-H, 4'-H and 5'-H), 3.4–3.8 (m, 2H, 6'-H), 5.3 (bs, 2H, 2'-H), 6.18 (s, 1H, CH), 6.5–7.4 (m, 12H, ArH and olefinic H)
29	OMe	OMe	175	$C_{23}H_{20}O_4$	360	($CDCl_3$) δ: 3.7 and 3.8 (2s, 6H, 2 x OCH_3), 6.14 (s, 1H, OCH), 6.3–7.4 (m, 12H, ArH and olefinic H)
30	Me	OMe	172	$C_{23}H_{20}O_3$	344	($CDCl_3$) δ: 2.2 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 6.18 (s, 1H, OCH), 6.5–7.4 (m, 12H, ArH and olefinic H)
31	Cl	OMe	189	$C_{22}H_{17}O_3Cl$	364.5	($CDCl_3$) δ: 3.8 (s, 3H, OCH_3), 6.18 (s, 1H, OCH), 6.5–7.4 (m, 12H, ArH and olefinic H)

Table III. Physical data of compounds **33–38**.

Compound	*R*	*R¹*	*Mp (°C)*	*Molecular formula*	*MS (M⁺)*	*¹H-NMR*
33	H	OH	110	$C_{28}H_{29}O_3N$	427	($CDCl_3$) δ: 1.20–1.70 (m, 6H, $(CH_2)_3$), 2.35–2.60 (m, 4H, N $(CH_2)_2$), 2.70 (t, 2H, NCH_2), 3.90 (t, 2H, OCH_2), 6.1 (s, 1H, OCH), 6.4–7.3 (m, 13H, ArH and olefinic H)
34	OH	OH	Oil	$C_{28}H_{29}O_4N$	443	(Acetone-d_6) δ: 1.3–1.7 (m, 6H, $(CH_2)_3$), 2.2–2.4 (m, 4H, $N(CH_2)_2$), 2.55 (t, 2H, NCH_2), 3.9 (t, 2H, OCH_2), 5.85 (bs, 2H exchangeable H), 6.0–6.3 (m, 3H, OCH and ArH, *ortho* to OH), 6.6–7.2 (m, 11H, ArH and olefinic H)
35	OH	OMe	102	$C_{29}H_{31}O_4N$	457	($CDCl_3$) δ: 1.4–1.7 (m, 6H, $CH_2)_3$), 2.4–2.6 (m, 4H, $N(CH_2)_2$), 2.62–2.8 (t, 2H, NCH_2), 3.8 (s, 3H, OCH_3), 3.84–4.0 (t, 2H, OCH_2), 4.4 (bs, 1H, OH), 6.16 (m, 1H, OCH), 6.2–7.4 (m, 12H, ArH and olefinic H)
36	OMe	OMe	86	$C_{30}H_{33}O_4N$	471	($CDCl_3$) δ: 1.4–1.9 (m, 6H, $(CH_2)_3$), 2.4–2.5 (m, 4H, $N(CH_2)_2$), 2.6–2.8 (t, 2H, NCH_2), 3.8 (s, 3H, OCH_3), 3.8 (t, 2H, OCH_2), 4.0 (t, 2H, OCH_2), 6.2 (m, 1H, OCH), 6.3–7.4 (m, 12H, ArH and olefinic H)
37	Me	OMe	114	$C_{30}H_{33}O_3N$	455	($CDCl_3$) δ: 1.4–1.6 (m, 6H, $(CH_2)_3$), 2.2 (s, 3H, CH_3), 2.4–2.5 (m, 4H, $N(CH_2)_2$), 2.6 (t, 2H, NCH_2), 3.8 (m, 3H, OCH_3), 4.0 (t, 2H, OCH_2), 6.2 (m, 1H, OCH), 6.5–7.4 (m, 12H, ArH and olefinic H)
38	Cl	OMe	107	$C_{29}H_{30}O_3NCl$	475	($CDCl_3$) δ: 1.4–1.6 (m, 6H, $(CH_2)_3$), 2.4–2.5 (m, 4H, $N(CH_2)_2$), 2.6–2.8 (t, 2H, NCH_2), 3.78 (s, 3H, OCH_3), 4.0 (t, 2H, OCH_2), 6.2 (s, 1H, OCH), 6.6–7.4 (m, 12H, ArH and olefinic H)

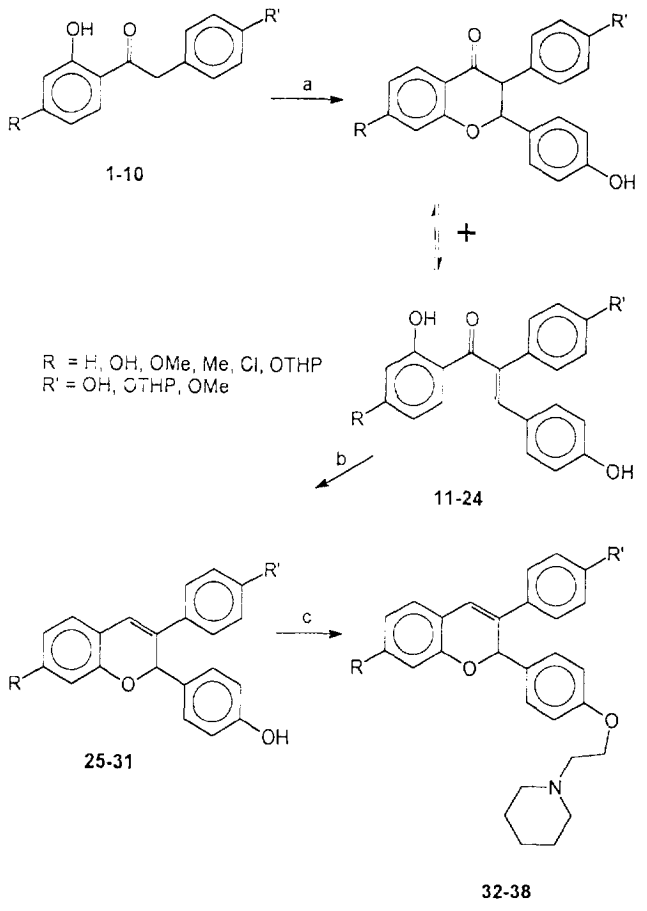
THP = tetrahydropyranyl.

cones and dihydrobenzopyranones **42–47**. Subsequent reduction, cyclization and alkylation of chalcones formed the desired basic ethers **51–53** (table IV) obtained as oils in satisfactory yield (scheme 2).

Results and discussion

The compounds **32–38** and **51–53** were tested for their antiimplantation (ie, post-coital contraceptive) activity in pregnant female albino rats of proven fertility. In the primary screening, the compounds were fed for 5 days from days 1–5 of pregnancy at a dose level of 2.5 mg/kg. Compounds **32–36** showed 100% inhibition, whereas compounds **37** and **38** exhibited 33 and 70% activity, respectively. The active compounds **32–36** were then tested in single day schedule at a dose level of 1.0 mg/kg. Again, all the compounds showed 100% inhibition. They were further tested at lower dose levels in single day schedule testing and the results are listed in table V.

Compound **32** bearing methoxy group at the 4'-position of 3-phenyl ring emerged as the most potent molecule. It consistently showed 100% antiimplantation activity when tested at dose levels of 0.5, 0.4 and 0.2 mg/kg. MED_{100} (po) (minimum effective dose) was found to be 0.2 mg/kg. No toxicity or mortality was observed during 48 h when administered up to a dose of 100 mg/kg post orally. The LD_{50} of compound **32** has been found to be 5.0 g/kg (po). Compound **33** with a hydroxy function instead of methoxy is equiactive with **32**, but exhibited toxicity. Similarly compound **34** with two hydroxy radicals at the 4'- and 7-positions has



Scheme 1. a) 4-OH C_6H_4CHO, $C_5H_{11}N$, C_6H_6, reflux; b) $NaBH_4$, EtOH, rt; c) $C_7H_{14}NCl{\cdot}HCl$, dry acetone, anhydrous K_2CO_3, reflux.

high activity but turned out to be more toxic than **33**. Compounds **35** and **36** with hydroxy/methoxy and methoxy/methoxy radicals at the 4'-position of 2-phenyl ring and 7-position of the benzopyran nucleus did not enhance the activity with decreasing dose levels, thereby indicating no substantial role of the groups at the 7-position on the activity. This fact was elaborated by compounds **37** and **38** substituted with methyl and chloro radicals showing only marginal inhibitions.

Compound **32** the most active member of the series was further tested through intraperitoneal and intramuscular routes and showed 100% antiimplantation activity at the MED dose of 0.2 mg/kg in rats.

None of the compounds **51–53** devoid of a phenyl ring at the 3-position of the pyran ring were found to be active, suggesting the crucial role of aromatic substituent at the 3-position in imparting high activity.

Since 2,3-diaryl-2*H*-1-benzopyrans have emerged as potent antiestrogens [21, 22], it was interesting to study in detail the antiestrogenic profile of the most active compound **32** to get an insight on the mechanism of action. Antiestrogens are known to be inhibitors of estrogen action and consequently interfere in the normal development of endometrium which is critical for the success of implantation.

The results of the uterotrophic and antiuterotrophic activity showed **32** to be a very weak uterotrophic agent and a potent antiestrogen. Estradiol administered at a dose of 0.1 μg/rat induced a sixfold increase in uterine weight (versus control $P < 0.0001$) and a dose of 1.0 μg/rat induced a sevenfold increase in the uterine wet weight (versus controls $P < 0.0001$). The dose of **32** required to counter estradiol (0.1 μg/rat) induced uterotrophic effect is 100 μg/kg and interestingly the same dose could counter the uterotrophic effect induced by 1.0 μg/rat of estradiol. It is thus important to note that the above dose is much lower than the single day contraceptive dose (tables VI and VII).

Compound **32** did not show any androgenic, antiandrogenic, progestational, antiprogestational, gonadotrophic or antigonadotrophic activities when tested in immature male and female Sprague–Dawley rats [25]. Further detailed biological testing of **32** and **33** for antibreast cancer activity is in progress and will form part of subsequent communication.

A comparison of the above activity results with the parent compound (2-(4-(2-*N*-piperidinoethoxy)-phenyl-2*H*-1-benzopyran), MED_{100} = 2.5 mg/kg body weight in single day testing [23]) show that benzopyran analogues featuring methoxy and hydroxy substituents at the 4'-position of the 3-phenyl ring exhibit very high activity. Further, when compared with the activity profile of established antiestrogen like tamoxifen [26] or other structurally similar compounds like 3,4-diarylchromenes [27], 1,2-diphenyl-3,4-dihydronaphthalenes [28] or 2,3-diarylindenes [29], it could logically be concluded that 2,3-substituted diaryl-2*H*-1-benzopyrans are the most active antifertility agents. The methyl ether analogue **32** gives 100% protection against pregnancy at a very low dose of 0.2 mg/kg body weight in single day testing and also shows very high antiestrogenic activity.

Experimental protocols

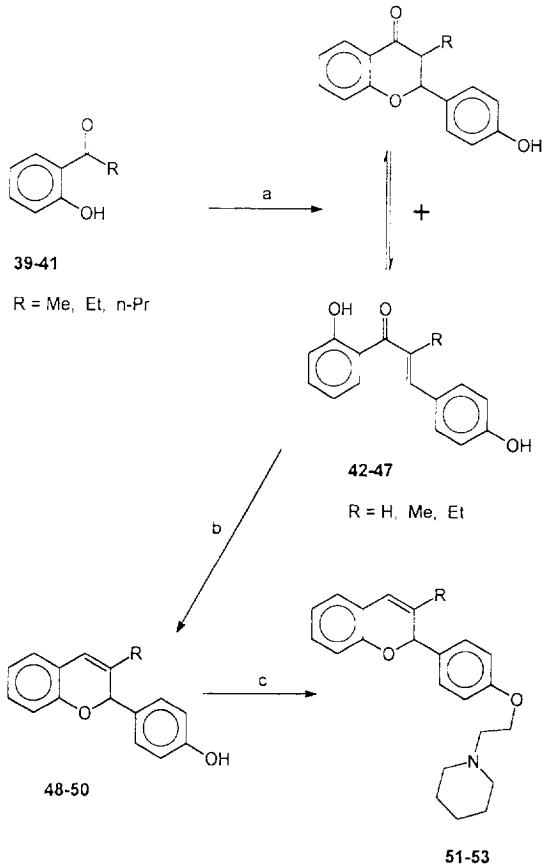
Chemistry

The melting points (mp) were determined on a Toshniwal melting point apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 157 instrument as KBr disks or neat and values are reported on the cm^{-1} scale. The ^1H-NMR

Table IV. Physical data of compounds **51–53**.

Compound	*R*	*Mp (°C)*	*Molecular formula*	*MS (M^+)*	*^{1}H-NMR*
51	H	Oil[a]	$C_{22}H_{25}O_2N$	335	($CDCl_3$) δ: 1.4–1.8 (m, 6H $(CH_2)_3$), 2.4 (m, 4H, $N(CH_2)_2$), 2.6–2.7 (t, 2H, NCH_2), 4.1 (t, 3H, OCH_3), 6.1 (m, 1H, olefinic H), 6.3 (s, 1H, OCH), 6.5–7.3 (m, 10H, ArH and olefinic H)
52	Me	Oil[a]	$C_{23}H_{27}O_2N$	349	($CDCl_3$) δ: 1.4–1.7 (m, 9H, CH_3 and $(CH_2)_3$), 2.4–2.5 (m, 4H, $N(CH_2)_2$), 2.6–2.8 (t, 2H, NCH_2), 4.0–4.1 (t, 3H, OCH_3), 6.3 (s, 1H, OCH), 6.4–7.4 (m, 9H, ArH and olefinic H)
53	Et	Oil[a]	$C_{24}H_{29}O_2N$	363	($CDCl_3$) δ: 1.2 (t, 3H, CH_3), 1.4–1.8 (m, 6H, $(CH_2)_3$), 2.4–2.5 (m, 4H, $N(CH_2)_2$), 2.6–2.8 (t, 2H, NCH_2), 4.0 (t, 2H, OCH_2), 4.2 (q, 2H, CH_2), 6.2 (m, 1H, OCH), 6.4–7.3 (m, 9H, ArH and olefinic H)

[a]Crystallized as their oxalate salts.



Scheme 2. a) 4-OH C_6H_4CHO, $C_5H_{11}N$, C_6H_6, reflux; b) $NaBH_4$, EtOH, rt; c) $C_7H_{14}NCl$•HCl, dry acetone, anhydrous K_2CO_3, reflux.

spectra were recorded on either a Perkin-Elmer R-32 or Jeol FT-90 Q multinuclear spectrometer with tetramethylsilane as the internal standard and $CDCl_3$ as the solvent, unless otherwise indicated. 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. Elemental analyses of C, H, N were within ±0.4% of theoretical values. Thin-layer chromatography was carried out on silica-gel or basic neutral alumina plates with ethyl acetate/hexane or chloroform/methanol as eluting solvent systems.

2-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one ***11*** *and 1-(2-hydroxyphenyl)-2-(4-methoxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one* ***12***

To a solution of deoxybenzoin **1** (2.42 g, 0.01 mol) and 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) in dry benzene (100 mL) was added piperidine (0.01 mL). The reaction mixture was refluxed for 30 h, removing water azeotropically. Fresh portions of benzene were added from time to time to replenish its loss during the reaction. The mixture was cooled and washed twice with water. The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was chromatographed over a column of silica gel eluting with ethyl acetate/hexane to afford compound **12** as a yellow oil (2.6 g). It could not be crystallized and was used as such in further reaction after characterization. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (s, 3H, OCH_3), 6.8–7.82 (m, 13H, ArH and olefinic H); MS *m/z* 346 (M^+); IR 1610 (CO), 3400 (OH). Further elution with increasing polarity afforded the dihydrobenzopyranone **11** (1.8 g) which was crystallized from ethyl acetate/hexane, mp 179 °C. ^{1}H-NMR ($CDCl_3$ + CD_3OD) δ: 3.75 (s, 3H, OCH_3), 4.15–4.20 (d, 1H, J = 12.0 Hz, COCH), 5.58 (d, 1H, J = 12.0 Hz, OCH), 6.7–7.2 (m, 12H, Ar-H); MS *m/z* 346 (M^+); IR 1675 (CO), 3300 (OH).

Compounds **13–25** were prepared in a similar manner.

2-(4-Hydroxyphenyl)-3-[4-(tetrahydropyran-2-yloxy)phenyl]-2,3-dihydro-4H-1-benzopyran-4-one ***13***. Mp 183 °C. ^{1}H-NMR (acetone-d_6) δ: 1.5–1.88 (m, 6H, 3'-H, 4'-H and 5'-H), 3.4–3.8

Table V. Post-coital contraceptive activity of compounds **32–38** and **51–53** in immature female rats.

Compound	*Route of administration*	*Dose (mg/kg, body weight/No of animals)*[a]	*Treatment (day of administration)*[b]	*No of implantation sites*[b]	*Inhibition (%) (MED_{100})*[c]
Control		– (5)	d1–d5	0/0	0.0 (All rats pregnant)
32	po	2.5	d1–d5	0/10	100.0
	po	1.0	d1	0/10	100.0
	po	0.5	d1	0/10	100.0
	po	0.25	d1	0/10	100.0
	po	0.20	d1	0/10	100.0
	po	0.15	d1	2/10	80.0
	Intraperitoneal	0.2	d1	0/10	100.0
	Intraperitoneal	0.1	d1	4/10	60.0
	Intramuscular	0.2	d1	0/10	100.0
	Subcutaneous	0.2	d1	6/10	40.0
33	po	2.5	d1–d5	0/10	100.0
	po	1.0	d1	0/10	100.0
	po	0.5	d1	1/10	90.0
	Intraperitoneal	2.0	d1	0/10	100.0
	Intraperitoneal	1.5	d1	2/10	80.0
34	po	2.5	d1–d5	0/10	100.0
	po	1.0	d1	0/10	100.0
	po	0.5	d1	2/10	80.0
35	po	2.5	d1–d5	0/10	100.0
	po	1.0	d1	0/10	100.0
	po	0.5	d1	4/10	60.0
36	po	2.5	d1–d5	0/10	100.0
	po	1.0	d1	0/10	100.0
	po	0.5	d1	2/10	80.0
37	po	2.5	d1–d5	7/10	33/0
38	po	2.5	d1–d5	3/10	70.0
51	po	2.5	d1–d5	8/10	Inactive
52	po	2.5	d1–d5	8/10	Inactive
53	po	2.5	d1–d5	9/10	Inactive

[a]Five animals were used for each dose test; [b]control rats had a mean of ten implantation sites (visibly thickened uteri); [c]MED_{100} = minimal effective dose for 100% inhibition of pregnancy. d1–d5 = 5 day schedule; d1 = 1 day schedule (ie, only on day 1 of pregnancy).

(m, 2H, 6'-H), 4.21 (d, 1H, J = 12.0 Hz, COCH), 5.45 (brs, 1H, 2'-H), 5.55 (d, 1H, J = 12.0 Hz, OCH), 6.5–6.7 (m, 4H, Ar-H, *ortho* to THP and OH), 6.85–7.7 (m, 8H, Ar-H); MS *m/z* 416 (M^+); IR 1680 (CO), 3400 (OH).

1-(2-Hydroxyphenyl)-2-[4-(tetrahydropyran-2-yloxy)phenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one ***14***. This was obtained as yellow solid, mp 146 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.5–1.8 (m, 6H, 3'-H, 4'-H and 5'-H), 3.3–3.65 (m, 2H, 6'-H), 5.5 (bs, 1H, 2'-H) and 6.6–7.8 (m, 13H, ArH); MS *m/z* 416 (M^+); IR 1610 (CO), 3450 (OH).

2-(4-Hydroxyphenyl)-3-[4-(tetrahydropyran-2-yloxy)phenyl]-7-(tetrahydropyran-2-yloxy)-2,3-dihydro-4H-1-benzopyran-4-one ***15***. Crystallized from ethyl acetate/hexane, mp 190 °C. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 1.3–1.8 (m, 12-H, 3'-H, 4'-H and 5'-H), 3.3–3.8 (m, 4H, 6'-H), 4.0 (d, 1H, J = 12.0 Hz, COCH), 5.1–5.5 (m, 3H, OCH and 2'-H), 6.4–7.1 (m, 10H, ArH) and 7.7 (d, 1H, J = 8.0 Hz, ArH, *ortho* to CO); MS *m/z* 431 (M^+); IR 1680 (CO), 3400 (OH).

1-[(2-Hydroxy-4-tetrahydropyran-2-yloxy)phenyl]-2-[4-(tetrahydropyran-2-yloxy)phenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one ***16***. This was obtained as an oil. It was used as such in the next reaction. MS *m/z* 431 (M^+).

Table VI. Uterotrophic activity of compound **32** in immature ovariectomized females rats.

	Group/dose (po)	*Uterine weight (mg)*	*Status of the vaginal opening*
1	OV control	21.2 ± 1.82	–
2	OV + 50 µg/kg	23.4 ± 2.45	Closed
3	OV + 100 µg/kg	28.6 ± 1.96	Closed
4	OV + 250 µg/kg	29.9 ± 1.64	Closed
5	OV + 400 µg/kg	31.4 ± 0.82	Closed

All groups had seven animals each. Values are means ± se. OV indicates ovariectomized animals.

2-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-7-(tetrahydropyran-2-yloxy)-2,3-dihydro-4H-1-benzopyran-4-one ***17***. Mp 179 °C. ^{1}H-NMR (acetone-d_6) δ: 1.3–2.0 (m, 6H, 3'-H, 4'-H and 5'-H), 2.8 (s, 2H, 6'-H), 3.7 (s, 3H, OCH_3), 4.15–4.22 (d, 1H, J = 12.0 Hz, COCH), 5.44–5.62 (brd, 2H, 2-H and 2'-H), 6.66–7.24 (m, 10H, Ar-H), 7.6–7.8 (d, 1H, ArH, *ortho* to CO); MS *m/z* 446 (M+); IR 1675 (CO), 3400 (OH).

1-[(2-Hydroxy-4-tetrahydropyran-2-yloxy)phenyl]-2-(4-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one ***18***. This was also obtained as an oil and could not be crystallized, it was used as such in the next reaction. MS *m/z* 446 (M+); IR 1610 (CO), 3450 (OH).

2-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-7-methoxy-2,3-dihydro-4H-1-benzopyran-4-one ***19***. Crystallized from ethyl acetate/benzene, mp 184 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.65 (s, 6H, OCH_3), 4.4 (d, 1H, COCH), 5.82 (d, 1H, OCH), 6.6–7.1 (m, 11H, ArH); MS *m/z* 376 (M+); IR 1680 (CO), 3400 (OH).

1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one ***20***. Yellow solid, mp 126 °C. MS *m/z* 376 (M+); IR 1610 (CO), 3350 (OH).

2-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-7-methyl-2,3-dihydro-4H-1-benzopyran-4-one ***21***. Mp 210 °C. ^{1}H-NMR (acetone-d_6) δ: 2.4 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.2–4.28 (d, 1H, J = 12.0 Hz, COCH), 5.46–5.64 (d, 1H, J = 12.0 Hz, OCH), 6.6–7.24 (m, 9H, ArH, *ortho* to CO); MS *m/z* 360 (M+); IR 1680 (CO), 3300 (OH).

1-(2-Hydroxy-4-methylphenyl)-2-(4-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one ***22***. This was obtained as yellow solid, mp 95 °C. MS *m/z* 360 (M+); IR 1610 (CO), 3300 (OH).

2-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-7-chloro-2,3-dihydro-4H-1-benzopyran-4-one ***23***. White crystalline solid, mp 204 °C. ^{1}H-NMR (acetone-d_6) δ: 3.7 (s, 3H, OCH_3), 4.22 (d, 1H, J = 12.0 Hz, COCH), 5.6 (d, 1H, J = 12.0 Hz, OCH), 6.6–7.2 (m, 10H, ArH *ortho* to CO); MS *m/z* 380 (M+); IR 1680 (CO), 3400 (OH).

1-(2-Hydroxy-4-chlorophenyl)-2-(4-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one ***24***. This was obtained as oil. MS *m/z* 380 (M+); IR 1680 (CO), 3300 (OH).

2-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran ***25***
To a stirred solution of 2-phenylchalcone **12** (3.46 g, 0.01 mol) in methanol (50 mL) was added sodium borohydride (740 mg, 0.02 mol) and the stirring was continued for 8 h. On completion of the reaction as checked by TLC, excess methanol was removed in vacuo and to the residue was added saturated ammonium chloride solution till the pH of the solution was neutral. The mixture was extracted with ethyl acetate, washed with water twice and dried (Na_2SO_4). The residue obtained on concentration was chromatographed over a column of silica gel, eluting with ethyl acetate/hexane to afford pure compound **25** (2.1 g) as a white solid. It was crystallized from benzene/hexane, mp 124 °C. ^{1}H-NMR (acetone-d_6) δ: 3.7 (s, 3H, OCH_3), 6.23 (s, 1H, OCH), 6.62–7.5 (m, 13H, ArH and olefinic H), 8.4 (bs, 1H, OH); MS *m/z* 330 (M+).

Compounds **26–31** were prepared in the same manner as described for compound **25**, their physical data is listed in table II.

Table VII. Antiuterotrophic activity of compound **32** in immature female rats.

Group	*Treatment*	*Dose of the test compound*	*Uterine weight (in mg)*	*Status of the vaginal opening*
1	OV control (7)	–	21.0 ± 5.7	–
2	Estradiol-17β	0.1 µg/rat	121.0 ± 21.6	Open
3	Estradiol-17β + 32	100 µg/rat	42.2 ± 3.8	Closed
4	Estradiol-17β + 32	250 µg/rat	32.0 ± 4.2	Closed
5	Estradiol-17β + 32	400 µg/rat	30.0 ± 4.2	Closed
6	Estradiol-17β	1.0 µg/rat	140.0 ± 7.7	Open
7	Estradiol-17β + 32	100 µg/rat	41.4 ± 6.4	Closed
8	Estradiol-17β + 32	250 µg/rat	40.0 ± 6.3	Closed
9	Estradiol-17β + 32	400 µg/rat	36.4 ± 6.4	Closed

All groups had seven animals each. Values are means ± se. OV = ovariectomized animals.

2-[4-(2-Piperidinoethoxy)phenyl]-3-(4-methoxyphenyl)-2H-1-benzopyran ***32***

Compound **25** (1.0 g, 3 mmol) was dissolved in dry acetone (50 mL) and to the resulting solution was added anhydrous K_2CO_3 (600 mg, 3.5 mmol) and 1-(2-chloroethyl) piperidine hydrochloride (600 mg, 3 mmol). The mixture was heated under reflux for 24 h. On completion of the reaction it was cooled, filtered to remove insoluble material and washed with acetone. The combined filtrate was concentrated and the residue obtained was chromatographed over a column of basic alumina eluting with ethyl acetate/hexane to afford the pure compound **32** as an oil (900 mg, 75%) which solidified on addition of petroleum ether (40–60 °C). It was crystallized from benzene/hexane, mp 98 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.4–1.64 (bs, 6H, $(CH_2)_3$), 2.4–2.46 (m, 4H, $N(CH_2)_2$), 2.6–2.8 (t, 2H, NCH_2), 3.78 (s, 3H, OCH_3), 3.99 (t, 2H, OCH_2), 6.2 (s, 1H, OCH), 6.6–7.6 (m, 13H, ArH and olefinic H); MS *m/z* 441 (M^+).

Similarly, compounds **33–38** and **51–53** were prepared following the above procedure. Their physical data are reported in tables III and IV.

Biological evaluation

Post-coital contraceptive activity

Immature female albino rats were caged overnight with coeval males of proven fertility and their vaginal smears were examined the next morning for the presence of spermatozoa. The day vaginal smears showed the presence of spermatozoa was considered as day one of the pregnancy. In the first test, the mated animals were administered orally compounds **32–38** and **51–53** suspended in gum acacia (vehicle) at a dose of 2.5 mg/kg body weight on day one (post-coitum) and continued for five successive days (d1–d5, ie, 5 day schedule). The control group of animals received the vehicle alone. Animals were fed with a gavage needle fitted to syringe. Rats of both control and treated groups were laparotomized on the 11th day of the test and their uteri examined for implantation sites. In subsequent tests, the contraceptive efficacy of active compounds showing 100% antiimplantation activity was established at different dose levels in single day schedule (d1, ie, only on day 1 of pregnancy) and the MED_{100} was determined. The results are reported in table V.

Estrogenic and antiestrogenic activity

To determine the uterotrophic activity, immature 21-day-old female rats weighing 35–40 g were bilaterally ovariectomized and after a rest of 10 days were randomly divided into five groups. Group 1 served as a control and groups 2–5 were administered graded doses of compound **32**. For the evaluation of antiuterotrophic potential of compound **32**, ovariectomized rats were divided into nine groups, animals of group 1 served as the control and the remaining groups 2–9 were treated with 17β-estradiol at doses of 0.1 μg/rat (groups 2–5) and 1.0 μg/rat (groups 6–9); in addition they received the test compound **32** at different doses once a day for 4 days. Vaginal smears were examined 24 h after the last treatment and then the rats were autopsied. Uterine wet weight was recorded on a balance after removing the uterine fluid between folds of a filter paper. The results are reported in tables VI and VII.

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