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Synthesis and Post-coital Contraceptive Activity of Ether and Ester Analogues of 2,3-Diaryl-2*H*-1-benzopyrans

Kanchan Hajela, Kamal K. Kapoor and Randhir S. Kapil*
Regional Research Laboratory, Jammu Tawi-180 001, India

Abstract—Ether and ester analogues of 2,3-diaryl-2*H*-1-benzopyrans have been synthesised and tested for their pregnancy inhibiting activity in immature rats. Some of the compounds exhibit potent activity. Structure–activity relationship relative to the hydroxy analogue has been discussed. In general, esters were found to be better inhibitory agents.

Introduction

Hormone antagonists have found several clinical applications in the treatment of disorders due to relative or absolute hormone excess, the most valuable contribution undoubtedly being in the treatment of hormone dependent cancers,[1] chiefly breast cancer. Furthermore, non-steroidal antagonists have also been the subject of intense investigation as post-coital contraceptives[2,3] because of their ability to antagonise oestrogen action in the uterus by interfering with the hormone during the pre-implantation and post-implantation phases of reproduction. In our concerted efforts to design and develop compounds which may be effective in females for the control of fertility, the emergence of 2,3-diaryl-2*H*-1-benzopyrans, as a new class of potent anti-oestrogens[4,5] aroused considerable interest to explore the possibility of such molecules as pregnancy inhibiting agents.

A series of compounds, incorporating the basic benzopyran nucleus and with different substituent groups, were synthesised and evaluated for their post-coital contraceptive activity. Most of the compounds showed 100% activity in rats, in preliminary screenings at a dose of 2.5 mg kg^{-1}. Structure–activity relationship studies revealed the importance of methoxy and hydroxy groups at the 4'-position of 3-phenyl ring and 7-position of the benzopyran nucleus.[6] Both the groups potentiated receptor affinity as well as antagonistic activity of the prototypes. Substituent at the 4'-position of the 3-phenyl was found to be more crucial in imparting greater activity. However, a comparative study of their inhibitory action showed the methyl ether was more active than phenol, probably because of the polar nature of the hydroxy which has a tendency of being excreted from the body faster than the non-polar analogue. Also, the phenol was found to be more toxic. Keeping these facts in mind, it was thought logical to synthesise analogues with increased hydrocarbon residue to minimise toxicity and increase bioavailability. These analogues could also be easily hydrolysed *in vivo*, thereby exhibiting comparable or better affinity and activity to that of the hydroxy analogues.

The present communication describes the synthesis and biological profile of ether and ester analogues of 2,3-diaryl-2*H*-1-benzopyrans. The results of the post-coital contraceptive activity show that the compounds are potent antifertility agents.

Synthesis

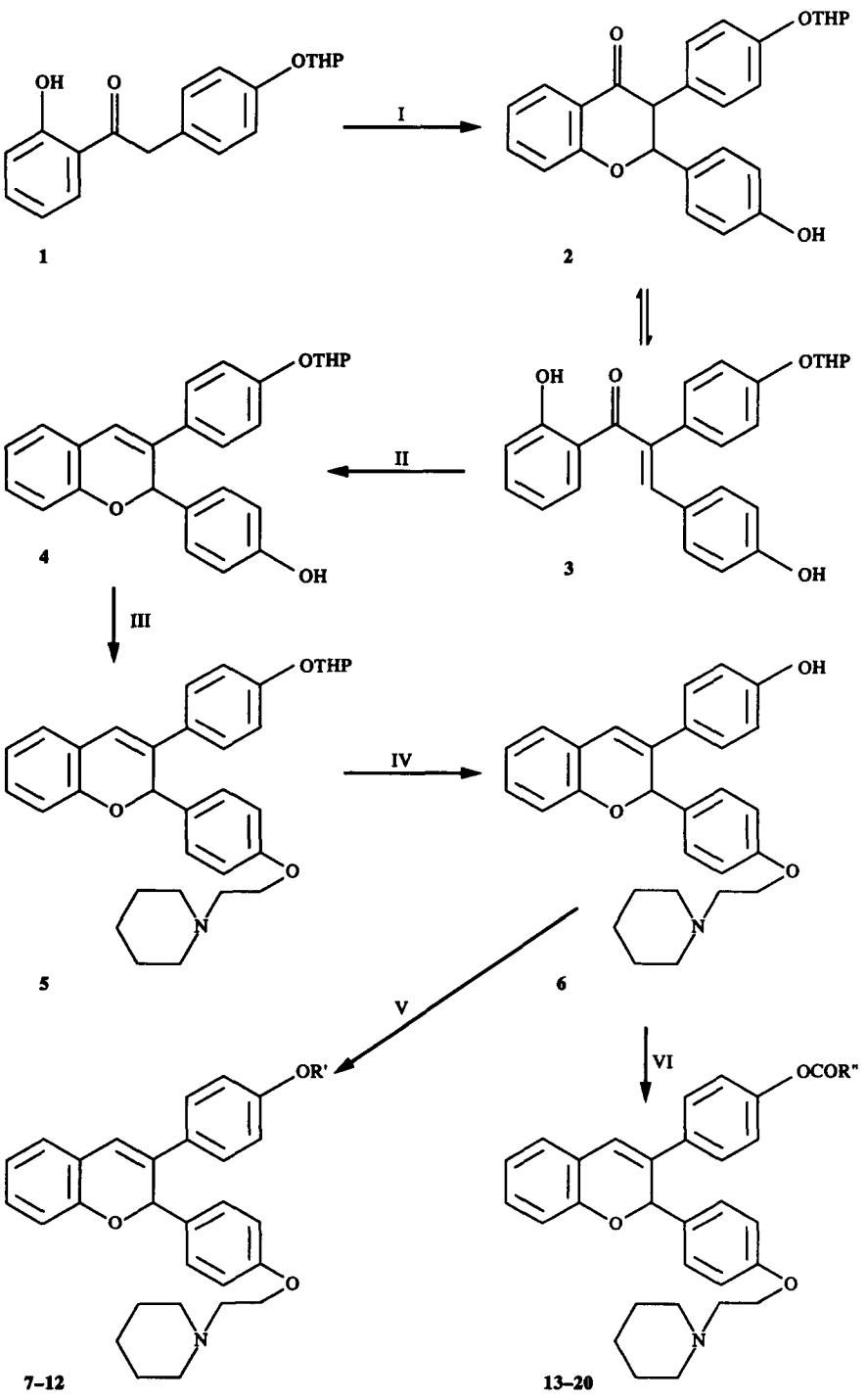
The title compounds were synthesised as follows (Scheme 1). The dihydroxydesoxybenzoin was converted to its monotetrahydropyranyl ether **1** which when reacted with 4-hydroxybenzaldehyde gave 2-phenyl-chalcone and 4-chromanone **2** and **3**. Sodium borohydride reduction of chalcone **3** initially formed an alcohol which rapidly cyclised on heating to chromene **4**. Chromene, on interaction with 2-piperidinoethyl chloride hydrochloride formed the basic ether **5** which was deprotected with 1 N HCl to give the desired monohydroxybenzopyran ether **6**. Alkylation of **6** with different alkyl halides formed the ethers **7–12** as crystalline solids, whereas acylation of **6** with different acyl halides formed the esters **13–20**, obtained as oils.

Biological Activity

All the synthesised compounds listed in Tables 1 and 2 were screened for their post-coital contraceptive activity in rats.

Immature female 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 that vaginal smears showed the presence of spermatozoa was considered as day one of the pregnancy. In the primary screening, compounds

suspended in gum acacia (vehicle) were administered orally at a dose of 2.5 mg kg^{-1} body weight on day one (post coitum) and continued for five successive days (D_1–D_5 i.e. five day schedule). The control group of animals received the vehicle alone. Animals were fed with a gavage needle fitted to a syringe. On the 11th day of the test, rats of both the control and treated groups were laparotomised and their uteri examined for implantation sites. The active compounds showing 100% anti-implantation activity were tested further in a single day schedule (D_1 i.e. only on day one of pregnancy) and also at lower doses and their contraceptive efficacy (MED_{100}) was determined (Table 3).



Reagents/conditions: I) 4-OHC_6H_4CHO/dry Bz/reflux; II) $NaBH_4$/EtOH/rt; III) C_7H_{14} NCl·HCl/dry Me_2CO/ anhydrous K_2CO_3/reflux; IV) 1 N HCl; V) R'Cl/dry Me_2CO/anhydrous K_2CO_3/reflux; VI) R"COCl/dry C_5H_5N/rt.

Scheme 1.

Table 1. Physical data of ether analogues of 2,3-diaryl-2*H*-1-benzopyrans **7–12**

Compound No.	R'	mp °C	Molecular formula	MS (m/z M^+)
7	CH_2CH_3	81	$C_{30}H_{33}O_3N$	455
8	$(CH_2)_2CH_3$	94	$C_{31}H_{35}O_3N$	469
9	$(CH_2)_3CH_3$	89	$C_{32}H_{37}O_3N$	483
10	$(CH_2)_4CH_3$	75	$C_{33}H_{39}O_3N$	497
11	$(CH_2)_5CH_3$	83	$C_{34}H_{41}O_3N$	511
12	$(CH_2)_6CH_3$	66	$C_{35}H_{43}O_3N$	525

All the compounds were recrystallised from benzene-hexane and characterised by their ^1H NMR spectra at FT-90 MHz.

Table 2. Physical data of ester analogues of 2,3-diaryl-2*H*-1-benzopyrans **13–20**

Compound No.	R"	Molecular formula	MS (m/z M^+)	IR (cm^{-1})
13	$-COCH_2CH_3$	$C_{31}H_{33}O_4N$	483	17 55 (CO)
14	$-CO(CH_2)_2CH_3$	$C_{32}H_{35}O_4N$	497	17 50 (CO)
15	$-CO(CH_2)_3CH_3$	$C_{33}H_{37}O_4N$	511	17 60 (CO)
16	$-CO(CH_2)_4CH_3$	$C_{34}H_{39}O_4N$	525	17 60 (CO)
17	$-CO(CH_2)_5CH_3$	$C_{35}H_{41}O_4N$	539	17 60 (CO)
18	$-CO(CH_2)_6CH_3$	$C_{36}H_{43}O_4N$	553	17 55 (CO)
19	$-CO(CH_2)_7CH_3$	$C_{37}H_{45}O_4N$	567	17 50 (CO)
20	$-CO(CH_2)_8CH_3$	$C_{38}H_{47}O_4N$	581	17 55 (CO)

All the compounds were characterised by their ^1H NMR spectra at FT-90 MHz.

The results of the biological activity reveal that both ether and ester analogues of 2,3-substituted diaryl-benzopyran exhibit promising post-coital contraceptive activity. Compounds **7**, **8**, **9**, **18**, **19** and **20** show 100% inhibition at 1.0 mg kg^{-1} body weight in single day schedule testing. Compound **18** is the most potent of the series with MED_{100} of 0.5 mg kg^{-1} body weight in single day testing. Further reduction of dose to 0.25 mg kg^{-1} of compound **18** decreased the potency to 90%.

From a comparison of the above activity results with the parent compound[7] {2-[4-(2-*N*-piperidinoethoxy)-phenyl]-3-phenyl-2*H*-1-benzopyran, MED_{100} = 2.5 mg kg^{-1} body weight in single day testing}, it could be inferred that both ethers and esters are relatively better anti-implantation agents. Further, comparison to the hydroxy analogues,[6] also showed them to be more potent. A study of their structure–activity relationship revealed that in ethers, compound **7** and **8** with small

Table 3. Post-coital contraceptive activity of compounds **7–12** (ether analogues) and **13–20** (ester analogues), post orally (p.o.) in immature rats

Compound No.	Dose (mg/kg/bw/ No. of animals)[a]	Treatment (Day of administration)	No. of implantation sites [b]	Inhibition % (MED_{100})
Control	- (5)	D_1-D_5	0/0	0.0 (All rats pregnant)
7	2.5	D_1-D_5	0/10	100.0
	1.0	D_1	0/10	100.0
	0.5	D_1	2/10	80.0
8	2.5	D_1-D_5	0/10	100.0
	1.0	D_1	0/10	100.0
	0.5	D_1	3/10	70.0
9	2.5	D_1-D_5	0/10	100.0
	1.0	D_1	1/10	90.0
10	2.5	D_1-D_5	3/10	70.0
11	2.5	D_1-D_5	3/10	70.0
12	2.5	D_1-D_5	3-4/10	66.6
13	1.0	D_1	3/10	70.0
14	1.0	D_1	3/10	70.0
15	1.0	D_1	1/10	90.0
16	1.0	D_1	1/10	90.0
17	1.0	D_1	1/10	90.0
18	1.0	D_1	0/10	100.0
	0.5	D_1	0/10	100.0
	0.25	D_1	1/10	90.0
19	1.0	D_1	0/10	100.0
	0.5	D_1	1/10	90.0
20	1.0	D_1	0/10	100.0
	0.5	D_1	1/10	90.0

[a]Five animals were used for each dose tested.
[b]Control rats had a mean of 10 implantation sites (visibly thickened uteri).
D_1 = Single day schedule testing i.e. only on day one of pregnancy.
D_1-D_5 = Five day schedule of testing.

alkyl residues are more potent and an increase in the length of carbon chain, compounds **10–12**, decreases the activity considerably, whereas the reverse is true with esters, higher carbon analogues, compounds **18–20** being more active. Thus, it can be concluded that introduction of easily hydrolysable groups like those in esters or small non-polar/hydrocarbon groups as in ethers, at the 4-position of the 3-phenyl ring have a marked effect on the activity, the compounds being more active than the hydroxy analogues.

On comparison with the activity profile of Tamoxifen[8] or other structurally similar compounds like 2,3-diarylindenes,[9] 1,2-diphenyl-3,4-dihydronaphthalenes[10] or 3,4-diarylchromene,[11] the 2,3-substituted diaryl-2*H*-1-benzopyrans have emerged as the most potent with some of the compounds giving 100% protection against pregnancy at very low doses of 0.2 mg kg^{-1} (Ref. 6) and 0.5 mg kg^{-1} (Ref. 12) body weight in single day testing, whereas all the above mentioned compounds are active with a contraceptive efficacy of MED_{50} when administered continuously for multiple days. To the best of our knowledge single day testing of these compounds is not reported so far.

Experimental

Chemistry

The melting points were determined on Toshniwal melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 157 instrument as KBr wafers or neat and values are

reported in the cm^{-1} scale. The ^1H NMR spectra were recorded on Jeol FT-90 Q multinuclear spectrometer with TMS as the internal standard and $CDCl_3$ as the solvent. The mass spectra were run on a Jeol JMS-D300 instrument fitted with a direct inlet system. Elemental analyses of the compounds were within ±0.4% of theoretical values. Thin layer chromatography was carried out on silica-gel or neutral/basic alumina plates with ethyl acetate or chloroform:methanol as developing solvent systems. Chromatographic purifications were performed either at atmospheric pressure or on flash chromatograph through columns using Merck silica-gel (60–120 mesh), flash silica-gel (230–400 mesh) and Merck aluminium oxide, activated, basic (150 mesh).

General method for the synthesis of ethers (7–12). A mixture of **6** (1.0 g, 2.3 mmol), appropriate alkyl halide (2.5 mmol), anhydrous K_2CO_3 (3 mmol) in dry acetone was refluxed for 24 h. On completion of the reaction the solid material was filtered off and residue washed with acetone. The combined filtrate was concentrated and chromatographed on a column of basic alumina to obtain compounds **7–12** in pure form. Their physical data are reported in Table 1.

General method for the preparation of esters (13–20). Compound **6** (10 mmol) was dissolved in minimum amount of dry pyridine. Appropriate acyl halide (15 mmol) was added and the solution allowed to stir at room temperature for 4 h. On completion of the reaction as monitored on TLC, excess of pyridine was removed *in vacuo*, the residue was chromatographed over a column of silica-gel (deactivated) eluting with ethyl acetate:hexane to give pure esters as oils in satisfactory yields. Their physical data are reported in Table 2.

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12. This communication (See Table 3, compound **18**).

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