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Jaya Pandey [α] & Kanchan Hajela [σ]

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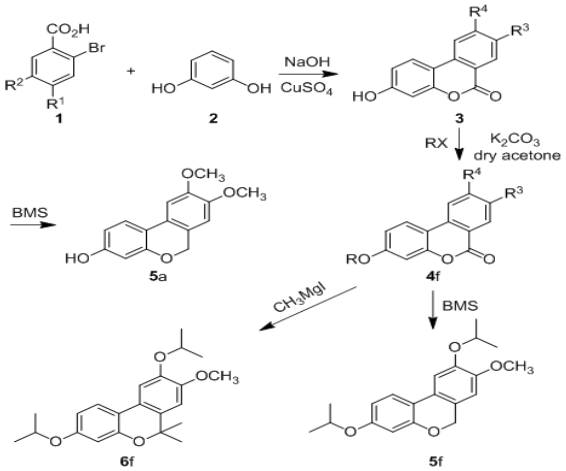
I. Introduction

Fused carbocyclic and heterocyclic fused ring systems constitute an important class of natural products with immense pharmacological properties.[1,2] The biological importance of pyrans as an anticoagulant3, aflatoxins as mycotoxins4 and of coumestrol as an estrogen and a phytoalexin5 has led to a considerable amount of work in the field of fused ring systems. Recently, the dibenzopyranone/pyrans and naphthopyran nucleus have surfaced as common ring system of a group of antibiotics, antibacterials, antitumors and immunomodulators, etc. exemplified by alternariol6, ravidomycin7, shilajit8, ellagic acid9 etc. Several carbocyclic and heterocyclic compounds have recently been reported in literature such as KCA-09812, LY-35615613, and coumestrol analogue14 etc. which Selectively modulate the activity of estrogen receptor (ER) showing complete antagonist effect at breast and uterus yet retain the positive effect on central nervous, cardiovascular and skeletal systems. These compounds termed as 'selective estrogen receptor modulators (SERMs)' cause increase in bone mineral density (BMD), reduce serum cholesterol level and are completely antagonists to breast and uterus tissues, therefore, are being evolved as antiosteoporotic agents. Our continuing effort on the development of 2,3-diarylbenzopyrans as selective estrogen receptor modulators10,11 led us to synthesize some dibenzopyranone/pyran molecules as potential antiestrogenic agents. As a critical balance of estrogenic as well as antiestrogenic effect is required in a molecule, therefore, various structural modifications at C-3, 6, 8 and 9 positions were done in the molecule to study structure-activity relationship and evolve a novel selective estrogen receptor modulator. The present paper describes synthesis, estrogenic, anti-estrogenic, RBA, anti-implantation and anti-osteoporotic activities of the synthesized compounds.

The respective orthobromobenzoic acids (1a-h), were condensed with resorcinol in aqueous alkaline medium in presence of copper (II) sulfate as a catalyst



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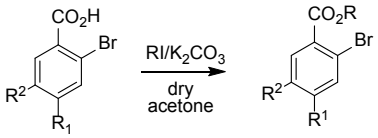
Compounds	a	b	c	d	e	f	g	h
1	R^1=H R^2=H	R^1=H R^2=OMe	R^1=OH R^2=H	R^1=OH R^2=OMe	R^1=OMe R^2=OMe	R^1=OBn R^2=OMe	R^1=O(CH$_2$)$_2$Py R^2=OMe	R^1=O(CH$_2$)$_2$Pi R^2=OMe
2	-	-	-	-	-	-	-	-
3	R^3=H R^4=H	R^3=OMe R^4=H	R^3=H R^4=OH	R^3=OMe R^4=OH	R^3=OMe R^4=OMe	R^3=OMe R^4=OBn	R^3=OMe R^4=O(CH$_2$)$_2$Py	R^3=OMe R^4=O(CH$_2$)$_2$Pi
4	R=O^{i}Pr R^3=H R^4=H	R=O^{i}Pr R^3=OMe R^4=H	R=O^{i}Pr R^3=OMe R^4=O^{i}Pr	R=O^{i}Pr R^3=OMe R^4=OH	R=O^{i}Pr R^3=OMe R^4=OMe	R=O^{i}Pr R^3=OMe R^4=O^{i}Pr	-	-
5	R=O^{i}Pr R^3=H R^4=H	R=O^{i}Pr R^3=OMe R^4=H	-	-	-	-	-	-
6	-	-	-	-	-	R=O^{i}Pr R^3=OMe R^4=O^{i}Pr	-	-

Py=pyrrolidine; Pi=piperidine

Scheme1 : Synthesis of 6H-dibenzopyran-6-one and dibenzopyran derivatives

to produce the corresponding dibenzopyranones (3a-h,) in good yields (Scheme 1).15a,b The various orthobromobenzoic acids, used in the Scheme 1 were in turn prepared by either known literature methods starting from simple starting materials16a, b, c or from bromovanillic acid esters 7 as shown in Scheme 2.



1 **7**

7a (R=Me, R^1= OH; R^2= OMe; **7b** (R=Me, R^1= OMe; R^2= OMe; **7c** (R=Bn, R^1= OBn; R^2= OMe; **7d** (R=Me, R^1=O(CH$_2$)$_2$Py, R^2= OMe); **7e** (R=Me, R^1=O(CH$_2$)$_2$Pi, R^2= OMe)

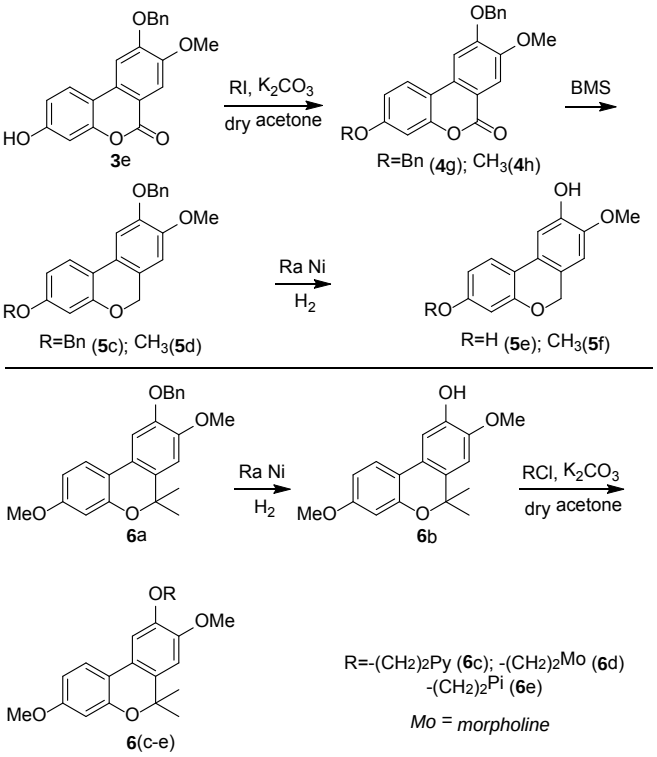
Scheme 2 : Synthesis of Substituted Orthobromobenzoic acid esters

The dibenzopyranones were alkylated with isopropyl bromide/methyl iodide, in dry acetone with anhydrous potassium carbonate as base to yield the respective alkylated products (4a-g, Scheme 1).

To obtain dibenzopyrans, the corresponding pyranones were reduced with borane methyl sulfide (BMS) (5a-d, Scheme I).

To study the structure-activity relationship various 6, 6-dimethyl dibenzopyran were also prepared. 9-Benzyloxy 8-methoxy 3-hydroxy dibenzopyranone (3f) was first protected with methoxy group (4g) and then reacted with methyl magnesium bromide to give 6, 6-dimethyl compound (6a). The 9-benzyloxy group was de-protected by hydrogenation with Raney Nickel in

methanol, to give 6b which was alkylated with various alkyl/aminoalkoxy chains (e.g. 1-2-chloroethyl piperidine /pyrrolidine/morpholine hydrochlorides etc.) to yield the corresponding products (6c-e, Scheme 3).



Scheme 3 : Synthesis of Substituted Orthobromobenzoic acid esters

All the synthesized compounds were characterized by spectral data NMR, Mass and elemental analysis and evaluated for estrogenic, anti-estrogenic, RBA (receptor binding affinity), anti-implantation and anti-osteoporosis activities.

II. Result and Discussion

The results of biological activity reveal that the dibenzopyran-6-ones possess both anti-estrogenic as well as inherent estrogenic property in the basic molecule. Hydroxy group at C-3 position analogous to C-3 of estradiol (E_2) is primary requisite for binding to ER and substitution by methoxy or isopropyl group cause decrease in binding affinity and biological activities. Although these molecules show poor binding affinity in in vitro RBA assay experiment, the reason for showing strong estrogenic or anti-estrogenic effects by some molecule is that there may be some other mechanism operative in vivo, like conversion into active metabolites or the molecules may be acting via some other mechanism than receptor modulation like modulation of certain enzymes/ cofactors involved in manifestation of estrogenic action. The 6,6-dimethyl compound 6e has emerged as most potent anti-estrogenic molecule in this series (24.7%) showing anti-implantation activity of 60% at 10 μg/kg dose in 1-5 day schedule. The compounds are also moderately agonist at skeletal tissue. 5a being most active (7.78%). Reduction into 6H-dibenzopyran has drastically increased the estrogenic property of the molecule (compound 3h – 78.4%) though substitution by alkyl chain at C-3 again blocks the binding of the molecule to ER decreasing the activity.

a) Biological Activities

Some of the compounds listed in Table III, IV, V and VI (3c, 3d, 3g, 3h, 4a, 4b, 4c, 4d, 4f, 5a, 5b, 5e, 5f, 6c, 6d, 6e, 6f) were screened for anti-implantation, estrogenic, anti-estrogenic, receptor binding affinity and anti-osteoporotic activities. The biological methods are described below and the results presented in Table VII.

b) Anti-implantation activity

Implantation activity was evaluated by known biological method in Sprague-Dawley rats (21 day old, weighing 22-30 g) by the method given in literature17. The compounds were administered per oral dose at 10 mg/kg dose as aqueous gum acacia suspension on day 1-5 schedule. 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 results were considered positive when implantation sites were totally absent in both the uterine horns.

c) Estrogenic activity

Different groups of animals were orally administered the test material in graded doses for 3

consecutive days. Uterine weight and status of vaginal opening were noted at the time of autopsy, i.e. 24 h after the last treatment. The activity was assessed by uterine weight gain.

d) Anti-estrogenic activity

17β estradiol [E2] at 0.1μ g in olive oil was given by subcutaneous route along with graded doses (5-15 μg) of compounds for three consecutive days. Inhibition was expressed as percent inhibition of estradiol induced increase in uterine wet weight.

e) Receptor Binding Affinity (RBA)

The RBA values of test compounds were evaluated by method described in literature18. Briefly, 50μl aliquots of cytosol (1 uterine equivalent/ml) were incubated at 4°C for 18 hour with increasing concentrations of test compounds (10-8-10-4 M). In triplicate and fixed concentrations of 3H-E2 (SR 10-9 M) dissolved in 20μl of DMF-TEA buffer. For separation of free from bound 3H-E2, each incubate was treated with 10μl of charcoal-dextran slurry (2.5 and 0.25% v/v, respectively) in TEA buffer for 20 minutes. Radioactivity of 50μl aliquot of each incubate was measured in Packard tricarb liquid scintillation spectrometer. The binding affinities of compounds relative to reference ligand (E_2=100) were calculated.

f) Anti-osteoporotic activity (In vitro anti-resorptive assay)

The in vitro assay of anti-resorptive activity using ^{45}Ca prelabelled rat fetal bone was done according to known literature method19. Three month old Sprauge Dawley female rats were mated to males of proven fertility. 250 Cl/30μl of $^{45}CaCl_2$ was administered to each rat on day μl of pregnancy and labelled humerus and radio-ulna bones were isolated 48 hours thereafter under sterile conditions. Bones were cultured in 300μl of the BGJB medium supplemented with antibiotic, antifungal and buffer (pH 7.3) for 24 hours. The bones were washed twice with PBS and transferred to BJGB medium containing PTH (0.4μM) and these cultured for 96 hours in the presence or absence of test compound (100μM) or the vehicle (0.1% ethanol/DMSO) in 300μ1 of BGJB, medium on termination of the culture, bones were transferred to 0.1 N HCl for 24 hours. Radioactivity due to ^{45}Ca in the spent medium collected at 48 and 96 hrs of culture and the HCl extracts was quantified by liquid scintillation spectrophotometer. Bone resorbing activity was expressed as percentage of released ^{45}Ca and the effect of test compounds as percent of control.

III. Conclusion

Compound 6e was found to inhibit estrogenic effect by 24.7% at 10 μg dose. Whereas compound 3g has shown estrogenic effect by 41.8%. RBA (ER) % of E2 for compound 3h was found to be the best (0.24%). Anti-implantation activity for compound 6e was recorded close to 60%. Compound 5a displayed anti-resorptive activity close to 7.78%. In essence, most of the compounds tested have shown good to moderate level of activities related to anti-estrogenic, receptor binding affinity and anti-osteoporotic activities.

IV. Acknowledgement

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Experimental Section

Procedure for one typical case for each step has been described. The melting points were determined in open capillaries Toshniwal melting point apparatus and are uncorrected. The 1H NMR were recorded on Brucker Avans DRX 300 (300 MHz, FT NMR) spectrometer using TMS as internal standard. The chemical shift values are reported in □ (ppm) scale and coupling constants in Hz. Electron impact (EIMS) mass spectra were run on a JEOL-JMSD 300 instruments fitted with a direct inlet system. Elemental analysis were performed on elemental analyser EA-1108 and were within +4% of theoretical values. The purity of the products was checked on precoated silica gel 60 F254 or aluminium oxide 60 F254 TLC plates and the spots were visualized by spraying with iodine vapors.

Methyl-2-bromo-5-methoxy 4-pyrrolidinoethoxy benzote-7c

To a solution of methyl 2-bromo 4-hydroxy 5-methoxy benzoate (261 mg; 1 mM) in dry acetone (60 ml) was added anhydrous potassium carbonate (276 mg; 2 mM) and 2-chloropyrrolidine hydrochloride (213 mg; 1.2 mM). The reaction mixture was stirred and refluxed (70-80oC) for 24 hrs. After the completion of reaction, the reaction flask was cooled and the contents filtered through G-3 sintered crucible. The residue was washed with acetone (5 ml x 3), the filtrate was concentrated and chromatographed over basic alumina column eluting with ethylacetate-hexane (2%). The product was obtained as yellow oil. Wt., 22.5 mg; Yield, 63%;

Methyl-2-bromo-5-methoxy-4-piperidinoethoxy benzoate 7d

It was prepared by similar procedure described for 3d. Ethyl acetate-hexane (2%) as yellow oil. Wt., 278 mg; Yield, 75%.

2-bromo-5-methoxy 4-pyrrolidino ethoxy benzoic acid hydrochloride 1f

To a solution of methyl 2-bromo 5-methoxy 4-pyrrolidinoethoxy benzoate (358 mg; 1 mM) in methanol (5 ml) was added sodium hydroxide solution (5N, 2 ml). The reaction mixture was stirred at room temperature for 48 hrs. After the completion of reaction, the excess methanol was evaporated off and the reaction flask was cooled in ice and neutralised with hydrochloric acid solution (6N, 3 ml). The precipitated product was filtered off and crystallized in methanol (3 ml) - water (6 drop) to yield pale yellow crystals of the product. Wt., 342 mg; Yield, 92%,m.p., 218°C.

2-bromo 5-methoxy 4-piperidino ethoxy benzoic acid hydrochloride 1g

It was prepared by similar procedure as described for 1g, Wt., 352mg; Yield, 90%; m.p., 216 °C.

3, 9-dihydroxy 8-methoxy dibenzo [b,d] pyran-6-one 3d

To a solution of methyl 2-bromovanillic acid (598 mg; 2.42 mM) in aqueous sodium hydroxide solution (8%, 2.5 ml) was added resorcinol (550 mg, 5 mM). The reaction mixture was refluxed (120oC) in an oil bath for 45 min, then aqueous copper sulfate solution (5%, 1 ml) was added into it and the reaction mixture was refluxed for another 15 min. The reaction mixture was cooled and the precipitated product was filtered off and washed with water (1 ml x 3), dried and crystallized in acetic acid (2 ml) - methanol (5 ml) to yield brown amorphous solid. Wt.,157 mg; Yield, 61%, m.p., 288oC.

It was prepared by similar procedure described for 3d from 4,s-dimethoxy z-bromobenzoic acid (568.98, 2.18 mM) and resorcinol (550 mg; 5 mM), Weight: 142 mg, Yield: 52% m.p. >280oC.

9-Benzyloxy 3-hydroxy 8-methoxy dibenzo [b,d] pyran-6-one 3f

It was synthesized by similar method starting from 4-benzyloxy 3-hydroxy 8-methoxy 2-bromobenzoic acid (630 mg; 2.18 mM) and resorcinol (550 mg; 5 mM). Wt., 141 mg; Yield, 52 %.

3-Hydroxy 8-methoxy 9-pyrrolidinoethoxy dibenzo [b,d] pyran-6-one 3g

It was prepared by similar procedure as above from 2-bromo 5-methoxy 4-pyrrolidinoethoxy benzoic acid (826 mg; 2.12 mM) and resorcinol (550 mg; 5 mM). The product was crystallized in methanol (2 ml)-water (0.5 ml) as white crystalline solid. Wt., 170 mg; Yield, 47.8%; m.p., 196°C.

3-hydroxy 8-methoxy 9-piperidinoethoxy dibenzo [b,d] pyran-6-one 3h

It was prepared by similar procedure described for 3d from 1g (830 mg; 2.18 mM) and resorcinol (550 mg, 5 mM) and crystallized in methanol (2 ml) - water (0.5 ml) to yield white crystalline solid.Wt., 184 mg; Yield, 49.8%; m.p., 205°C.

3-isopropyloxy 8-methoxy dibenzo [b,d] pyran-6-one 4b

To a solution of 3-hydroxy 8-methoxy dibenzo [b,d] pyran-6-one (242 mg; 1 mM) in dry acetone (60 ml) was added anhydrous potassium carbonate (276 mg; 2 mM) and isopropyl bromide (0.19 ml; 2mM). The reaction mixture was stirred and refluxed (70°C) for 24

hr. After the completion of reaction, the reaction flask was cooled and the contents filtered through G-3 sintered crucible and the residue washed with acetone (5 ml x 3). The filtrate was concentrated and chromatographed over silica gel column eluting the product with ethyl acetate-hexane (2%). Wt., 260 mg; Yield, 91.5%; m. p., 96°C.

It was prepared by similar procedure described for 4b from 3-hydroxy dibenzopyranone (212; 1 MM) and isopropyl bromide. Wt. 170 mg; Yield: 70.24%, m. p. 78°C.

3, 9-Diisopropyloxy dibenzo [b,d] pyran-6-one 4c

It was synthesized by similar method from 3, 9-dihydroxy dibenzopyranone (228 mg; 1 mM). Wt.,130 mg; Yield, 42%; m. p., 78°C.

3, 8-Diisopropyloxy dibenzo [b, d] pyran-6-one 4d

It was synthesized by similar method described for 4a from 3, 8-dihydroxy dibenzo [b, d] pyran-6-one (228 mg; 1 MM) and isopropyl bromide (0.19 ml; 2 MM) in dry acetone using potassium carbonate as base. Wt., 295mg; Yield, 94.5%; m .p., 98°C.

3, 9-Diisopropyloxy 8-methoxy dibenzo [b,d] pyran-6-one 4e

It was synthesized by similar method described for 4a from 3-hydroxy 8, 9-dimethoxy dibenzopyranone (272 mg; 1 MM). Wt., 240 mg; Yield, 88.23%; m. p., 218°

3-Isopropyloxy 8, 9-dimethoxy dibenzopyranone 4f

It was synthesized by similar method from 3, 9-dihydroxy 8-methoxy dibenzopyranone (258 mg; 1mM).Wt., 148 mg; Yield, 43.2%; m.p., 196°C.

3, 9-dibenzyloxy 8-methoxy dibenzo [b,d] pyran-6-one 4g

It was prepared by similar method described for 4b from 3-hydroxy 9-benzyloxy 8-methoxy dibenzo [b,d] pyran-6-one (348 mg; 1 mM) and benzyl bromide (0.239 ml; 2 mM) in dry acetone (60 ml) using anhydrous K2CO3 as base. The product crystallized in ethylacetate (3 ml) hexane (1 ml) as white crystalline solid. Weight 368 mg; Yield: 90.05%; m .p. 186°C.

9-Benzyloxy 3, 8-dimethoxy dibenzo [b, d] pyran-6-one 4h

It was prepared by similar procedure described for 4g from methyl iodide (0.124 ml; 2 MM) Weight: 326 mg; Yield: 90.05%; m.p. 192°C.

3, 9-Diisopropyloxy 3-methoxy dibenzo [b, d] pyran 5a

The mixture of 3, 9-diisopropyloxy 8-methoxy dibenzopyranone (342 mg; 1 MM) in borane methyl sulfide complex (0.5 ml; 2M solution in THF) was left overnight in dry RB flask (50 ml) with guard tube. After the completion of reaction, the reaction flask was cooled in ice-bath and quenched with cold saturated solution of ammonium chloride (5 ml) with stirring. The reaction mixture was refluxed on water bath with ethanol (5 ml) for 10 minutes. The ethanol was distilled of and the product extracted with dichloromethane (10 ml). The organic layer was washed with water (3 ml x 3), dried Na_2SO_4 and concentrated. The product was recrystallized in ethyl acetate (5 ml) - hexane (2 ml) to yield the product s pure white crystals. Wt., 260 mg; Yield, 79.2%; m. p., 96°C.

9-benzyloxy 3, 8-dimethoxy 6, 6-dimethyldibenzo[b, d] pyran 6a

A solution of 9-benzyloxy 3,8-dimethoxy dibenzo pyranone 13c (372 mg; 1 mM) in dry THF (20 ml) was added dropwise over 15 minutes to a solution of methyl magnesium iodide, prepared from Mg-turnings (360 mg; 15 mM) and methyl iodide (0.74 ml; 15 mM) in dry ether (5 ml). The reaction mixture was heated under reflux for 8 hours. The reaction mixture was cooled and poured into a mixture of conc. H2SO4 (0.2 ml) and ice (4 gm) with vigorous stirring. The product was extracted in benzene (20 ml), the organic layer was washed with water (3 ml x 3), dried (Na2SO4), concentrated in vacuo. The concentrate was chromatographed over silica gel column. The product was crystallized in benzene (2 ml)-hexane (0.5 ml) to give white crystalline solid. Wt., 280 mg; Yield, 74.4%; m.p.152oC.

Preparation of 9-hydroxy 3, 8-dimethoxy 6,6-dimethyl dibenzo [b,d] pyran 6b

To a solution of 3, 8-dimethoxy 9-benzyloxy 6, 6-dimethyl dibenzopyran (376 mg; 1 MM) in methanol (10 ml) was added Raney-nickel (10 mg). The reaction mixture was hydrogenated (60 psi) and shaken for 4 hr. After the completion of reaction, the reaction mixture was filtered through G-3 sintered crucible with cellite bed (2 cm) and washed with methanol (5 ml x 3). The filtrate was concentrated and the product crystallized in methanol (2 ml) to yield the product as white crystalline solid. Wt.,230 mg; Yield, 80.4%.

3, 8-dimethoxy 9-piperidinoethoxy 6, 6-dimethyl dibenzo [b,d] pyran 6c

It was prepared by same procedure as describe above for 4a from 3,8-dimethoxy 9-hydroxy 6,6-dimethyl dibenzopyran (286 mg; 1 mM) and 1-(2-chloroethyl piperidine hydrochloride) (222 mg; 1.2 mM) in dry acetone (60 ml) using anhydrous K_2CO_3as base. The product was crystallized in benzene (0.5 ml)-hexane (4 drops) as white crystalline solid. Wt., 320 mg; Yield, 80.6%; m.p., 118°C.

3, 8-Dimethoxy 9-morpholinoethoxy 6,6-dimethyl dibenzo [b,d] pyran 6d

It was prepared by similar procedure as described above for 4a from 3,8-dimethoxy 9-hydroxy 6,6-dimethyldibenzo pyran (286 mg; 1 mM) and 1-(2-chloroethyl) morpholine hydrochloride. The product was

crystallized in ethyl acetate (3ml). Wt., 248 mg;Yield, 62%; m.p., 126°C.

3, 8-Dimethoxy 9-pyrrolidinoethoxy 6,6-dimethyl dibenzopyran 6e

It was prepared by same procedure as described above for 4a from 3,8-dimethoxy 9-hydroxy 6,6-dimethyl dibenzopyran (286 mg; 1 mM) and 1-(2-chloroethyl) pyrrolidine hydrochloride (204 mg; 1.2 mM) in dry acetone (60 ml) using anhydrous K_2CO_3 as base. The product was crystallized in ethyl acetate (3ml). Wt., 237 mg; Yield, 61.8%; m.p., 124°C.

3,9-Diisoprophyloxy-8-methoxy 6,6-dimethyl dibenzo [b, d] pyran 6f

It was prepared by similar procedure as described above from 3,9-diisopropyloxy 8-methoxy 6,6-dimethyl dibenzo [b, d] pyran (356 mg; 1 MM). The product was crystallized in ethyl acetate (3ml). Wt., 206 mg; Yield, 58%; m.p., 82°C.

3, 9-Dibenzyloxy 8-methoxy dibenzo [b,d] pyran-6- one 5c

It was prepared by similar method described for 5a from 3, 9-dibenzyloxy 8-methoxy dibenzo [b,d]pyran-6-one (438 mg; 1 mM) and BMS (0.5 ml). The product crystallized in benzene (5 ml) hexane (2 ml) as white crystalline solid. Wt. 324 mg; Yield: 77.2% m.p. 122°C.

3, 9-Dihydroxy 8-Methoxy dibenzo [b,d] pyran 5e

It was prepared by similar method described for 5a from 3,9-dibenzyloxy 8-methoxy dibenzo [b,d] pyran (424 mg; 1 mM) and Raney Nickel (50 mg) in methanol (10 ml). The product was crystallized in ethyl acetate (4 ml), Wt. 152 mg; Yield: 62.29%; m.p. 194°C.

9-Benzyloxy 3, 8-dimethoxy dibenzo [b,d] pyran 5d

It was prepared by similar method described for 5a from 9-benzyloxy 3, 8-dimethoxydibenzopyran-6-one (362 mg; 1 mM) and BMS (0.5 ml). The product was crystallised in ethyl acetate (2 ml) hexane (0.5 ml) as white crystalline solid. Wt. 294 mg; Yield: 84.4%; m.p. 124°C.

9-Hydroxy 3, 8-dimethoxy dibeno [b,d] pyran 5f

It was prepared by similar method described for 6b from 9-benzyloxy 3, 8-dimethoxy dibenzo [b,d] pyran (348 mg; 1 mM) and Raney nickel in methanol (5 ml). The product was crystallised as white solid. Wt. 182 mg; Yield: 70.8%; m.p. 188°C.

Table I : Physical data and characterization of orthobromobenzoic acid (1d-1h)

Compd. No.	Mol. Formula	Mass: m/z	m.p. °C	^{1}H NMR ($CDCl_3$, δ ppm)
1e	$C_9H_9O_4Br$	261(M^+), 263 (M^++2), 246, 200, 160	178	3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 7.13 (s, 1H, H^3), 7.58 (s, 1H, H^6)
1f	$C_{11}H_{13}O_4Br$	426 (M^+), 181, 105, 91	160	3.9 (s, 3H, OCH_3), 5.2 (s, 2H, $COCH_2$), 5.4 (s, 2H, CH_2), 7.3-7.6 (m, 12H, Ar-H), 7.59 (s, 1H, H^6)
1g	$C_{14}H_{18}O_4BrN$	344 (M^+), 246, 98, 84	218	2.0-2.1 (m, 4H, $(CH_2)_2$ of pyrrolidine ring), 2.8-2.9 (m, 4H, $N(CH_2)_2$ of pyrrolidine ring), 2.8-2.9 (m, 4H, $N(CH_2)_2$), 3.56-3.61 (t, 2H, NCH_2), 3.8 (s, 3H, OCH_3), 4.28-4.33 (t, 2H, OCH_2), 7.23 (s, 1H, H^3), 7.42 (s, 1H, H^6)
1h	$C_{15}H_{20}O_4BrN$	357 (M^+), 237, 137, 120, 112, 98	210	1.5-1.8 (m, 6H, $(CH_2)_3$ of piperidine ring), 2.4-2.48 (m, 4H, $(CH_2)_2$ of piperidine ring), 2.50 (t, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 4.46-4.51 (t, 2H, OCH_2), 7.30 (s, 1H, H^3), 7.40 (s, 1H, H^6)

Table II : Physical data and characterization of substituted orthobromobenzoates (7a-d)

Compd. No.	Mol. Formula	Mass: m/z	m.p. °C	^{1}H NMR ($CDCl_3$, δ ppm)
3d	$C_{14}H_{10}O_5$	258 (M^+) 243, 219, 215, 187, 131, 91, 69	>250	3.91 (s, 3H, OCH_3), 6.72-6.73 (d, 1H, H^4), 6.79-6.85 (dd, 1H, H^2), 7.40 (s, 1H, H^{10}), 7.50 (s, 1H, H^7), 7.88-7.92 (d, 1H, H^1)
3e	$C_{15}H_{12}O_5$	272 (M^+), 258, 228, 214, 158, 121	>280	3.85 (s, 3H, 8-OCH_3), 3.98 (s, 3H, 9-OCH_3), 6.70-6.71 (d, 1H, H^4), 6.78-6.82 (dd, 1H, H^2), 7.5 (s, 1H, H^{10}), 7.6 (s, 1H, H^7), 8.13-8.18 (d, 1H, H^1)

3f	$C_{20}H_{16}O_5$	272 (M^+), 258, 228, 214, 158, 121	198	3.91 (s, 3H, OCH_3), 5.49 (s, 2H, OCH_2), 6.86-6.87 (d, 1H, H^4), 6.94-6.98 (dd, 1H, H^2), 7.49-7.69 (m, 7H, H^7, H^{10} and Ar-H), 7.93 (s, 1H, H^7), 8.26-8.30 (d, 1H, H^1)
3g	$C_{20}H_{21}O_5N$	355 (M^+), 307, 289, 242, 154, 136	196	1.70-1.80 (m, 4H, $(CH_2)_2$ of pyrrolidine), 2.50-2.57 (m, 4H, $N(CH_2)_2$ of pyrrolidine), 2.88-3.08 (t, 2H, NCH_2), 3.98 (s, 1H, OCH_3), 4.30-4.36 (t, 2H, OCH_2), 6.73-6.79 (d, 1H, H^4), 6.84-6.86 (dd, 1H, H^2), 7.53 (s, 1H, H^7), 7.64 (s, 1H, H^{10}), 8.18-8.22 (s, 1H, H^1), 9.13 (s, 1H, OH)
3h	$C_{21}H_{23}O_5N$	369 (M^+), 149, 121, 91, 55	205	1.4-1.5 (m, 6, $(CH_2)_3$ of piperidine rign), 2.4-2.7 (m, 4H, $N(CH_2)_2$ of piperidine ring), 2.71-2.76 (t, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 4.30-4.36 (t, 2H, OCH_2), 6.72-6.74 (d, 1H, H^4), 6.79-6.85 (dd, 1H, H^2), 7.5 (s, 1H, H^7), 7.71 (s, 1H, H^{10}), 8.18-8.23 (dd, 1H, H^2)

Table III : Physical data and characterization of 6H-dibenzo [b,d] pyron-6-ones (3d-3h)

Compd. No.	Mol. Formula	Mass: m/z	m.p. °C	^{1}H NMR ($CDCl_3$, δ ppm)
3d	$C_{14}H_{10}O_5$	258 (M^+) 243, 219, 215, 187, 131, 91, 69	>250	3.91 (s, 3H, OCH_3), 6.72-6.73 (d, 1H, H^4), 6.79-6.85 (dd, 1H, H^2), 7.40 (s, 1H, H^{10}), 7.50 (s, 1H, H^7), 7.88-7.92 (d, 1H, H^1)
3e	$C_{15}H_{12}O_5$	272 (M^+), 258, 228, 214, 158, 121	>280	3.85 (s, 3H, 8-OCH_3), 3.98 (s, 3H, 9-OCH_3), 6.70-6.71 (d, 1H, H^4), 6.78-6.82 (dd, 1H, H^2), 7.5 (s, 1H, H^{10}), 7.6 (s, 1H, H^7), 8.13-8.18 (d, 1H, H^1)
3f	$C_{20}H_{16}O_5$	272 (M^+), 258, 228, 214, 158, 121	198	3.91 (s, 3H, OCH_3), 5.49 (s, 2H, OCH_2), 6.86-6.87 (d, 1H, H^4), 6.94-6.98 (dd, 1H, H^2), 7.49-7.69 (m, 7H, H^7, H^{10} and Ar-H), 7.93 (s, 1H, H^7), 8.26-8.30 (d, 1H, H^1)
3g	$C_{20}H_{21}O_5N$	355 (M^+), 307, 289, 242, 154, 136	196	1.70-1.80 (m, 4H, $(CH_2)_2$ of pyrrolidine), 2.50-2.57 (m, 4H, $N(CH_2)_2$ of pyrrolidine), 2.88-3.08 (t, 2H, NCH_2), 3.98 (s, 1H, OCH_3), 4.30-4.36 (t, 2H, OCH_2), 6.73-6.79 (d, 1H, H^4), 6.84-6.86 (dd, 1H, H^2), 7.53 (s, 1H, H^7), 7.64 (s, 1H, H^{10}), 8.18-8.22 (s, 1H, H^1), 9.13 (s, 1H, OH)
3h	$C_{21}H_{23}O_5N$	369 (M^+), 149, 121, 91, 55	205	1.4-1.5 (m, 6, $(CH_2)_3$ of piperidine rign), 2.4-2.7 (m, 4H, $N(CH_2)_2$ of piperidine ring), 2.71-2.76 (t, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 4.30-4.36 (t, 2H, OCH_2), 6.72-6.74 (d, 1H, H^4), 6.79-6.85 (dd, 1H, H^2), 7.5 (s, 1H, H^7), 7.71 (s, 1H, H^{10}), 8.18-8.23 (dd, 1H, H^2)

Table IV : Physical data and characterization of substituted 6H-dibenzo [b,d] pyron-6-ones (4a-h)

Compd. No.	Mol. Formula	Mass: m/z	m.p. °C	^{1}H NMR ($CDCl_3$, δ ppm)
4a	$C_{16}H_{14}O_3$	254 (M^+), 212, 184, 128, 83	78	1.37 x 4.00 (s, 6H, $(CH_3)_2$ of isopropyl gp), 4.59-4.68 (q, 1H, –CH– of isopropyl gp), 7.4-7.7 (m, 2H, H^2 & H^4), 7.5-7.6 (t, 1H, H^8), 7.78-7.81 (t, 1H, H^9), 7.90-7.97 (m, 2H, H^7 and H^{10}), 8.33-8.37 (d, 1H, H^1)
4b	$C_{17}H_{16}O_4$	284 (M^+), 282, 241, 226, 212, 170, 105, 68	96	1.37-1.40 (m, 6H, $(CH_3)_2$ of isopropyl gp), 3.92 (s, 3H, OCH_3), 4.51-4.69 (m, 1H, –CH– of isopropyl gp.), 6.75-6.95 (m, 2H, H^4 & H^2), 7.34-7.39 (dd, 1H, H^9), 7.76-7.77 (d, 1H, H^7), 7.83-8.12 (m, 2H, H^{10} & H^1).
4c	$C_{19}H_{20}O_4$	312 (M^+), 270, 228, 200, 170, 83, 57	78	1.25-1.44 (m, 12H, $(CH_3)_2$ of isopropyl group x 2), 4.55-4.67 (m, 1H, –CH–), 4.71-4.83 (m, 1H, –CH–), 6.83-6.88 (m, 2H, H^8 and H^4) 6.97-7.02 (dd, 1H, H^2), 7.14-7.16 (d, 1H, H^{10}), 7.82-7.86 (d, 1H, H^1), 8.25-8.29 (d, 1H, H^7)
4d	$C_{19}H_{20}O_4$	312 (M^+), 228, 171, 149, 115, 91	98	1.36-1.39 (m, 12H, $(CH_3)_2$ x 2 of isopropyl gp), 4.54-4.64 (m, 1H, –CH–), 4.66-4.76 (m, 1H, –CH–), (m, 1H, –CH– of isopropyl gp.), 6.84-6.85 (s, 1H, H^4), 6.88-6.89 (d, 1H, H^2), 7.30-7.34 (dd, 1H, H^{10}), 7.75-7.76 (d, 1H, H^7), 7.82-8.19 (m, 2H, H^9 & H^1)
4e	$C_{18}H_{18}O_5$	314 (M^+), 272, 257, 229, 159, 146	218	1.37-1.40 (d, 6H, $(CH_3)_2$), 3.99 (s, 3H, 8-OCH_3), 4.07 (s, 3H, 9-OCH_3), 4.35-4.67 (s, 1H, CH-isopropyl gp.), 6.85-6.86 (d, 1H, H^4), 6.90-6.95 (d, 1H, H^2), 7.32 (s, 1H, H^7), 7.77 (s, 1H, H^{10}), 7.79-7.84 (d, 1H, H^1)
4f	$C_{18}H_{18}O_5$	342 (M^+), 300, 258, 243	196	1.37-1.59 (m, 12H, $(CH_3)_2$ x 2 of isopropyl gps), 4.0 (s, 3H,OCH_3), 4.54-4.66 (m, 1H, –CH–), 4.76-4.92 (m, 1H, –CH–), 6.75 (s, 1H, H^4), 6.84-6.89 (dd, 1H, H^2), 7.39 (s, 1H, H^7), 7.72 (s, 1H, H^{10}), 7.81-8.12 (d, 1H, H^1)
4g	$C_{28}H_{22}O_5$	438	186	3.88 (s, 3H, OCH_3), 5.02 (s, 2H, CH_2 benzylic) 5.12 (s, 2H, –CH_2- benzylic), 6.60-6.61 (d, 1H, H^4), 6.62-6.66 (m, 2H, H^7 and H^2), 7.35-7.56 (m, 14H, ArH benzylic, H^{10} and H^{11})
4h	$C_{22}H_{18}O_5$	362	192	3.80 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 5.44 (s, 2H, OCH_2), 6.83 (s, 1H, H^4), 6.85-6.89 (d, 1H, H^2), 7.34-7.52 (m, 7H, Ar-H, H^7 and H^{10}), 7.72-7.74 (d, 1H, H^1)

Table V : Physical data and characterization of substituted 6H-dibenzo [b,d] pyrans (5a-f)

Compd.	Mol. Formula	Mass: m/z	m.p. °C	^{1}H NMR ($CDCl_3$, δ ppm)
5a	$C_{20}H_{24}O_4$	328 (M^+), 286, 244, 228, 215, 201, 155	96	1.33-1.40 (m, 12H, $(CH_3)_2$x2 of isopropyl groups), 3.86 (s, 3H, OCH_3), 4.47-4.57 (m, 2H, –CH– x 2 of isopropyl groups), 5.04 (s, 2H, $–CH_2–$ of pyran ring), 6.51-6.52 (d, 1H, H^4), 6.55-6.61 (m, 2H, H^2 & H^7), 7.15 (s, 1H, H^{10}), 7.35-7.50 (d, 1H, H^1)
5b	$C_{15}H_{14}O_4$		224	
5c	$C_{28}H_{24}O_4$	424 (M^+), 334, 306, 242, 91		3.90 (s, 3H, OCH_3), 5.04 (s, 2H, $–CH_2$ benzylic), 5.06 (s, 2H, $–CH_2–$ of pyran ring), 6.59-6.60 (d, 1H, H^2), 6.62-6.66 (m, 2H, H^7 and H^2), 7.35-7.56 (m, 14H, Ar-H benzylic, H^{10} and H^1)
5d	$C_{22}H_{20}O_4$	348 (M^+), 257, 229, 201, 141, 115, 91		3.80 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 5.04 (s, 2H, $–CH_2$ of pyran ring), 5.20 (s, 2H, $–OCH_3–$), 6.51-6.53 (d, 1H, H^4), 6.55-6.66 (dd, 1H, H^2), 6.76 (s, 1H, H^7), 7.14 (s, 1H, H^{10}), 7.30-7.49 (m, 6H, Ar-H and H^1)
5e	$C_{14}H_{12}O_4$	244 (M^+), 229, 201, 115, 44	194	3.78 (s, 3H, OCH_3), 4.96 (s, 2H, CH_2 of pyran ring), 6.32-6.33 (d, 1H, H^4), 6.43-6.49 (dd, 1H, H^2), 6.82 (s, 1H, H^7), 7.05 (s, 1H, H^{10}), 7.40-7.44 (d, 1H, H^1), 9.03 (s, 1H, 3-OH), 9.58 (s, 1H, 9-OH)
5f	$C_{15}H_{14}O_4$	257 (M^+), 242, 214, 114, 82		3.80 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 5.13 (s, 2H, $–CH_2–$ of pyran ring), 5.60 (s, 1H, OH), 6.52-6.53 (d, 1H, H^4), 6.58-6.72 (m, 2H, H^2 and H^7), 7.15 (s, 1H, H^{10}), 7.41-7.57 (m, 1H, H^1)

Table VI : Physical data and characterization of substituted 6, 6-dimethyl dibenzo [b,d] pyrans (6a-d)

Compd. No.	Mol. Formula	Mass: m/z	m.p. °C	^{1}H NMR ($CDCl_3$, δ ppm)
6a	$C_{24}H_{24}O_4$	376 (M^+), 361, 269, 147, 91	152	1.56 (s, 3H, CH_3 of pyran ring), 1.60 (s, 3H, CH_3 of pyran ring), 3.79 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.20 (s, 2H, CH_2 of benzyloxy group), 6.59-6.60 (d, 1H, H^4), 6.70-6.76 (dd, 1H, H^2), 7.03 (s, 1H, H^7), 7.47-7.65 (m, 6H, Ar-H & H^{10}), 7.80-7.85 (dd, 1H, H^1)
6b	$C_{17}H_{18}O_4$	286 (M^+), 271, 256, 135, 105		1.56 & 1.60 (s, s, 6H, CH_3 x 2 of pyran ring), 3.80 (s, 3H, 8.0 CH_3), 3.92 (s, 3H, 3-OCH_3), 5.58 (s, 1H, OH), 6.39 (s, 1H, H^4), 6.49-6.54 (dd, 1H, H^2), 6.68 (s, 1H, H^7), 7.36 (s, 1H, H^{10}), 7.50-7.45 (dd, 1H, H^2), 6.68 (s, 1H, H^7), 7.36 (s, 1H, H^{10}), 7.50-7.45 (dd, 1H, H^1)
6c	$C_{24}H_{31}O_4N$	397 (M^+), 366, 269, 121, 112, 98	64	1.60-1.70 (m, 12H, $(CH_2)_3$ of piperidine ring and CH_3 x 2 of pyran ring), 2.51-2.56 (m, 4H, $N(CH_2)_2$), 2.81-2.87 (t, 2H, $N(CH_2)_2$), 3.80 (s, 3H, 8.0 CH_3), 3.98 (s, 3H, 3-OCH_3), 4.18-4.25 (t, 2H, OCH_2), 6.49-6.50 (d, 1H, H^4), 6.55-6.60 (d, 1H, H^2), 6.70-7.06 (s, 1H, H^7 and H^{10}), 7.47-7.51 (d, 1H, H^1)

6d	$C_{23}H_{29}O_5N$	399 (M^+), 296, 270, 196, 152, 113, 99	126	1.60-1.70 (s, s, 6H, CH_3x2 of pyran ring), 2.50-2.54 (m, 4H, $N(CH_2)_2$ of morpholine ring), 3.68-3.80 (m, 4H, $(CH_2)_2O$ of morpholine ring), 3.90 (s, 3H, OCH_3), 3.98-4.22 (t, 2H, OCH_2), 6.49-6.51 (d, 1H, H^4), 6.55-6.60 (dd, 1H, H^2), 6.71 (s, 1H, H^7), 7.16 (s, 1H, H^{10}), 7.46-7.51 (d, 1H, H^1)
6e	$C_{23}H_{29}O_4N$	383 (M^+), 219, 149, 131, 99, 86	124	1.49 & 1.50 (s, s, 3H x 2, CH_3 x 2 of pyran ring), 1.79-1.86 (m, 4H, $(CH_2)_2$ of pyrrolidine ring), 2.64-2.67 (m, 4H, $N(CH_2)_2$), 2.95-3.02 (t, 2H, NCH_2), 3.80 (s, 3H, 3-OCH_3), 3.99 (s, 3H, 8-OCH_3), 4.19-4.26 (t, 2H, OCH_2), 6.49-6.50 (d, 1H, H^4), 6.55-6.59 (dd, 1H, H^2), 6.60 (s, 1H, H^7), 7.16 (s, 1H, H^{10}), 7.46-7.51 (d, 1H, H^1).
6f	$C_{22}H_{28}O_4$	356 (M^+), 341, 299, 257, 141, 83, 47	82	1.31-1.39 (m, 12H, $(CH_3)_2$ x 2 isopropyl groups), 1.55 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.50-4.61 (m, 2H, –CH– x 2 of isopropyl groups), 6.48-6.49 (d, 1H, H^4), 6.52-6.56 (dd, 1H, H^1), 6.57 (s, 1H, H^7), 7.15 (s, 1H, H^{10}), 7.44-7.48 (d, 1H, H^1)

Table VII : Results of Biological Activity

Compd. No.	Antiestrogenic effect (% inhibition at 10 μg dose)	Estrogenic effect (% uterine wt. gain)	RBA (ER) % of E_2	Anti-implantation activity (%) 10 μg dose (1-5 day schedule)	Antiresorptive activity % inhibition in PTH induced resorption
3c	0.61	12.2	0.01	6	1.1
3d	8.6	10.8	0.11	11	NIL
3g	9.8	41.8	0.8	22	5.6
3h	4.3	78.4	0.24	17	6.2
4a	12.7	6.1	0.02	18	2.8
4b	14.9	12.4	0.09	12	1.9
4c	10.2	7.2	0.04	20	2.1
4d	16.8	8.9	0.02	24	3.4
4e	9.4	13.4	0.11	12	2.64
4f	0.62	16.2	0.10	10	1.2
5a	9.9	6.9	0.18	33	7.78
5b	4.8	20.8	0.07	35	3.1
5e	7.2	11.2	0.12	51	1.4
5f	10.1	12.8	0.16	30	2.1
6c	18.6	10.9	0.18	26	3.1
6d	20.2	20.1	0.14	32	0.8
6e	24.7	20.4	0.10	60	4.2
6f	12.8	15.8	0.12	35	

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