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Synthesis and biological evaluation of 2,3,4-triarylbenzopyran derivatives as SERM and therapeutic agent for breast cancer ☆

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ABSTRACT

A novel class of 2,3,4-triarylbenzopyrans has been synthesized and were evaluated for their selective estrogen receptor modulation activity and as a therapeutic agent for breast cancer. Among the compounds synthesized, compounds **11a** and **12c** exhibited 73.91% and 69.24% inhibition as estrogen antagonistic activity, respectively. Compound **12a** showed the lowest IC_{50} at 6.97 μM against MCF-7 and **11f** showed the lowest IC_{50} value of 5.6 μM against MDA-MB-231 cell line in spite of their low receptor binding affinity implicating these compounds probably act through ER independent mechanism.

1. Introduction

Estrogens are known to play an important role in the regulation of the development and maintenance of the female reproductive system, in particular of the uterus, ovaries and breast. Moreover, estrogens are involved in the growth and/or function of several other tissues such as the bone, liver, brain, and the cardiovascular system.[1] More recently their involvement in the estrogen deficient syndrome such as osteoporosis, Alzheimer, and cardiovascular diseases in females as well as males has also been established.[2–4]

By definition, selective estrogen receptor modulators (SERMs) are ligands that exert estrogen agonist action in some target tissues while acting as estrogen antagonists in others tissues.[5] In this light, at first tamoxifen,[6] and later a second generation compounds with an agonist/antagonist behavior[7] were developed and among them, raloxifene[8] was the first selective estrogen receptor modulator SERM approved for the treatment and prevention of osteoporosis (Fig. 1). The efforts to obtain compounds with a better activity profile led to a third generation of SERMs characterized by improved potency and absence of adverse effects, such as those on breast and the cardiovascular system.[9] In medicinal chemistry the benzopyran/chroman scaffold are present in wide variety of biologically active molecules.[10] The naturally occurring leads genistein, daidzein, and coumestrol exhibit a moderate selectivity for ERβ and possess a common benzopyran motif. Further exploitation of the chroman scaffold has also provided some non-subtype selective, potent chromenes **I,**[11] **II,**[12] and **III**[13] as SERMs of commercial interest (Fig. 1).

A number of 2,3-disubstituted and 3,4-disubstituted benzopyran derivatives[10a,11,12] have been reported as potential estrogen antagonists/SERMs. CDRI-85/287[14] and EM-652[15] among 2,3-disubstituted benzopyrans, are potent estrogen antagonists. Ormeloxifene (centchroman), a 3,4-disubstituted benzopyran derivative is an oral contraceptive and anti-breast cancer agent. The stereospecific presence of different aryl substituents in the pyran ring was also found to affect the activity. Based upon the above findings, and to extend the scope of ER ligands through introducing an additional phenolic ether basic side chain, it was envisaged that a hybrid of 2,3-diaryl and 3,4-diaryldihydrobenzopyran, that is, 2,3,4-triarylbenzopyran would have superior SERM activity. We herein present synthesis and invitro anti-breast cancer activity of a novel class of *trans, trans*-2,3,4-triarylsubstituted benzopyran **IV** and related diaryl benzopyran (Fig. 2). The rationale to design stereospecifically substituted 2,3,4-triarylbenzopyran was to build a scaffold with stereospecific alignment of three aryl substituents based on precedented ligands or leads. Structural resemblance of 2,3,4-triarylsubstituted benzopyran of prototype **IV** in ring A, B, D, and E to ormeloxifene, and in ring A, B, D, and F to CDRI 85/287 and EM 652 prompted us to explore this pharmacophore as potential lead for developing new estrogen receptor ligands.

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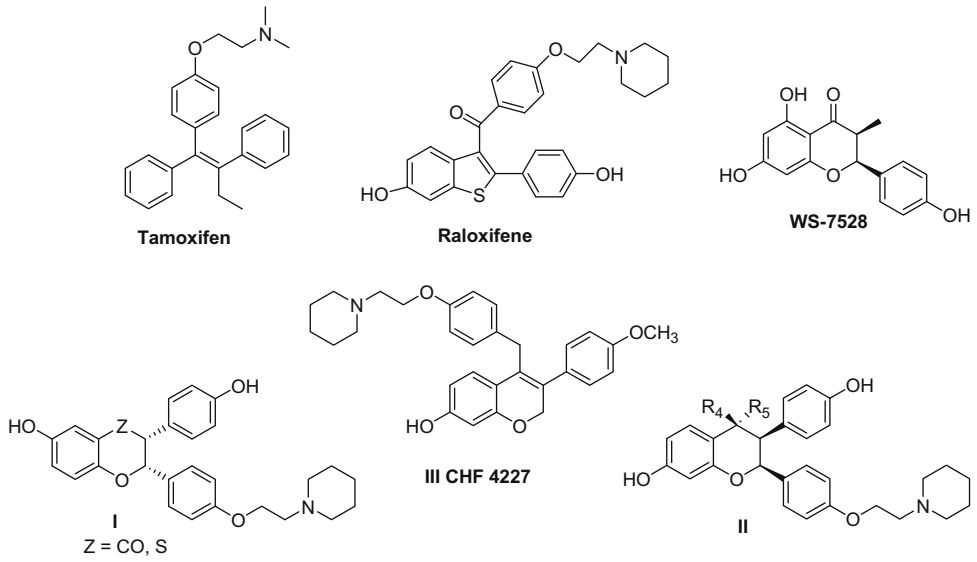


Figure 1. Structures of some important SERMs.

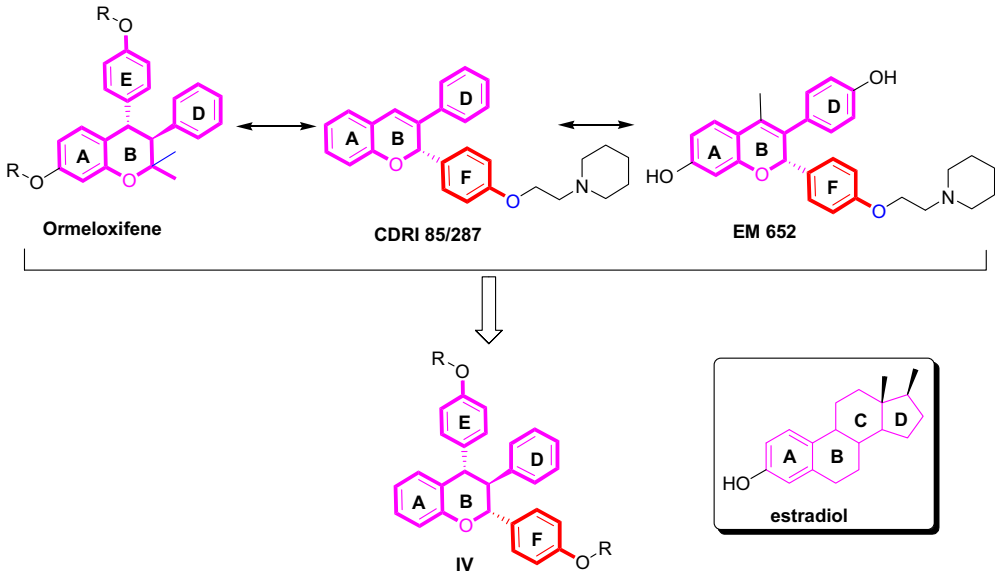


Figure 2. Structural resemblance of 2,3,4-triaryl benzopyrans I to potential SERMs.

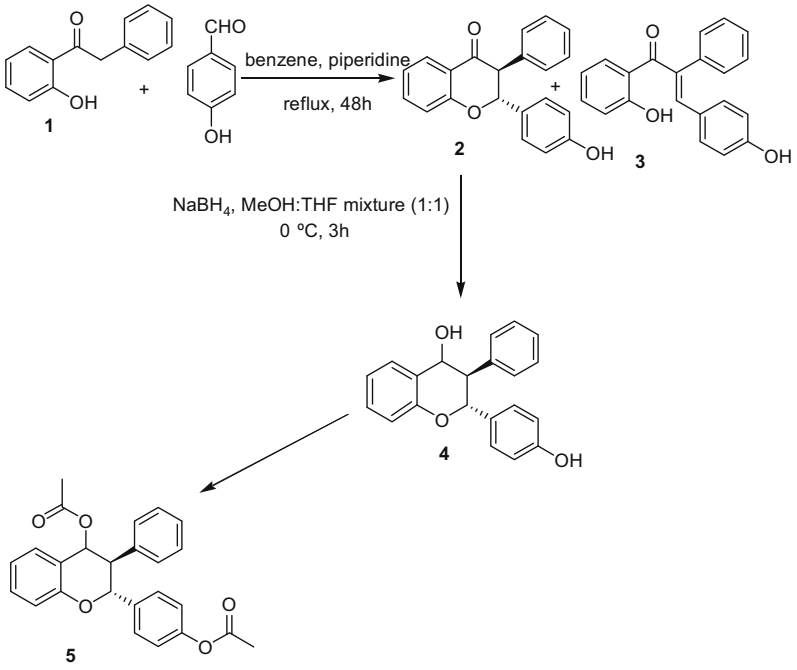
2. Chemistry

The titled compounds were synthesized by selective deacetylative direct arylation of arene **5** with phenol by aluminum chloride catalyzed C–H and C–OAc bond functionalization (Scheme 2). The diacetylated compound **5** was prepared by successive reduction and acetylation of compound **2**. Dihydrobenzopyran-4-one **2** was prepared by base catalyzed condensation of 4-hydroxybenzaldehyde with 2′-hydroxy-2-phenylacetophenone **1** by a known method.[16] Chalcone **3** as side product was also formed along with compound **2** and could be easily separated by column chromatography.

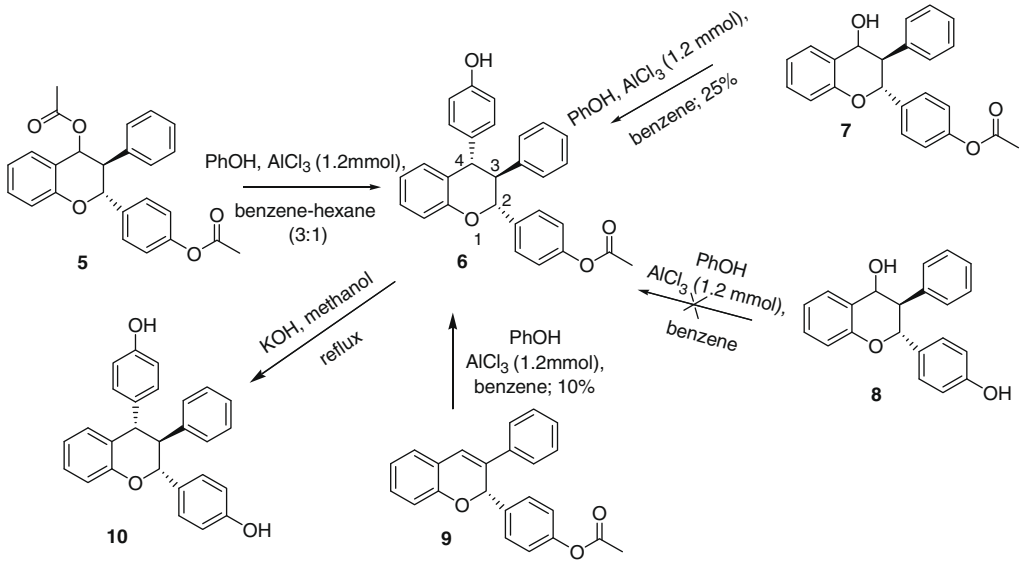
The 4-hydroxy-2,3-dihydro-4*H*-1-benzopyran **4** was prepared from dihydrobenzopyran-4-one **2** by sodium borohydride reduction in mixture of methanol–THF (1:1). (Scheme 1).

trans-2,3-Disubstituted-2,3-dihydro-4*H*-1-benzopyran-4-ol **4** was further acetylated by acetic anhydride to the diacetylated compound **5**. The purpose of acetylation was to increase the non-polarity of the compound so as to make it soluble in non polar solvents commonly used for aluminum chloride catalyzed reactions. Herein, we used benzene–hexane mixture (3:1) as an optimal reaction solvent for the deacetylative arylation of phenols. The diacetylated benzopyran **5** was regio-selectively arylated by phenol in stereospecific manner in the presence of anhydrous aluminum chloride to obtain *trans, trans*-2,3,4-trisubstituted-2,3-dihydro-4*H*-1-benzopyran, (2,3,4-triarylchroman), **6** in quantitative yield. This route was much more facile and gave the optimal yield, compared to arylation of phenol with monohydroxy chroman **7,** dihydroxy compound **8** or monoacetylated chromene **9** (Scheme 2). Compound **10** was obtained by basic hydrolysis of **6.**

The *trans*, *trans* geometry in compound **6** was confirmed by the ^{1}H NMR experiment. The appearance of a proton triplet at δ 3.24 is assigned for H-3 (J = 10.8 Hz) and two doublets at δ 4.46 (J = 11.2 Hz) and δ 5.24 (J = 10.4 Hz) for H-4 and H-1, respectively, is a characteristic features in the ^{1}H NMR spectrum of compound **6**.



Scheme 1.



Scheme 2.

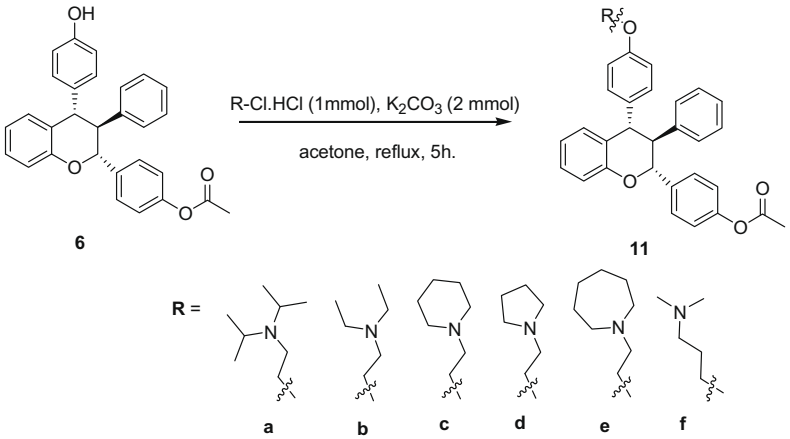
The *J* values together indicated the *trans*, *trans* relationship between these three protons.

A series of compounds **11a–f, 13,** and **14** with different basic ether side chains were prepared in the usual manner by alkylation of the phenol **6**, **2**, and **4**, respectively, with corresponding ammonium hydrochloride in presence of potassium carbonate in acetone (Scheme 3). Basic hydrolysis of compound **11a, c**, and **d** afforded **12a–c** (Scheme 4).

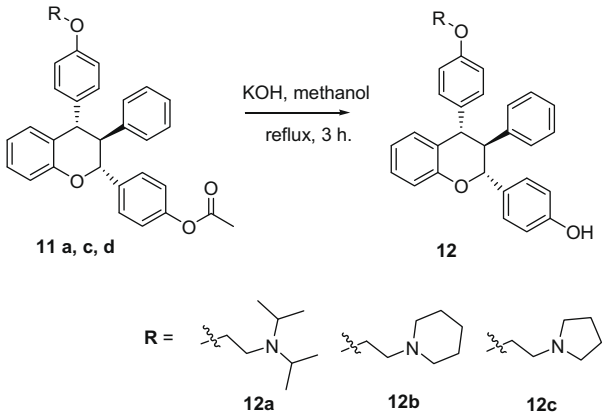
In order to prepare compounds **13** and **14** with basic ether side chains at position 4 of 2-hydroxy phenyl ring of dihydrobenzopyran-4-one **2** and its reduced product **4,** compounds **2** and **4** were alkylated with the corresponding amine hydrochloride under the similar conditions as mentioned above (Scheme 5 and 6).

3. Results and discussion

The biological activities results are shown in Table 1. The compounds **11a, c, e**, and **f** administered orally showed an average estrogenic activity of >100% gain except compound **11b** with estrogen-like activity of 41.2%. The same compounds **11a, c, e**, and **f** also possessed estrogen antagonistic activity >30% to a highest value of 73.91% shown by compound **11a,** but the compound **11a** possessed the estrogenic activity of 146.6% compared to centchroman. The compounds **12a–c** with free hydroxyl group in the phenyl ring at position 2, showed enhanced estrogen antagonistic activity from 51.47% to 69.24% with a decrease in estrogenic activity from 28.20% to 11.25% for compounds **12b** and **12c**, respectively.



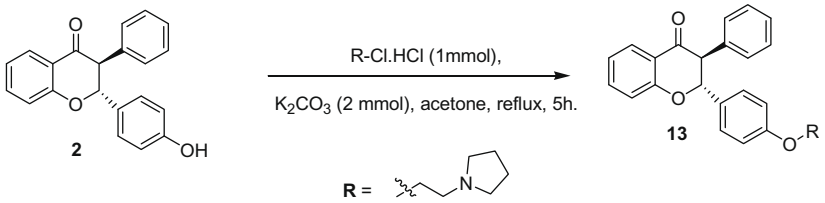
Scheme 3.



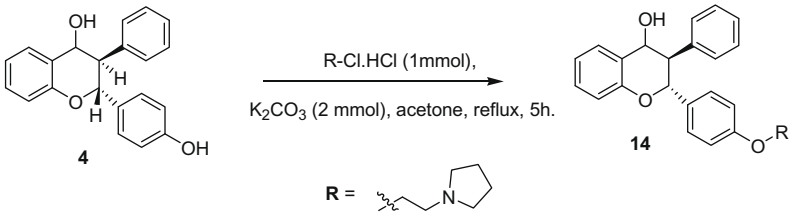
Scheme 4.

Compound **13** with a carbonyl function and compound **14** with a 2° hydroxyl group at position 4 of benzopyran ring together with an ethoxy pyrrolidine side chain at position 4 of 2-substituted phenyl ring were tested, and it was found that the estrogen antagonistic activity of compound **13** (45.39%) is comparatively higher than **14** (29.01%). There is also a remarkable decrease in estrogenic activity of 124.5% (**14**) to 13.17% (**13**). Compounds **6** and **10** without basic ether side chain in any of the phenyl rings possessed higher estrogenic activity compared to compounds with basic ether side chains.

In order to rationalize the anti-estrogenic profile of the benzopyran derivatives (Table 1), molecular docking studies were performed involving 12b and other known structurally related molecules namely, centchroman, and EM-652.[17] The reference protein coordinates of crystal structures of ligand binding domains (LBDs) of estrogen receptor complexed with 4-hydroxytamoxifen (pdb code: 3ERT) and 17β-estradiol (pdb code: 1ERE) were used for the docking experiments. The docking study was carried out in molecular operating environment MOE.[18] The starting conformations of 12b, centchroman, and EM-652 were generated in MOE using systematic conformational search with energy minimization (forcefield, MMFF94x). These conformations were flexibly docked into the protein coordinates (3ERT and 1ERE) to take their final shapes. The docking orientation and interactions of the 12b, centchroman, and EM-652 within the LBD of ERα are shown in Figure 1 along with 4-hydroxy tamoxifen and 17b-estradiol. In the docking study, the core skeleton benzopyran and its 3- and 4-aryl rings have favorably positioned similar to 4-hydroxy tamoxifen (Fig 1a). Also, centchroman, and EM-652 have docked in ERα as expected for their anti-estrogenic property (Fig. 1a). However, in the



Scheme 5.



Scheme 6.

Table 1
Estrogen agonistic and antagonistic activities of triarylbenzopyrans and their anti-proliferative activities

Entry	Compd	Dose (oral) (mg/kg/day)	Estrogen antagonistic activity[18]		Estrogen agonistic activity[18]		RBA[17] (% of E2)	Anti-proliferative activity[19] (IC_{50} in μM)		
			Uterine weight[a] (mg)	Inhibition[b] (%)	Uterine weight[a] (mg)	Gain[c] (%)		MCF-7	MDA-MB-231	HEK-293
1	Control		15.2 ± 1.24		15.2 ± 1.24					
	EE	0.02	113.68		113.68					
	11a	10	40.77 ± 0.59	73.91	37.0 ± 0.59	146.6	0.01	Inactive	Inactive	ND
2	Control		33.8 ± 0.97		33.8 ± 0.97					
	EE	0.02	112.5 ± 2.50		112.5 ± 2.50					
	11b	10	65.8 ± 1.20	59.3	47.8 ± 0.97	41.2	0.184	11.66	Inactive	16.11
3	Control		14.48 ± 0.88		14.48 ± 0.88					
	EE	0.02	104.82 ± 1.64		104.82 ± 1.64					
	11c	10	64.62 ± 1.11	51.41	39.32 ± 1.29	171.4	0.083	16.84	14	29.79
4	Control		14.48 ± 0.88		14.48 ± 0.88					
	EE	0.02	104.82 ± 1.64		104.82 ± 1.64					
	11e	10	85.42 ± 0.79	30.61	30.17 ± 3.13	108.3	0.15	Inactive	Inactive	88.63
5	Control		15.02 ± 1.24		15.02 ± 1.24					
	EE	0.02	113.68		113.68					
	11f	10	41.14 ± 1.51	58.4	32.63 ± 4.76	117.2	0.15	10.95	5.61	13.99
6	Control		14.48 ± 0.88		14.48 ± 0.88					
	EE	0.02	104.82 ± 1.64		104.82 ± 1.64					
	12a	10	47.06 ± 1.76	68.97	47.01 ± 1.76	225	0.1	6.97	7.48	20.47
7	Control		33.8 ± 0.97		33.8 ± 0.97					
	EE	0.02	112.5 ± 2.50		112.5 ± 2.50					
	12b	10	72.0 ± 1.54	51.47	36.6 ± 2.40	28.2	0.53	7.79	8.65	38.3
8	Control		33.8 ± 0.97		33.8 ± 0.97					
	EE	0.02	112.5 ± 2.50		112.5 ± 2.50					
	12c	10	58.0 ± 1.09	69.24	37.6 ± 0.68	11.25	0.25	18.36	17.75	36.27
9	Control		16.68 ± 0.51		16.68 ± 0.51					
	EE	0.02	96.75 ± 1.25		96.75 ± 1.25					
	13	10	60.38 ± 1.97	45.39	38.66 ± 0.42	13.17	0.109	Inactive	Inactive	34.02
10	Control		15.02 ± 1.24		15.02 ± 1.24					
	EE	0.02	113.68		113.68					
	14	10	86.22 ± 1.85	29.01	33.73 ± 0.42	124.5	NIL	Inactive	Inactive	ND
11	Control		21.2 ± 0.80		21.2 ± 0.80					
	EE	0.02	85.0 ± 1.0		85.0 ± 1.0					
	6	10	84.7 ± 1.89	4.2	43.5 ± 0.87	105.18	0.07	Inactive	Inactive	>100
12	Control		21.2 ± 0.80		21.2 ± 0.80					
	EE	0.02	85.0 ± 1.0		85.0 ± 1.0					
	10	10	71.5 ± 1.91	21.2	51.5 ± 0.96	142.9	0.09	Inactive	Inactive	>500
13	Control		17.4		17.4					
	EE	0.02	101.23		101.23					
	Cent.[d]	10	36.0	77.9	46.0	164.3	5.24	ND	ND	
14	Control		15.0 ± 0.57		15.0 ± 0.57					
	EE	3	66.35 ± 0.44		66.35 ± 0.44					
	TAM[e]		52.3 ± 5.3	27.4	46.32 ± 2.92	208.8	2.33	7.65	9.86	

EE = 17α-ethynylestradiol; E2 = 17β-estradiol; ND: not done.
[a] Values represent means ± SEM of a minimum of six observations in each group.
[b] Percent of 17α-ethynylestradiol per se treated group.
[c] Percent of vehicle control group.
[d] Centchroman.
[e] Tamoxifen.

LBD of 1ERE, the 12b, centchroman, and EM-652 have docked in different postures when compared to that of estradiol (Fig 1b). The absence of 7-hydroxyl on benzopyran scaffold made all the difference in the docking posture of these analogues. In docking dynamics a 7-hydroxyl group on benzopyran scaffold may have fulfilled the 2-OH role of estradiol. This may explain the weak estrogenic property of these compounds (Fig. 3).

All the above compounds were also evaluated for anti-proliferative activity. Two compounds **12a** and **12b** were found to possessed significant anti-proliferative activity similar to that of tamoxifen against MCF-7 and MDA-MB-231 cancer cell lines. Compounds having estrogenic activity are usually considered to have promoting activity in breast cancer. From estrogenicity results compound **12a** (225%) appeared to have higher estrogen-like activity than **12b** (28.2%). Therefore, though compound **12a** has better anti-proliferative activity with IC_{50} 6.971 μM and 7.482 μM against MCF-7 and MDA-MB-231, respectively, **12b** is devoid of high estrogenicity. Compound **12b** (0.53%) showed highest RBA followed by **12c** (0.25%). Compounds **11c** (0.083%), **11e** and **11f** (0.15%), **13** (0.109%) and **6** (0.07%) and **10** (0.09%) showed very low affinity for estrogen receptor whereas compound **14** is completely devoid of affinity for estrogen receptor. From RBA results, it appears that the compound **12b** may interact with estrogen receptor with moderate affinity and thereby, there is possibility that its anti-proliferative activity may be mediated by such interaction. Interestingly, **12a** although exhibited reasonably higher anti-breast cancer activity and estrogenic activity (225%), the compound failed to interact significantly with estrogen receptor (Table 1). Compound **12c** which exhibited marginal anti-proliferative activity, however, showed highest anti-estrogenic activity (69.24%) and moderately low estrogen-like activity (11.25%).

The compounds were also tested for their non-specific cytotoxicity in non-cancer originated cell line HEK-293. The results

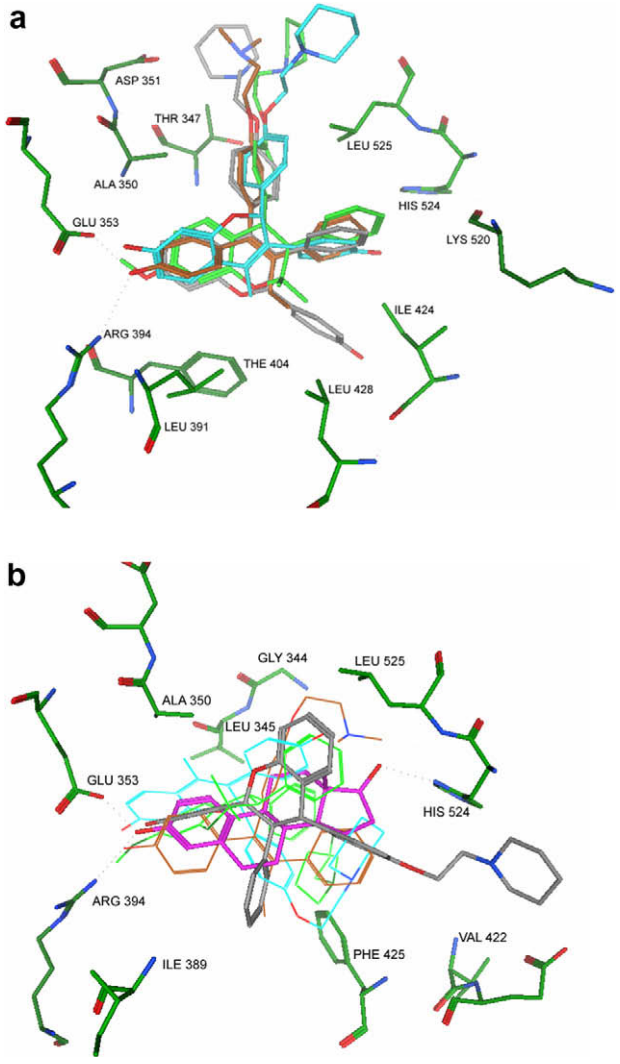


Figure 3. Superimposed docking poses of 12b, centchroman (backbone carbons in green) and EM-652 (cyan) with (a) 4-OH-tamoxifen (brown) in 3ERT coordinates and with (b) 17β-estradiol (megenta) in 1ERE coordinates of LBD of ERα.

revealed that compound **10** showed lowest cytotoxicity (>500 μM) followed by **6** (>100 μM) and **11f** (13.99 μM). Also, the compound **12a** (20.47 μM) appeared to be more toxic than **12b** (38.30 μM).

4. Biology

4.1. Estrogen receptor binding affinity[19]

The relative binding affinity (RBA) of the compounds for the estrogen receptor was determined[15] by competition assay, employing radiolabeled estradiol ^{3}H-[E_2] as the reference compound. The test ligands and ^{3}H-[E_2] were incubated (4 °C) with cytosol estrogen receptors obtained from immature 20–21-day-old rat uteri. Aliquots of the uterine cytosol (100 μL) prepared in TEA buffer (10 mM Tris, 1.5 mM EDTA, and 0.02% sodium azide, pH 7.4) were incubated in triplicate with a fixed concentration of radiolabeled estradiol with or without various concentrations of the competitor substance dissolved in 30 μL of the TEA buffer containing DMF as co-solvent (final concentration of DMF in the incubation medium never exceeded 5%) for 18 h at 4 °C. At the end of this period, dextran-coated charcoal (DCC) (2.5% Norit 0.25% dextran) suspension in 100 μL of TEA buffer was added into each tube, which was briefly vortexed and allowed to stand for 15 min. DCC was precipitated by centrifugation (800g × 10 min) and the supernatants counted for radioactivity in 5 mL of a dioxane-based scintillation fluid. RBA of the test compound was computed from a graph plotted between percent bound radioactivities versus log concentration of the test substance. At 50% inhibition, log of the competitor concentration relative to that of estradiol gave the affinity of the test compound to estrogen receptor relative to estradiol. This when multiplied with 100 gave the percentage value designated as RBA.

4.2. Estrogen agonistic activity[20]

Twenty-one-day-old immature female Sprague–Dawley rats were bilaterally ovariectomized under light ether anesthesia and after post-operative rest for 7 days were randomized into different treatment groups. Each rat received the compound once daily for three consecutive days by oral route. A separate group of animals received only the vehicle for similar duration served as control. At autopsy 24 h after the last treatment on day 31 of age, vaginal smear of each rat was taken and uterus was carefully excised, gently blotted, and weighed. Premature opening of vagina, cornification of vaginal epithelium, and increase in uterine fresh weight were taken as parameters for evaluation of estrogen agonistic activity in comparison to rats of vehicle control group. The objective was to evaluate estrogen agonistic effect of the compounds on the uterus and vagina.

4.3. Estrogen antagonistic activity[20]

Twenty-one-day-old immature female Sprague–Dawley rats were bilaterally ovariectomized under light ether anesthesia and after post-operative rest for 7 days were randomized into different treatment groups. Each rat received the compound of the invention and 0.02 mg kg^{-1} dose of 17α-ethynylestradiol in 10% ethanol–distilled water once daily for three consecutive days by oral route. A separate group of animals receiving only 17α-ethynylestradiol (0.02 mg kg^{-1}) in 10% ethanol–distilled water for similar duration were used for comparison. At autopsy on day 31 of age, vaginal smear of each rat was taken and uterus was carefully excised, gently blotted, weighed, and fixed for histology. Inhibition in ethynylestradiol induced cornification of vaginal epithelium and increase in uterine fresh weight were taken as parameters for evaluation of estrogen antagonistic effect of the compounds.

4.4. Anti-proliferative activity

4.4.1. Cell lines

MCF-7 is a breast cancer cell line derived from pleural effusion and most commonly used cell line for screening of anti-cancer breast agents (Soule et al., 1973), whereas MDA-MB-231 is an ER negative model of aggressive breast cancer.

4.4.2. Assay for anti-proliferative activity

The anti-proliferative activities[21] of the compounds were determined using MTT assay 1 × 10^4 cells/well were seeded in 100 μL DMEM, supplemented with 10% FBS in each well of 96-well micro culture plates and incubated for 24 h at 37 °C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, media were removed and to each well 100 μL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg/mL) was added and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazon crystals were dissolved in 100 μL of DMSO and absorbance at 540 nm wavelength were recorded.

5. Experimental

5.1. Preparation of 2-(4-hydroxyphenyl)-3-phenylchroman-4-one (2)

To a solution of 2′-hydroxydesoxybenzoin **1** (26.5 g, 0.125 mol) and 4-hydroxybenzaldehyde (15.3 g, 0.125 mol) in dry benzene (300 mL) was added dry piperidine (0.01 mol, 1 mL). The mixture was heated under reflux for 48 h, while water was removed azeotropically. After completion of reaction, the reaction mixture was cooled, and washed with water (30 mL × 3) and then with brine and dried over sodium sulfate and concentrated. The residue was purified on silica gel column chromatography using 10% EtOAc–hexane as eluent, to furnish the dihydrobenzopyran-4-one **2** (12 g) which was recrystallized from EtOAc–hexane.

Yield 32%; mp 195–196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (d, 1H, J = 11.5 Hz), 5.51 (d, 1H, J = 11.5 Hz), 6.72 (d, 2H, J = 8.5 Hz), 6.97–7.00 (m, 2H), 7.04–7.09 (m, 4H), 7.16–7.22 (m, 3H), 7.49–7.56 (m, 1H), 7.97 (dd, 1H, J = 8.2 and 1.7 Hz), 8.49 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 59.02 (CH), 84.27 (CH), 115.11 (CH), 117.84 (CH), 120.64 (C), 121.24 (CH), 126.87 (CH), 127.11 (CH), 128.05 (C), 128.11 (CH), 128.27 (CH), 129.37 (CH), 135.00 (C), 135.92 (CH), 157.26 (C), 160.98 (C), 192.70 (CO); ν_{max} (KBr, cm^{-1}) 3380, 1670, 1601, 1190; ES-MS (m/z) 317 [M+H]$^+$.

5.2. Preparation of 2-(4-Hydroxy-phenyl)-3-phenyl-chroman-4-ol (4)

To a solution of dihydrobenzopyran-4-one **2** (20 g, 0.06 mol) in methanol–THF (1:1) (200 mL), cooled in an ice bath. Sodium borohydride (6.8 g, 0.18 mol) was added in four portions at 5-min intervals. The reaction mixture was then stirred for 4 h. The reaction mixture was concentrated to 100 mL and the resulting solution was neutralized with saturated NH_4Cl solution and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with brine and dried over sodium sulfate and concentrated. The solid residue obtained was further crystallized from EtOAc–hexane to obtain pure **4** (19.6 g).

Yield 98.3%; mp 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 3.22 (t, 1H, J = 10.5 Hz), 3.51 (br s, 1H, OH), 5.10–5.17 (m, 2H), 6.62 (d, 2H, J = 8.5 Hz), 6.87–6.89 (m, 1H), 6.94–7.04 (m, 5H), 7.08–7.22 (m, 4H), 7.57 (d, 1H, J = 7.5 Hz), 8.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 54.03, 70.47, 81.66, 115.17, 116.21, 120.64, 126.13, 126.74, 127.44, 128.41, 128.64, 128.82, 129.57, 139.01, 139.04, 154.31, 156.73; ν_{max} (KBr, cm^{-1}) 3375, 1611, 1224, 755; ES-MS (m/z) 319 [M+H]$^+$; $[\alpha]_D^{20}$ −1.56, (c 0.105, $CHCl_3$).

5.3. Preparation of acetic acid 2-(4-acetoxy-phenyl)-3-phenyl-chroman-4-yl ester (5)

A mixture of compound **4** (10 g, 0.03 mol) and acetic anhydride (0.05 mol, 4.6 mL) in pyridine (50 mL) was refluxed for 4 h, and during this period the reaction was monitered by TLC. After completion of the reaction, pyridine was distilled off and the resulting reaction mixture was poured into crushed ice (300 mL). The reaction mixture was extracted with EtOAc (50 mL × 3), and the organic layer was washed with brine and dried over sodium sulfate and concentrated. The solid residue obtained was further crystallized from EtOAc–hexane to obtain pure **5** (12 g).

Yield 96.0%; mp 160–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.25 (s, 3H), 3.47 (t, 1H, J = 9.8 Hz), 5.33 (d, 1H, J = 10.1 Hz), 6.59 (d, 1H, J = 9.6 Hz), 6.92–7.00 (m, 4H), 7.04–7.06 (m, 2H), 7.14–7.20 (m, 6H), 7.24–7.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.95 (CH_3), 21.32 (CH_3), 51.45 (CH), 71.22 (CH), 81.24 (CH), 117.05 (CH), 121.31 (CH), 121.41 (CH), 121.97 (C), 127.52 (CH), 127.72 (CH), 128.32 (CH), 128.68 (CH), 128.69 (CH), 129.84 (CH), 136.38 (C), 137.33 (C), 150.48 (C), 154.82 (C), 169.34 (CO), 171.04 (CO); ν_{max} (KBr, cm^{-1}) 1761, 1729, 1223, 1010, 764; ES-MS (m/z) 403 [M+H]$^+$; $[\alpha]_D^{20}$ −1.73, (c 0.337, $CHCl_3$).

5.4. Typical procedure for preparation of acetic acid 4-[4-(4-hydroxy-phenyl)-3-phenyl-chroman-2-yl]-phenyl ester (6)

To a cooled solution of phenol (2.4 g, 25 mmol) and aluminum chloride (0.158 g, 1.2 mmol) in 100 mL benzene–hexane mixture (3:1) at 0–5 °C, a mixture of compound **5** (10 g, 24.8 mmol) and phenol (2.5 g, 25 mmol) in 100 mL benzene–hexane mixture (3:1) was added dropwise in 30 min. The reaction mixture was allowed to stir at this temperature during the addition, and then allowed to stir at room temperature for the completion of reaction (3 h). The reaction mixture was concentrated to 100 mL. To the resulting mixture crushed ice (100 mL) was added with continuous stirring for 15 min and then was extracted with EtOAc (50 mL × 3). The organic layer was washed with water, brine and dried over sodium sulfate and concentrated. The crude product obtained was further purified by column chromatography using 5–10% EtOAc–hexane mixture as white solid (9.9 g).

Yield 92%; mp 156–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.24 (t, 1H, J = 10.8 Hz), 4.46 (d, 1H, J = 11.2 Hz), 4.74 (s, 1H), 5.24 (d, 1H, J = 10.4 Hz), 6.57–6.59 (m, 2H), 6.77–6.84 (m, 6H), 6.88–6.91 (m, 2H), 6.96–7.06 (m, 4H), 7.14–7.19 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.34 (CH_3), 49.55 (CH), 55.19 (CH), 82.31 (CH), 115.33 (CH), 117.03 (CH), 121.01 (CH), 121.22 (CH), 126.77 (CH),126.82 (C), 127.86 (CH), 128.41 (C), 128.51 (CH), 128.81 (CH), 130.36 (CH), 130.39 (CH), 135.37 (C), 137.29 (C), 139.55 (C), 150.33 (C), 154.23 (C), 155.32 (C), 169.44 (CO); ν_{max} (KBr, cm^{-1}) 3362, 1762, 1720, 1194, 759; ES-MS (m/z) 437 [M+H]$^+$.

5.5. General procedure for preparation of ethers (11a–f), (13) and (14)

A mixture of compound **6** (1 mmol) for **11a–f** or **2** (1 mmol) for **13** or **4** (1 mmol) for **14** and corresponding 1-(2-chloroethyl) alkyl amine hydrochloride (1 mmol), anhydrous potassium carbonate (2 mmol) in dry acetone (15 mL) was refluxed for 5 h. The reaction mixture was then cooled to rt and the solid material was filtered off and washed with acetone (5 mL × 3). The combined filtrate was concentrated and the residue was purified by silica gel column chromatography using 2% methanol–chloroform mixture.

5.5.1. Acetic acid 4-{4-[4-(2-diisopropylaminoethoxy) phenyl]-3-phenylchroman-2-yl}phenyl ester (11a)

Yield 89.2%; mp 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, 12H, J = 6.5 Hz), 2.22 (s, 3H), 2.75 (t, 2H, J = 7.5 Hz), 2.96–3.05 (m, 2H), 3.26 (t, 1H, J = 10.9 Hz), 3.78 (t, 2H, J = 7.6 Hz), 4.46 (d, 1H, J = 11.2 Hz), 5.24 (d, 1H, J = 10.4 Hz), 6.64–6.67 (m, 2H), 6.78–6.85 (m, 6H), 6.88–6.91 (m, 2H), 6.96–7.06 (m, 4H), 7.13–7.19 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.97 (CH_3 × 4), 21.31 (CH_3), 44.64 (CH_2), 49.49 (CH), 49.85 (CH), 55.07 (CH), 69.19 (CH_2), 82.29 (CH), 114.29 (CH), 116.95 (CH), 120.95 (CH), 121.19 (CH), 126.69 (CH), 126.93 (C), 127.77 (CH), 128.36 (CH), 128.48 (CH), 128.78 (CH), 130.14 (CH), 130.37 (CH), 134.96 (C),137.26 (C), 139.55 (C), 150.28 (C), 155.25 (C), 157.60 (C), 169.30 (CO); ν_{max} (KBr, cm^{-1}) 2360, 1756, 1508, 1216, 760; ES-MS (m/z) 564 [M+H]$^+$. HRMS-EI: found 563.7297, calcd 563.7291. Microanalysis: $C_{37}H_{341}NO_4$.

5.5.2. Acetic acid 4-{4-[4-(2-diethylaminoethoxy)phenyl]-3-phenylchroman-2-yl}phenyl ester (11b)

Yield 89.7%; mp 85–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 6H, J = 7.1 Hz), 2.21 (s, 3H), 2.60 (br m, 4H), 2.81 (t, 2H, J = 6.3 Hz), 3.25 (t, 1H, J = 10.9 Hz), 3.94 (t, 2H, J = 6.5 Hz), 4.46 (d, 1H, J = 11.2 Hz), 5.24

(d, 1H, J = 10.5 Hz), 6.65–6.68 (m, 2H), 6.77–6.85 (m, 6H), 6.88–6.91 (m, 2H), 6.96–7.05 (m, 4H), 7.13–7.19 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.99 ($CH_3 \times 2$), 21.30 (CH_3), 48.02 ($CH_2 \times 2$), 49.53 (CH), 51.87 (CH_2), 55.11 (CH), 66.47 (OCH_2), 82.28 (CH), 114.37 (CH), 116.96 (CH), 120.95 (CH), 121.18 (CH), 126.69 (CH), 126.89 (C), 127.78 (CH), 128.36 (CH), 128.49 (CH), 128.78 (CH), 130.13 (CH), 130.36 (CH), 135.13 (C), 137.26 (C), 139.55 (C), 150.29 (C), 155.27 (C), 157.55 (C), 169.28 (CO); ν_{max} (KBr, cm^{-1}) 2361, 1762, 1509, 1216, 759; ES-MS (m/z) 536 $[M+H]^+$; HRMS-EI: found 535.2720, calcd 535.2723.

5.5.3. Acetic acid 4-{3-phenyl-4-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-chroman-2-yl}-phenyl ester (11c)

Yield 88.5%; mp 48–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44–1.45 (m, 2H), 1.58–1.65 (m, 4H), 2.22 (s, 3H), 2.43–2.51 (m, 4H), 2.74 (t, 2H, J = 5.94 Hz), 3.25 (t, 1H, J = 10.80 Hz), 4.02 (t, 2H, J = 6.00 Hz), 4.46 (d, 1H, J = 11.28 Hz), 5.24 (d, 1H, J = 10.44 Hz), 6.65–6.71 (m, 2H), 6.77–6.93 (m, 8H), 6.96–7.04 (m, 4H), 7.09–7.19 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.32 (CH_3), 24.21 (CH_2), 25.89 (CH_2), 49.49 (CH), 55.09 (CH), 55.17 (CH_2), 58.08 (CH_2), 65.71 (OCH_2), 82.28 (CH), 114.42 (CH), 116.97 (CH), 120.97 (CH), 121.19 (CH), 126.71 (CH), 126.86 (C), 127.79 (CH), 128.37 (CH), 128.48 (CH), 128.77 (CH), 130.14 (CH), 130.36 (CH), 135.27 (C), 137.24 (C), 139.52 (C), 150.28 (C), 155.26 (C), 157.43 (C), 169.30 (CO); ν_{max} (KBr, cm^{-1}) 2361, 1761, 1509, 1217, 757; ES-MS (m/z) $[M+H]^+$: 548; HRMS-EI: found 547.2722, calcd 547.2723.

5.5.4. Acetic acid 4-{3-phenyl-4-[4-(2-pyrrolidin-1-yl-ethoxy) phenyl]chroman-2-yl}phenyl ester (11d)

Yield 95%; mp 54–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99–2.02 (m, 4H), 2.23 (s, 3H), 3.07 (br m, 4H), 3.18–3.29 (m, 3H), 4.26–4.31 (m, 2H), 4.49 (t, 1H, J = 10.83 Hz), 5.23 (t, 1H, J = 9.70 Hz), 6.65–6.71 (m, 2H), 6.77–6.97 (m, 8H), 6.99–7.08 (m, 4H), 7.10–7.19 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.33, 23.49, 50.19, 54.36, 54.40, 55.16, 64.57, 82.25, 114.31, 117.09, 121.21, 121.34, 126.79, 127.96, 128.44, 128.72, 128.89, 130.10, 130.34, 130.48, 136.24, 137.19, 139.53, 140.87, 149.36, 155.51, 169.51; ν_{max} (KBr, cm^{-1}) 1759, 1490, 1360, 1216, 758; ES-MS (m/z) $[M+H]^+$ 534; HRMS-EI: found 533.2571, calcd 533.2566.

5.5.5. 4-(4-(4-(2-(Azepan-1-yl)ethoxy)phenyl)-3-phenylchroman-2-yl)phenyl acetate (11e)

Yield 86.3%; mp 61–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60–1.66 (m, 8H), 2.22 (s, 3H), 2.76–2.81 (m, 4H), 2.93 (t, 2H, J = 6.0 Hz), 3.25 (t, 1H, J = 10.9 Hz), 4.00 (t, 2H, J = 6.4 Hz), 4.46 (d, 1H, J = 11.2 Hz), 5.24 (d, 1H, J = 10.5 Hz), 6.65–6.68 (m, 2H), 6.77–6.91 (m, 8H), 6.96–7.06 (m, 4H), 7.12–7.19 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.31 (CH_3), 27.18 (CH_2), 27.51 (CH_2), 49.47 (CH), 55.05 (CH), 55.92 (CH_2), 56.44 (CH_2), 65.98 (OCH_2), 82.25 (CH), 114.39 (CH), 116.95 (CH), 120.95 (CH), 121.19 (CH), 126.69 (CH), 126.83 (C), 127.79 (CH), 128.35 (CH), 128.47 (CH), 128.75 (CH), 130.13 (CH), 130.35 (CH), 131.69 (C), 135.25 (C), 137.21 (C), 139.49 (C), 150.25 (C), 155.23 (C), 157.40 (CH), 158.46 (C), 169.33 (CO); ν_{max} (KBr, cm^{-1}) 1750, 1511, 1400, 1206, 777; ES-MS (m/z) 562 $[M+H]^+$. HRMS-EI: found 561.7135, calcd 561.7132.

5.5.6. Acetic acid 4-{4-[4-(3-dimethylaminopropoxy) phenyl]-3-phenylchroman-2-yl}phenyl ester (11f)

Yield 85%; mp 54–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93–2.00 (m, 2H), 2.22 (s, 3H), 2.31 (s, 6H), 2.49–2.56 (m, 2H), 3.21–3.31 (t, 1H, J = 9.9 Hz), 3.91 (t, 2H, J = 6.2 Hz), 4.49 (d, 1H, J = 10.9 Hz), 5.24 (d, 1H, J = 9.9 Hz), 6.64–6.69 (m, 2H), 6.77–6.93 (m, 8H), 6.97–7.05 (m, 4H), 7.09–7.19 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.32 (CH_3), 27.13 (CH_2), 45.22 ($NCH_3 \times 2$), 49.48 (CH), 55.00 (CH), 56.45 (CH_2), 65.91 (OCH_2), 77.45 (CH), 114.23, 116.96, 120.97, 121.19, 126.66, 126.87, 127.79, 128.35, 130.11, 130.36, 131.68, 135.21, 137.26, 139.53, 140.95, 149.33, 150.31, 155.25, 157.54, 169.30; ν_{max} (KBr, cm^{-1}) 2360, 1757, 1511, 1216, 760; ES-MS (m/z) 522 $[M+H]^+$; HRMS-EI: found 521.2548, calcd 521.2566.

5.5.7. 3-Phenyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl) chroman-4-one (13)

Yield 78%; viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76–1.78 (m, 4H), 2.58–2.60 (m, 4H), 2.83 (t, 2H, J = 5.7 Hz), 3.86 (t, 2H, J = 5.7 Hz), 3.96 (d, 1H, J = 10.9 Hz), 5.50 (d, 1H, J = 10.9 Hz), 6.73–6.75 (m, 2H), 6.95–7.00 (m, 2H), 7.01–7.05 (m, 2H), 7.09–7.21 (m, 5H), 7.45–7.53 (m, 1H), 7.96 (dd, 1H, J = 8.1 and 1.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.59, 54.89, 55.17, 59.62, 67.02, 84.65, 114.51, 118.23, 121.10, 121.76, 127.46, 127.73, 128.61, 130.31, 130.11, 135.11, 136.29, 159.02, 161.31, 192.06; ES-MS (m/z) 414 $[M+H]^+$. HRMS-EI: found 413.5097, calcd 413.5106. Microanalysis data agreed: for $C_{27}H_{27}NO_3$.

5.5.8. 3-Phenyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-chroman-4-ol (14)

Yield 78%; mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77–1.80 (m, 4H), 2.58 (br m, 4H), 2.82 (t, 2H, J = 5.9 Hz), 3.22 (t, 1H, J = 10.4 Hz), 3.99 (t, 2H, J = 5.9 Hz), 5.18 (d, 1H, J = 10.9 Hz), 5.23 (d, 1H, J = 10.1 Hz), 6.70–6.73 (m, 2H), 6.91–6.93 (m, 1H), 6.98–7.10 (m, 5H), 7.14–7.26 (m, 4H), 7.58 (d, 1H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.64 ($CH_2 \times 2$), 54.69 (CH), 54.90 ($CH_2 \times 2$), 55.17 (CH_2), 67.03 (OCH_2), 70.88 (CH), 81.53 (CH), 114.44 (CH), 116.65 (CH), 121.08 (CH), 125.43 (C), 127.32 (CH), 127.42 (CH), 128.72 (CH), 128.94 (CH), 129.19 (CH), 131.00 (C), 138.49 (C), 154.41 (C), 158.71 (C); ν_{max} (KBr, cm^{-1}) 3398, 1265, 1037, 738; ES-MS (m/z) $[M+H]^+$ 416. HRMS-EI: found 415.5272, calcd 415.5265. Microanalysis data agreed: for $C_{27}H_{29}NO_3$.

5.6. General procedure for preparation of hydroxy-ethers (12a–c) and (10)

To a solution of compound **11a, c**, and **d** (1 mmol) (for **12**) or **6** (1 mmol) (for compound **10**) in methanol (10 mL) was added potassium hydroxide (1.2 mmol) and the mixture was refluxed for 1 h. The reaction mixture was allowed to cool to rt and then concentrated to 2–5 mL, and to it was poured ice cooled water (20 mL). The mixture was then extracted with ethyl acetate (3×15 mL). The organic layer was washed with brine and dried over sodium sulfate and concentrated. The crude product was purified on silica gel column chromatography using 2–5% methanol–chloroform mixture.

5.6.1. 4-{4-[4-(2-Diisopropylamino-ethoxy)-phenyl]-3-phenyl-chroman-2-yl}-phenol (12a)

Yield 100%; mp 64–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 12H, J = 6.5 Hz), 2.18–2.26 (br s, OH), 2.78 (t, 2H, J = 7.4 Hz), 3.00–3.09 (m, 2H), 3.28 (t, 1H, J = 8.1 Hz), 3.82 (t, 2H, J = 7.4 Hz), 4.44 (d, 1H, J = 11.2 Hz), 5.19 (d, 1H, J = 10.4 Hz), 6.61–6.67 (m, 4H), 6.77–6.84 (m, 6H), 6.96–7.08 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.80 ($CH_3 \times 4$), 44.76 (CH_2), 49.87 (CH), 50.20 (CH), 54.96 (CH), 68.84 (OCH_2), 82.56 (CH), 114.37, 115.25, 117.02, 120.85, 126.49, 127.02, 127.74, 128.28, 128.84, 128.93, 130.20, 130.42, 131.80, 135.36, 140.10, 155.61, 157.52; ν_{max} (KBr, cm^{-1}) 3427, 1363, 1216, 761; ES-MS (m/z) $[M+H]^+$ 522; HRMS-EI: found 521.2925, calcd 521.2930.

5.6.2. 4-{3-Phenyl-4-[4-(2-piperidin-1-yl-ethoxy)phenyl]-chroman-2-yl}phenol (12b)

Yield 97.3%; mp 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43–1.45 (m, 2H), 1.58–1.60 (m, 4H), 1.99–2.04 (br s, OH), 2.51 (br m, 4H), 2.73 (t, 2H, J = 5.9 Hz), 3.26 (t, 1H, J = 10.8 Hz), 3.99 (t, 2H, J = 6.00 Hz), 4.43 (d, 1H, J = 11.1 Hz), 5.18 (d, 1H, J = 10.3 Hz), 6.58–6.68 (m,

4H), 6.76–6.83 (m, 7H), 6.97–7.08 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.06 (CH_2), 25.43 (CH_2), 29.90 (CH_2), 49.82 (CH), 55.01 (CH_2), 57.93 (CH), 65.12 (OCH_2), 82.59 (CH), 114.37, 115.43, 115.52, 117.02, 120.81, 126.43, 127.74, 128.24, 128.84, 130.17, 130.40, 131.16, 135.65, 140.08, 155.58, 156.22, 157.25; ν_{max} (KBr, cm^{-1}) 3416, 1358, 1217, 760; ES-MS (*m/z*) 506 $[M+H]^+$. HRMS-EI: found 505.6503, calcd 505.6497. Microanalysis data agreed: for $C_{34}H_{35}NO_5$.

5.6.3. 4-{3-Phenyl-4-[4-(2-pyrrolidin-1-yl-ethoxy) phenyl] chroman-2-yl}phenol (12c)

Yield 96.8%; mp 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (br m, 4H), 2.65–2.67 (br m, 4H), 2.84–2.89 (m, 2H), 3.19–3.28 (m, 1H), 3.95 (t, 2H, J = 5.70 Hz), 4.40 (t, 1H, J = 11.01 Hz), 5.17 (t, 1H, J = 10.77 Hz), 5.99 (br s, 1H, OH), 6.50–6.60 (m, 4H), 6.70–6.84 (m, 6H), 6.91–6.99 (m, 5H), 7.06–7.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.44, 49.92, 54.67, 54.92, 55.05, 66.19, 82.38, 114.23, 115.57, 116.98, 120.81, 126.42, 127.03, 127.68, 128.24, 128.76, 130.14, 130.27, 130.45, 132.06, 134.48, 135.66, 140.10, 155.54, 158.22; ν_{max} (KBr, cm^{-1}) 3376, 1449, 1029, 758; ES-MS (*m/z*) 492 $[M+H]^+$. HRMS-EI: found 491.6237, calcd 491.6230. Microanalysis data agreed: for $C_{33}H_{33}NO_5$.

5.6.4. 2,4-Di-(4-hydroxyphenyl)-3-phenyldihydrobenzo-pyran (10)

Yield 91%; mp 151–153 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.26 (t, 1H, J = 10.8 Hz), 4.43 (d, 1H, J = 11.1 Hz), 4.81 (br s, 1H, OH, exchangeable with D_2O), 4.89 (br s, 1H, OH, exchangeable with D_2O), 5.19 (d, 1H, J = 10.5 Hz), 6.57–6.64 (m, 4H), 6.76–6.83 (m, 6H), 6.95–7.09 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.80, 54.56, 82.55, 115.23, 115.32, 116.76, 120.56, 126.20, 127.12, 127.47, 128.04, 128.70, 128.73, 130.09, 130.30, 130.62, 134.13, 140.16, 155.29, 155.43, 156.53; ν_{max} (neat) 3475, 1360, 756; ES-MS (*m/z*) 395 $[M+H]^+$. HRMS-EI: found 394.4633, calcd 394.4642.

6. Conclusion

In conclusion, synthesis of *trans*, *trans*-2,3,4-trisubstituted-2,3-dihydro-4*H*-1-benzopyran, (2,3,4-triarylchroman), by selective deacetylative direct arylation of *trans*-2,3-disubstituted-2,3-dihydro-4*H*-1-benzopyran with phenol and its further derivatization with different alkyl amine chains were disclosed. The biological activity of the synthesized compounds found to sensitive to amino component in the side chain. Significant estrogenic and anti-estrogenic activities exhibited by **11a** and **12c** point to their ability to bind to estrogen receptor as such or as possible hydroxyl metabolite. In in vitro evaluation of anti-breast cancer activity, **11f** and **12a** showed promising activity comparable with that of tamoxifen, in spite of their poor receptor binding affinity suggests that these compounds might have different mechanism than through ER binding. Further optimization of these prototype molecules as anti-cancer agents is in progress.

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References and notes

1. Ciocca, D. R.; Vargas Roig, L. M. *Endocr. Rev.* **1995**, *16*, 35.
2. Smith, E. P.; Boyd, J.; Frank, G. R.; Takahashi, H.; Cohen, R. M.; Specker, B.; Williams, T. C.; Lubahn, D. B.; Korach, K. S. *N. Eng. J. Med.* **1994**, *331*, 1056.
3. Carani, C.; Qin, K.; Simoni, M.; Faustinifustini, M.; Serpente, S.; Boyd, J.; Korach, K. S.; Simpson, E. R. *N. Eng. J. Med.* **1997**, *337*, 91.
4. Farhat, M. Y.; Lavigne, M. C.; Ramwell, P. W. *FASEB J.* **1996**, *10*, 615.
5. Grese, T. A.; Dodge, J. A. *Curr. Pharm. Des.* **1998**, *4*, 71.
6. Wakeling, A. E.; Valcaccia, B. *J. Endocr.* **1983**, *99*, 445.
7. Miller, C. P.; Komm, B. S. *Ann. Rep. Med. Chem.* **2001**, *36*, 149.
8. Black, L. J.; Sato, M.; Rowley, E. R.; Magee, D. E.; Bekele, A.; Williams, D. C.; Cullinan, G. J.; Bendele, R.; Kauffman, R. F.; Bensch, W. R.; Frolik, C. A.; Termine, J. D.; Bryant, H. U. *J. Clin. Invest.* **1994**, *93*, 63.
9. Miller, C. P. *Curr. Pharm. Des.* **2002**, *8*, 2089.
10. (a) Gupta, A.; Dwivedy, A.; Keshri, G.; Sharma, R.; Balapure, A. K.; Singh, M. M.; Ray, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6006; (b) Pandey, J.; Jha, A. K.; Hajela, K. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 2239; (c) Emamia, S.; Falahatib, M.; Banifatemib, A.; Moshirib, K.; Shafieea, A. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *7*, 318; (d) Li, X.; Reuman, M.; Russell, R. K.; Adams, R.; Ma, R.; Beish, S.; Branum, S.; Youells, S.; Roberts, J.; Jain, N. K.; Kanojia, R.; Sui, Z. *Org. Process Res. Dev.* **2007**, *11*, 414; (e) Saeed, A.; Sharma, A. P.; Durani, N.; Jain, R.; Durani, S.; Kapil, R. S. *J. Med. Chem.* **1990**, *33*, 3210. and references mentioned therein.
11. Tan, Q.; Blizzard, T. A.; Morgan, J. D.; Birzin, E. T.; Chan, W.; Yang, Y. T.; Pai, L. Y.; Hayes, E. C.; DaSilva, C. A.; Warrier, S.; Yudkovitz, J.; Wilkinson, H. A.; Sharma, N.; Fitzgerald, P. M. D.; Li, S.; Colwell, L.; Fisher, J. E.; Adamski, S.; Reszka, A. A.; Kimmel, D.; DiNinno, F.; Rohrer, S. P.; Freedman, L. P.; Schaefferb, J. M.; Hammonda, M. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1675.
12. Chen, H. Y.; Dykstra, K. D.; Birzin, E. T.; Frisch, K.; Chan, W.; Yang, Y. T.; Mosley, R. T.; DiNinno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1417.
13. Civelli, M.; Galbiati, E.; Caruso, G. P.; Amari, G.; Armani, E.; Ghirardi, S.; Delcanale, M. World Congress of Pharmacology 2002, 24: July 7–12 (Abs 96.19).
14. Saeed, A.; Sharma, A. P.; Durani, N.; Jain, R.; Durani, S.; Kapil, R. S. *J. Med. Chem.* **1990**, *33*, 3210. 3216, 3211.
15. Gauthier, S.; Caron, B.; Cloutier, J.; Dory, Y. K.; Favre, A.; Larouche, D.; Mailhot, J.; Ouellet, C.; Schwerdtfeger, A.; Leblanc, G.; Martel, C.; Simard, J.; Mérand, Y.; Bélanger, A.; Labrie, C.; Labrie, F. *J. Med. Chem.* **1997**, *40*, 2117.
16. Sharma, A. P.; Saeed, A.; Durani, S.; Kapil, R. S. *J. Med. Chem.* **1990**, *33*, 3216.
17. (a) Srivastava, S.; Sharma, R.; Balapure, A. K. *Ind. J. Pharmacol.* **2004**, *36*, 238; (b) Picard, F.; Deshaies, Y.; Lalonde, J.; Samson, P.; Labrie, C.; Bélanger, A.; Labrie, F.; Richard, D. *Int. J. Obes. Relat. Metab. Disord.* **2000**, *24*, 830.
18. MOE: The Molecular Operating Environment from Chemical Computing Group Inc., 1255 University St., Suite 1600, Montreal, Quebec, Canada H3B 3X3. http://www.chemcomp.com.
19. Dhar, J. D.; Dwivedi, A.; Srivastava, A.; Setty, B. S. *Contraception* **1994**, *49*, 609.
20. Ghosh, R.; Kamboj, V. P.; Singh, M. M. *Contraception* **2001**, *64*, 261.
21. Sashidhara, K. V.; Rosaiah, J. N.; Kumar, A.; Bid, H. K.; Konwar, R.; Chattopadhyay, N. *Phytother. Res.* **2007**, *21*, 1105.