5-Benzylidene-1,2-dihydrochromeno[3,4-*f*]quinolines as Selective Progesterone Receptor Modulators

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A series of 5-benylidene-1,2-dihydrochromeno[3,4-*f*]quinolines (**4**) were synthesized and tested in bioassays to evaluate their progestational activities, receptor- and tissue-selectivity profiles as selective progesterone receptor modulators (SPRMs). Most of the new analogues exhibited as highly potent progestins with more than 100-fold receptor selectivity over other steroid hormone receptors and LG120920 **(7b)** demonstrated tissue selectivity toward uterus and vagina versus breasts in a rodent model after oral administration.

Introduction

Progestins and estrogens are two kinds of female reproductive hormones with multiple target organs beyond the reproductive system. Their biological actions are mainly through activating their own transcription factors: progesterone receptors (PR) and estrogen receptors (ER). Estrogen upregulates both isoforms of progesterone receptor (PR-A and PR-B), while progestin can suppress estrodial-stimulated ER activity in numerous tissues through binding to PR-A or PR-B.[1] The coordinate role of progestins with estrogens compose the intriguing biology of the two female hormones.[2]

Synthetic steroidal progestins, in combination with estrogens, have been widely used in oral contraception (OC), female hormone replacement therapy (HRT), and the treatment of a number of female reproductive disorders for decades.[3] Addition of a progestin in estrogen replacement therapy has proven to significantly reduce endometrial cancer risk due to its antiestrogenic activity in the uterus.[4] However, in breasts, progestins demonstrate stimulative activity in addition to the proliferative effect of estrogens. There has been a potential breast cancer risk for women to have a long term use of progestins in OC and HRT in combination with estrogens, even though the clinical results have been controversial.[5] The latest results from the Women's Health Initiative confirmed the increased breast cancer risk for women who used combined hormone preparation of conjugated equine estrogens and medroxyprogesterone acetate (MPA, **3**).[6] Like the natural ligand progesterone, all of the currently marketed progestins possess some degree of cross-reactivities with other steroid hormone receptors, which can cause potential side-effects. The cross-reactivities of MPA with androgen and glucocorticoid receptors might contribute to the increased risk of cardiovascular diseases in women who took the combination hormone preparation in the Women's Health Initiative trials. It was reported that a new steroidal progestin, trimegestone, had improved receptor selectivity and also demonstrated a beneficial effect on bone in an adult rat model when it was combined with estradiol.[7] There is a need for and a growing interest in searching for selective pharmaceutical agents in the area of steroid hormone receptors to improve safety profiles of current drugs. In comparison with the success of selective estrogen receptor modulators (SERMs),[8] the development of receptor- and tissue-selective progesterone receptor modulators (SPRMs) is in a very early stage.[9]

The 5-substituted 1,2-dihydrochromeno[3,4-*f*]quinolines (**1**) have been demonstrated to be robust nonsteroidal pharmacophores for human progesterone receptor (hPR) modulators.[10] One of the appealing series developed from the tetracyclic core contains a unique achiral 5-phenylmethylidene moiety. For example, LG120838 (**2**) exhibited highly potent progestational activity similar to steroidal progestin MPA (**3**) in rodent models via oral administration.[11] To further explore the structure−activity relationship (SAR) around the 5-benzylidenes, we synthesized a number of novel analogues (**4**) with a fluorine substitution at the 9- or 7-position and evaluated their biological activities as SPRMs in cotransfection, competitive binding assays and in an in vivo model.[12]

Chemistry

The syntheses of most analogues of structure **4** were completed by a two-step general procedure described in Scheme 1. Addition of a benzyl Grignard or organolithium reagent to the tetracyclic lactone **5**[10b] provided good to excellent yield of hemiacetal **6**, and an acid-catalyzed dehydration afforded the desired compounds **7**−**9** exclusively as *Z*-isomers under dim or yellow light conditions.[13] HCl salts of selected low melting point analogues (**7a** and **7b**) were prepared to increase crystallinity of these compounds. A new synthetic route was developed for analogue **15** (Scheme 2) since the 2-aminobenzyl Grignard or lithium reagent is not easily accessible. The benzylic lithiation of 2-(methylamino)-toluene was directed by the adjacent carbonate group that formed in situ to give dianion **11**.[14] Addition of **11** to lactone **5b** went smoothly to afford hemiacetal **12** in high yield. Treatment of **12** with chloroformate provided intermediate **13** with selective acylation of the phenol oxygen and the aniline nitrogen but not the quinoline

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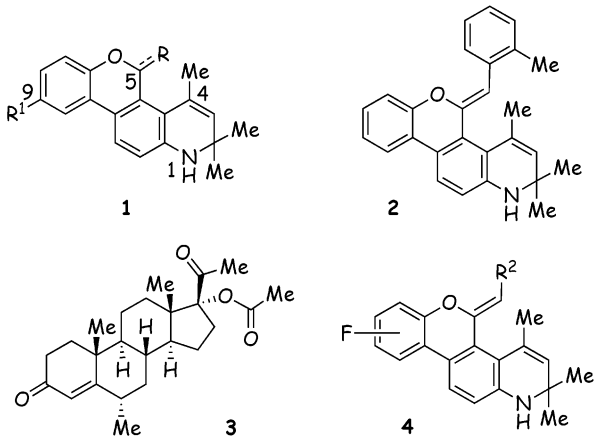


Figure 1. The new progestins and reference compound.

nitrogen, presumably due to the steric hindrance of the geminal dimethyl groups. Selective hydrolysis of the carbonate **13** followed by a standard dehydration procedure afforded benzylidene product **14**. The carbamate in compound **14** that served as a methylamine precursor was reduced by DIBAL-H in THF to afford the desired product **15** in good yield.

Scheme 3 describes a novel general synthetic route to prepare special benzylidene or heteroaryl methylidene compounds that were not available by the routes described in Schemes 1 and 2. Treatment of lactone **5b** with Tebbe reagent[15] afforded 5-methylidene compound **16**, which was brominated with NBS to provide compound **17** in moderate yield with the exclusive *Z*-olefin configuration. Palladium-catalyzed cross-coupling reaction[16] of vinyl bromide **17** and boronic acids or tributyltin compounds gave analogues of structure **18** in 40−70% yield without isomerization of the *Z*-olefin configuration.

Results and Discussion

Our previous reports demonstrated that fluorine or chlorine at C(9) significantly enhanced the hPR agonist activity in the 5-aryl series,[10b] and compounds with a *m*- or *p*-fluorine or an *o*-methyl group at the 5(*Z*)-benzylidene phenyl ring had the highest efficacy in the cotransfection assay.[11] However, chlorine at C(9) also increased glucocorticoid receptor binding affinity.[10c] To access the similar enhancement effect on the 5-benzylidene series, we prepared a number of analogues with a fluorine substituent at C(9) or at the electronic equivalent C(7) position in combination with the best possible substitution in the benzylidene ring. Table 1 summarizes the SAR results of the new 5(*Z*)-benzylidene analogues in the cotransfection and competitive binding assays.

All of the 7-fluorine analogues (**9a**, **9b**, **9c**, and **9d**) have similar high efficacy (>160% of progesterone) and demonstrated improved potency in the cotransfection assay comparing to their corresponding 7-H analogues[11] (only 2-Me analogue is shown in Table 1). The fluorine enhancement on hPR agonist activity was also confirmed in the 9-fluorine series (data are not shown for the 9-H analogues).

We noticed in our initial study that the ortho-position of the 5(*Z*)-benzylidene phenyl ring had more tolerance for substitution, and the 2-methyl compound LG120838 (**2**) gave the best progestational activity.[11] To systematically investigate the biological effect of the ortho-substitution, a number of 9-fluoro ortho-substituted 5(*Z*)-benzylidene analogues were evaluated (Table 1). The testing results in both cotransfection and binding assays clearly indicate that the electronic rather than steric differences have a bigger impact on progestational activity, and electron-rich groups result in better progestins. The total electronic influence of the ortho-substituents on the biological activity can be nicely correlated between the EC_{50} mean value in hPR cotransfection assay and the ordinary Hammett substituent constants (σ-meta)[17] (see Figure 2).

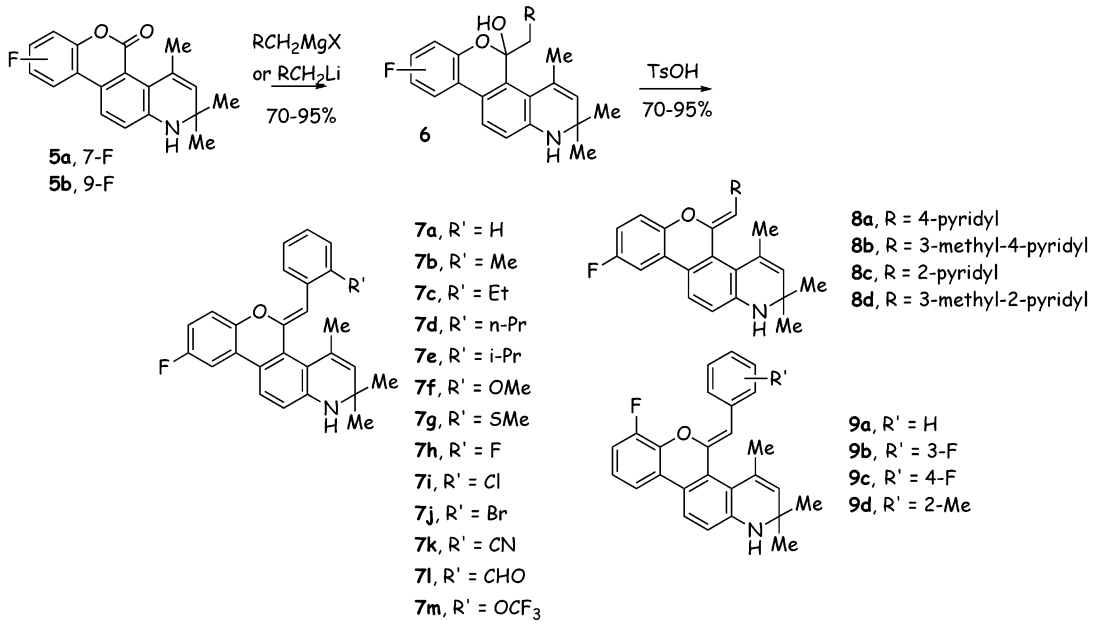
The SAR study around the 5-benzylidene moiety generated a large number of highly potent progestins, which motivated us to evaluate the scope of the benzylidene pharmacophore. Our first attempt was to evaluate pyridyl analogues (Table 1, **8**). The assay results indicated that the pyridine moiety was well tolerated, and three out of four compounds (except **8c**) exhibited potent progestational activity. Expansion of the benzylidene to five-member-ring heterocycle methylidenes is very successful, and 3-thiophene analogue **18b** is one of the best hPR agonists in the series with sub-nanomolar potency as well as 174% efficacy relative to progesterone. Compound **18c** also demonstrates excellent activity.

In searching for SPRMs with full antiestrogenic activity in uterus and diminished proliferative activity in breasts, we evaluated the new progestins in the T47D human breast cancer cell line.[18] The results show that, in contrast with steroidal progestins such as progesterone and MPA, our new analogues behaved as partial agonists in the breast cell assay although they scored as super agonists in CV-1 cotransfection assay.

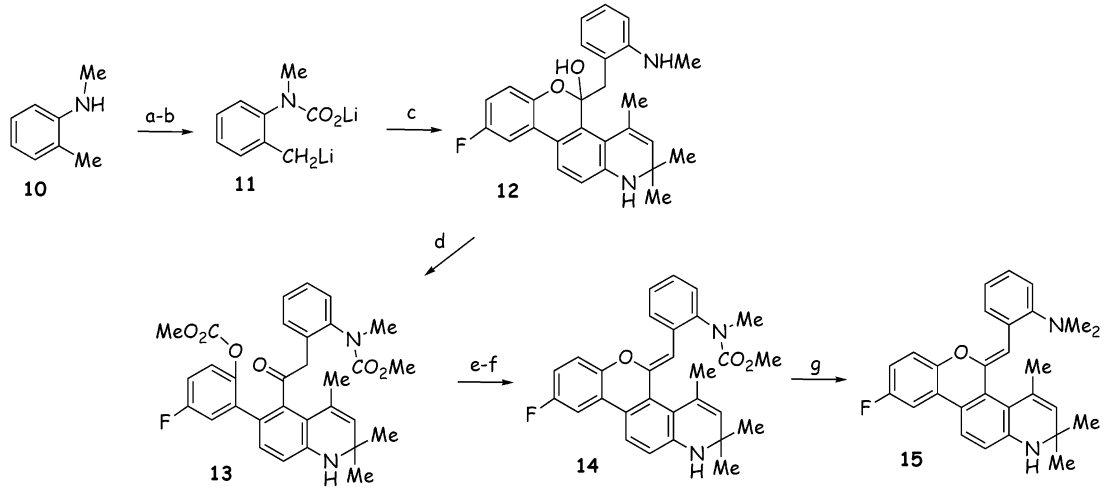
The receptor selectivity profile of the new analogues was examined by using other steroid hormone receptor cotransfection and competitive binding assays. Tables 2 and 3 list the results of a group of representative compounds. Most of them demonstrated more than 100-fold selectivity toward hPR over human androgen receptor (hAR) and human glucocorticoid receptor (hGR) in binding affinities and transcriptional activities, as well as over human mineralocorticoid receptor (hMR) and human ER in the cotransfection assay, which makes them superior in this regard compared to progesterone and MPA.

To characterize the tissue-selectivity profile of the new progestins and reference compounds, we employed a multi-endpoint adult rat model. In this assay, advantage is taken of the fact that in the uterus and vagina, estrogens induce a proliferation and increase in the epithelial cell height, which can be antagonized by progestins. In the breast, estrogens induce a proliferation of the ductal network while progestins stimulate the growth of the lobular-alveolar end buds, which grow from the distal end of the ducts. The assay is carried out in ovariectomized female rats by treating them for 3 days with estrone or estrone plus varying doses of a progestin. Proliferating cells or inhibition of proliferating cells were quantitated either by measurements of cell height in sectioned and stained tissue samples or, in the case of the breast, immuno-histochemically labeled Brdu incorporated nuclei. Compound **7b** was

Scheme 1

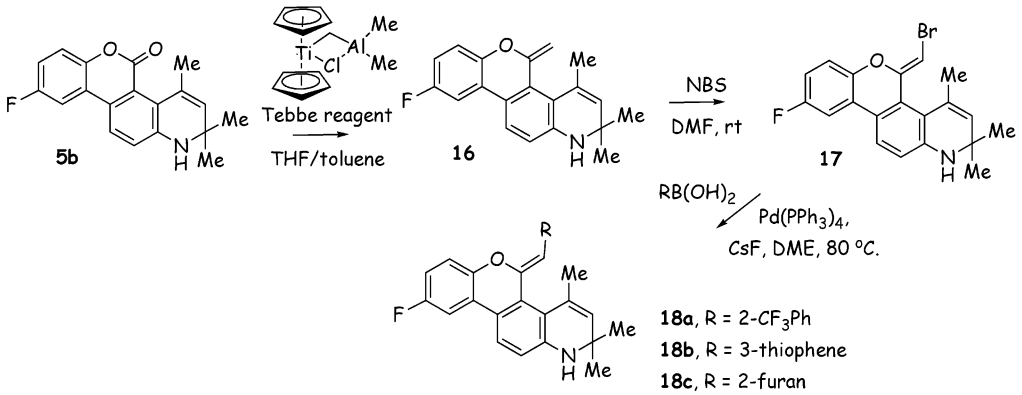


Scheme 2[a]



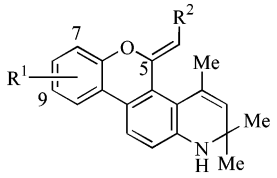
[a] Reagents: (a) *n*-BuLi, THF, −70 °C, CO_2; (b) *n*-BuLi; (c) **5b**, THF; (d) $ClCO_2Me$, pyridine, CH_2Cl_2, rt, 1 h; (e) Na_2CO_3, $MeOH/H_2O$, rt; (f) TsOH, CH_2Cl_2, rt, 2 h; (g) DIBAL-H, THF, rt, 2 h.

Scheme 3



selected for the in vivo study based on its excellent potency and good cross-reactivity profile in vitro (more than 100-fold separation from other receptors as shown in Table 3), relative ease of synthesis, and desirable property for recrystallization. MPA was used as a standard. Figure 3 shows the results of these measurements for MPA and **7b**. These results show that while **7b** has similar potency and efficacy to MPA to inhibit

Table 1. Cell-Based Assay and Competitive Binding Data for the New Analogues[a]



			hPR agonist (mean ± SEM)[b]				
			CV-1 cells		T47D cells		
no.	R^1	R^2	eff (%)	EC_{50} (nM)[c]	eff (%)	EC_{50} (nM)[c]	hPR-A binding K_i (nM)
	progesterone		100	2.9 ± 0.9	100	1.8 ± 0.3	3.5 ± 0.2
3	MPA		80 ± 7	0.15 ± 0.05	90 ± 15	0.33 ± 0.05	0.34 ± 0.04
2	H	2-MePh	166 ± 35	5.7 ± 3.7	45 ± 10	28 ± 2	0.66 ± 0.20
9a	7-F	Ph	171 ± 49	2.1 ± 0.6	45	11	0.61 ± 0.06
9b	7-F	3-FPh	170 ± 42	2.7 ± 0.5	51	18	5.5 ± 1.3
9c	7-F	4-FPh	175 ± 22	4.0 ± 1.0	36	8	0.71 ± 0.16
9d	7-F	2-MePh	163 ± 12	1.4 ± 0.7	43	9	1.5 ± 0.4
7a	9-F	Ph	176 ± 15	5.3 ± 1.0	55 ± 9	28 ± 9	0.62 ± 0.39
7b	9-F	2-MePh	178 ± 14	3.6 ± 0.3	49 ± 6	19 ± 6	0.55 ± 0.14
7c	9-F	2-EtPh	161 ± 17	2.0 ± 0.8	51	18	2.3 ± 0.91
7d	9-F	2-*n*-PrPh	123 ± 15	4.5 ± 1.3	46	59	1.6 ± 0.51
7e	9-F	2-*i*-PrPh	156 ± 13	4.0 ± 2.1	43	54	1.9 ± 0.8
7f	9-F	2-OMePh	154 ± 23	0.93 ± 0.24	40	8	3.8 ± 1.7
7g	9-F	2-SMePh	132 ± 13	6.2 ± 2.2	53	41	0.59 ± 0.06
7h	9-F	2-FPh	190 ± 21	7.3 ± 3.1	47	29	0.62 ± 0.1
7i	9-F	2-ClPh	146 ± 13	12 ± 5	not available		22.4 ± 8.2
7j	9-F	2-BrPh	147 ± 18	9.0 ± 6.1	37	50	16.4 ± 4.8
7k	9-F	2-CNPh	78 ± 20	11 ± 4	62	97	11.4 ± 4.3
7l	9-F	2-CHOPh	107 ± 19	11 ± 2	72	48	2.6 ± 0.9
7m	9-F	2-OCF_3Ph	136 ± 31	11 ± 6	56	190	6.4 ± 3.2
8a	9-F	4-pyridyl	105 ± 8	5.8 ± 3.6	49	4.9	1.5 ± 0.4
8b	9-F	3-Me-4-pyridyl	138 ± 3	2.0 ± 0.2	46	4.6	1.4 ± 0.5
8c	9-F	2-pyridyl	50 ± 2	15 ± 5	40	44	9.2 ± 3.1
8d	9-F	3-Me-2-pyridyl	125 ± 18	4.5 ± 2.1	49	12	0.42 ± 0.06
15	9-F	2-NMe_2Ph	172 ± 25	2.7 ± 1.1	59	26	1.2 ± 0.3
18a	9-F	2-CF_3Ph	127 ± 14	14 ± 6	56	161	45.5 ± 9.6
18b	9-F	3-thienyl	174 ± 10	0.71 ± 0.20	48	5.5	1.3 ± 0.5
18c	9-F	2-furyl	138 ± 37	1.7 ± 0.9	64	21	4.7 ± 1.5

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations, values without standard deviation represent $N < 3$. [b] Agonist efficacies were compared to that of progesterone (100%). [c] All EC_{50} values were determined from full dose−response curves ranging from 10^{-12} to 10^{-5} M.

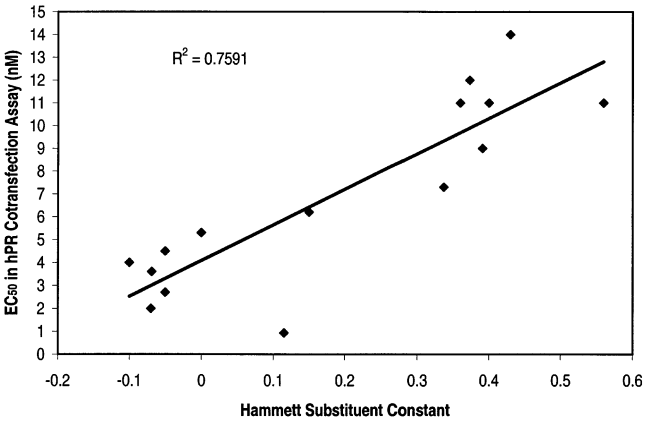


Figure 2. Correlation between hPR EC_{50} of the new progestins and Hammett substituent constants (σ-meta) of their 2′-substituent at the 5-benzylidene moiety.

Table 2. Competitive Binding Data of 5-Benzylidene Analogues with hPR, hAR, and hGR[a]

compound	hPR K_i (nM)	hAR K_i (nM)	hGR K_i (nM)
progesterone	3.5 ± 0.2	8.5 ± 3.1	30.5 ± 1.9
MPA	0.34 ± 0.04	2.9 ± 0.2	13.2 ± 1.8
9a	0.61 ± 0.06	1456 ± 289	321 ± 32
9d	1.5 ± 0.4	960 ± 202	232 ± 40
7a	0.62 ±0.39	>1000	207 ± 122
7b	0.55 ± 0.14	>1000	236 ± 60
7c	2.3 ± 0.91	1589 ± 733	270 ± 2
7f	3.8 ± 1.7	439 ± 7	277 ± 59
7g	0.59 ± 0.06	>1000	386 ± 94
8b	0.42 ± 0.06	>1000	232 ± 53
8d	1.4 ± 0.5	>1000	874 ± 290
15	1.2 ± 0.3	819 ± 423	493 ± 14
18b	1.3 ± 0.5	669 ± 206	84 ± 10
18c	4.7 ± 1.5	>1000	140 ± 32

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments on receptor expressed in SF_{12} cells in a baculovirus expression system.

estrone-induced epithelial cell height in both the uterus and vagina, **7b** has a greatly reduced potency and efficacy at equivalent doses relative to MPA at inducing the proliferative response in lobular-alveolar buds in the breast.

In summary, the SAR around the 5-methylidene moiety provided a large number of nonsteroidal progestins that have low nanomolar potency in the cotrasfection assay as full agonists and as partial agonists in the T47D assay. The Hammett σ constant of the ortho substituent of the benzylidene moiety correlates with PR agonist potency. Heteroaromatic methylidenes such as pyridyl, thienyl, and furyl methylidenes are well tolerated to replace the 5-benzylidene group. Most of the analogues showed improved selectivity toward hPR from other steroid hormone receptors in comparison with progesterone and MPA. In addition, LG120920 was demonstrated to be a full agonist in the uterus and vagina and a partial agonist in the breasts in a rodent model.

Table 3. Cross-Reactivity Profiles of Selected Analogues with hAR, hGR, hMR, and hER[a]

no.	hAR effic (%)[b]	hAR IC_{50} (nM)[b]	AR/PR[e]	hGR effic (%)[b]	hGR IC_{50} (nM)[b]	GR/PR[e]	hMR effic (%)[b]	hMR IC_{50} (nM)[b]	ER/PR[e]	hER effic (%)[b]	hER IC_{50} (nM)[b]	ER/PR[e]
Pr	46 ± 7	37 ± 2	13	39 ± 8	>1000	>344	83 ± 14	14 ± 4	5	–	–	>1000
MPA	159 ± 10[c]	6.1 ± 1.0[c]	41	157 ± 22[c]	10 ± 1[c]	67	67 ± 10	1197 ± 852	>1000	46 ± 5[c]	924 ± 203[c]	>1000
9a	60	900	429	82	250	119	–[d]	–	>1000	–	–	>1000
9d	–	–	>1000	89 ± 4	297 ± 24	212	70 ± 9	1850 ± 500	>1000	41 ± 2	2443 ± 908	>1000
7a	37 ± 7	640 ± 150	121	73 ± 16	2050 ± 319	387	–	–	>1000	–	–	>1000
7b	38 ± 6	820 ± 210	228	84 ± 15	650 ± 128	181	–	–	>1000	–	–	>1000
7c	–	–	>1000	86 ± 10	77 ± 11	39	50 ± 4	334 ± 49	167	–	–	>1000
7f	–	–	>1000	81 ± 12	90 ± 14	97	–	–	>1000	34	1885	>1000
7g	–	–	>1000	98 ± 1	860 ± 110	139	–	–	>1000	–	–	>1000
8b	–	–	>1000	99 ± 1	245 ± 50	54	71 ± 10	363 ± 120	511	44	1149	255
8d	93 ± 4	203 ± 10	101	99 ± 1	188 ± 72	94	–	–	>1000	–	–	>1000
15	60	1500	556	88 ± 3	320 ± 113	119	–	–	>1000	–	–	>1000
18b	52 ± 2	215 ± 49	303	45	100	141	63 ± 15	1900 ± 780	>1000	36 ± 10	3488 ± 1184	>1000
18c	94 ± 4	258 ± 86	152	74 ± 9	109 ± 65	64	–	–	>1000	51	1273	749

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations, values without standard deviation represent $N < 3$. [b] Antagonist efficacies were determined as a function (%) of maximal inhibition of a standard agonist at EC_{50} value, and the IC_{50} values were determined from full dose−response curves ranging from 10^{-12} to 10^{-5} M. [c] Agonist efficacy and EC_{50}. [d] Stands for the efficacy <20% or potency >5000 nM. [e] Potency ratio of the two receptors.

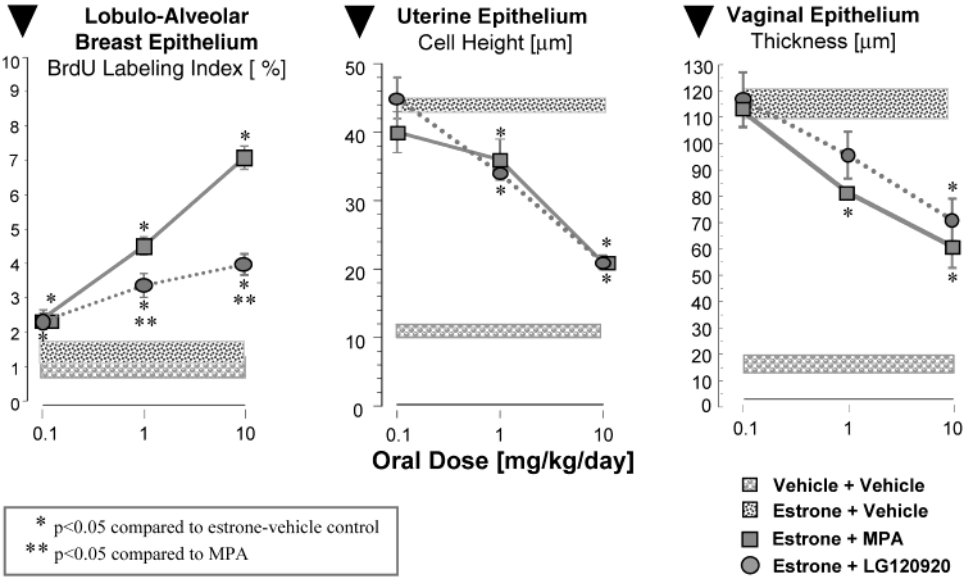


Figure 3. Inhibition of estrone-induced uterine or vaginal epithelial cell height (center and right panels) and proliferative induction of lobular-alveolar buds in the breast (left panel) in the ovariectomized rat by compound **7b** or MPA in three different doses ($n = 4$ for all groups). All values represent the mean percent change ± SEM.

Experimental Section

General experimental methods have been previously described,[10] and reported yields are not optimized. ^{1}H NMR spectra were obtained on a Bruker AC400 spectrometer at 400 MHz. General procedure for preparing 5(*Z*)-benzylidene compounds **7**−**9** from lactones **5** and benzyl Grignard reagents have also been described[11]

***(Z)*-9-Fluoro-5-benzylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7a).** This compound was prepared by the general procedure from benzylmagnesium chloride (1.0 mL of a 1 M solution in Et_20, 5 equiv) and lactone **5b** (62 mg, 0.20 mmol) in 91% yield as a yellow solid (70 mg): ^{1}H NMR ($CDCl_3$) 7.75 (d, $J = 7.5$, 2 H), 7.41 (d, $J = 8.4$, 1H), 7.40−7.34 (m, 3H), 7.22 (t, $J = 7.3$, 1H), 7.09 (dd, $J = 8.8$ and 4.8, 1 H), 6.86 (td, $J = 8.3$ and 3.0, 1H), 6.66 (d, $J = 8.4$, 1H), 5.62 (s, 1H), 5.53 (s, 1H), 4.18 (bs, 1H), 2.12 (s, 3H) and 1.33 (bs, 6H). To a solution of **7a** (70 mg, 0.18 mmol) in ether at 0 °C was added HCl (1.0 M in ether, 0.18 mL), and the precipitate was filtered and recrystallized in methanol to give the HCl salt of **7a** as yellow crystalline solid:[19] mp > 200 °C dec; ^{1}H NMR ($CDCl_3$) 7.97 (d, $J = 8.4$, 1H), 7.73 (d, $J = 7.3$, 2H), 7.65 (d, $J = 8.4$, 1H), 7.46 (dd, $J = 9.2$ and 3.0, 1H), 7.40 (t, $J = 7.6$, 2H), 7.28 (t, $J = 7.2$, 1H), 7.18 (dd, $J = 8.8$ and 4.4, 1H), 7.05 (td, $J = 8.3$ and 3.0, 1H), 5.97 (s, 1H), 5.47 (s, 1H), 2.23 (s, 3H), and 1.77 (bs, 6H). Anal. ($C_{26}H_{22}FNO{\cdot}HCl{\cdot}^1/_3CH_4O$) C, H, N.

***(Z)*-9-Fluoro-5-(2-methylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7b).** This compound was prepared by the general procedure from 2-methylbenzyl bromide (1.6 mL, 11 mmol) and lactone **5b** (0.24 g, 0.78 mmol) in 86% yield as a yellow solid (0.26 g): mp 69−71 °C; ^{1}H NMR ($CDCl_3$) 8.16 (d, $J = 7.5$, 1 H), 7.42 (d, $J = 8.4$, 1 H), 7.36 (dd, $J = 9.0$ and 1.8, 1 H), 7.28−7.10 (m, 3 H), 7.01 (dd, $J = 8.5$ and 4.3, 1 H), 6.82 (td, $J = 8.3$ and 3.0, 1 H), 5.88 (s, 1 H), 5.51 (s, 1 H), 4.18 (bs, 1 H), 2.28 (s, 3 H), 2.15 (s, 3 H) and 1.33 (bs, 6 H). The HCl salt of **7b** was made in a similar fashion to that described in the preparation of **7a** as yellow solid:[19] mp 191−193 °C; ^{1}H NMR ($CDCl_3$) 8.09 (d, $J = 8.0$, 1H), 7.93 (d, $J = 7.5$, 1H), 7.66 (d, $J = 8.3$, 1H), 7.46 (dd, $J = 9.2$ and 2.3, 1H), 7.30−7.24 (m, 1H), 7.20−7.17 (m, 2H), 7.08 (dd, $J = 8.9$ and 4.8, 1H), 7.03 (td, $J = 8.4$ and 3.0, 1H), 5.94 (s, 1H), 5.72 (s, 1H), 2.27 (s, 3H), 2.25 (s, 3H), and 1.77 (bs, 6H). Anal. ($C_{27}H_{24}FNO{\cdot}HCl$) C, H, N.

***(Z)*-9-Fluoro-5-(2-ethylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7c). Preparation of 2-Ethylbenzyl Bromide.** To a solution of 2-methylbenzyl alcohol (1.0 g, 8.2 mmol) in ether was added n-BuLi (2.5 M in hexane, 6.5 mL, 16 mmol), and the resulting cloudy mixture was heated at reflux for 4 h.[20] Iodomethane (0.40 mL, 8.2 mmol) was added at room temperature and the reaction was stirred for 1 h and quenched with water. Extraction with EtOAc followed by chromatography afforded 2-ethylbenzyl

alcohol as a colorless oil (0.36 g, 33%). The alcohol (0.36 g, 2.6 mmol) in ether (10 mL) was treated with PBr_3 (0.70 g, 2.6 mmol) at room temperature for 10 min and was quenched with satd $NaHCO_3$. Extraction with EtOAc followed by chromatography provided 2-ethylbenzyl bromide as colorless oil (0.53 g, 94%).

Compound **7c** was prepared by the general procedure from 2-ethylbenzyl bromide (0.20 g, 1.0 mmol) and lactone **5b** (20 mg, 0.065 mmol) in 74% yield as a yellow foam (20 mg): ^{1}H NMR ($CDCl_3$) 8.21 (d, J = 7.5, 1H), 7.41 (d, J = 8.3, 1H), 7.35−7.22 (m, 2H), 7.20−7.13 (m, 2H), 7.00 (dd, J = 8.8 and 4.3, 1H), 6.82 (td, J = 8.4 and 2.9, 1H), 6.67 (d, J = 8.4, 1H), 5.90 (s, 1H), 5.52 (s, 1H), 4.20 (bs, 1H), 2.61 (q, J = 7.5, 2H), 2.14 (s, 3H), 1.34 (bs, 6H), and 1.13 (t, J = 7.5, 3H). Anal. ($C_{28}H_{26}$FNO) C, H, N.

(*Z*)-9-Fluoro-5-(2-propylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7d). Preparation of 2-Propylbenzyl Bromide. This compound was made from 2-methylbenzyl alcohol (1.0 g, 8.2 mmol) by the alkylation/bromide-conversion procedure as described in the preparation of 2-ethylbenzyl bromide. 2-Propylbenzyl alcohol was obtained in 63% (0.75 g), and 2-propylbenzyl bromide was isolated in 91% yield (1.0 g) as a colorless oil.

Compound **7d** was prepared by the general procedure from 2-propylbenzyl bromide (0.21 g, 1.0 mmol) and lactone **5b** (50 mg, 0.16 mmol) in 74% yield as a yellow solid (50 mg): mp 135−137 °C; ^{1}H NMR ($CDCl_3$) 8.25 (d, J = 7.5, 1H), 7.41 (d, J = 8.4, 1H), 7.34 (dd, J = 9.2 and 3.0, 1H), 7.30−7.22 (m, 1H), 7.20−7.15 (m, 2H), 7.02 (dd, J = 8.8 and 4.3, 1 H), 6.82 (td, J = 8.4 and 2.9, 1H), 6.67 (d, J = 8.4, 1H), 5.90 (s, 1H), 5.52 (s, 1H), 4.19 (bs, 1H), 2.54 (t, J = 7.9, 2H), 2.13 (s, 3H), 1.60−1.50 (m, 2H), 1.34 (bs, 6H), and 0.90 (t, J = 7.3, 3H). Anal. ($C_{29}H_{28}FNO\cdot{}^1/_4H_2O$) C, H, N.

(*Z*)-9-Fluoro-5-(2-isopropylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7e). Preparation of 2-Isopropylbenzyl Bromide. To a solution of 2-isopropyl bromobenzene (2.5 g, 12 mmol) in THF (30 mL) at −78 °C was added n-BuLi (2.5 M in hexane, 5.0 mL, 12 mmol), and the mixture was warmed to −30 °C. A separate flask charged with paraformaldehyde (1.7 g, 56 mmol) was heated in 160 °C oil bath, and the monomeric formaldehyde gas was bubbled by dry nitrogen through a tube to the reaction mixture till the reaction went to completion. The mixture was quenched with water, extracted with methylene chloride, and concentrated to afford crude 2-isopropylbenzyl alcohol (1.0 g, 56%). The alcohol was converted to 2-isopropylbenzyl bromide by PBr_3, under the conditions described previously, in 90% yield.

Compound **7e** was prepared by the general procedure from 2-isopropylbenzyl bromide (0.21 g, 1.0 mmol) and lactone **5b** (50 mg, 0.16 mmol) in 71% yield as an orange solid (48 mg): mp 156−158 °C; ^{1}H NMR ($CDCl_3$) 8.08 (dd, J = 6.9 and 2.0, 1H), 7.40 (d, J = 8.4, 1H), 7.37 (dd, J = 9.6 and 2.8, 1H), 7.30−7.17 (m, 3H), 6.96 (dd, J = 8.4 and 4.8, 1H), 6.78 (td, J = 8.0 and 3.2, 1H), 6.67 (d, J = 8.4, 1H), 5.94 (s, 1H), 5.52 (s, 1H), 4.20 (bs, 1H), 3.10 (sept, J = 6.9, 1H), 2.14 (s, 3H), 1.32 (bs, 6H), and 1.15 (d, J = 6.9, 6H). Anal. ($C_{29}H_{28}$FNO) C, H, N.

(*Z*)-9-Fluoro-5-(2-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7f). This compound was prepared by the general procedure from 2-methoxybenzyl chloride (0.31 g, 2.0 mmol) and lactone **5b** (0.10 g, 0.33 mmol) in 55% yield as a yellow solid (75 mg): mp 80−83 °C; ^{1}H NMR ($CDCl_3$) 8.15 (dd, J = 7.6 and 1.6, 1H), 7.38 (d, J = 8.4, 1H), 7.33 (dd, J = 10.0 and 2.8, 1H), 7.20 (dd, J = 8.4 and 1.6, 1H), 7.04−6.99 (m, 2H), 6.86 (d, J = 8.0, 1H), 6.82 (td, J = 8.0 and 3.2, 1H), 6.63 (d, J = 8.4, 1H), 6.08 (s, 1H), 5.51 (s, 1H), 4.19 (bs, 1H), 3.80 (s, 3H), 2.14 (s, 3H), and 1.34 (bs, 6H). Anal. ($C_{27}H_{24}FNO_2$) C, H, N.

(*Z*)-9-Fluoro-5-(2-methylthiobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7g). Preparation of 2-Thiomethoxybenzyl Bromide. To a solution of methyl 2-methylthio benzoate (1.0 g, 5.5 mmol) in THF (20 mL) at 0 °C was added LAH (0.48 g, 3.0 mmol), and the reaction mixture was stirred for 30 min. The reaction was quenched with water, extracted with EtOAc, and concentrated to give crude benzyl alcohol. The alcohol was treated with PBr_3 under the condition described previously to provide 2-methylthiobenzyl bromide in 58% overall yield (0.69 g): ^{1}H NMR ($CDCl_3$) 7.35 (d, J = 7.0, 1H), 7.32−7.25 (m, 2H), 7.14 (m, 1H), 4.65 (s, 2H), and 2.52 (s, 3H).

Compound **7g** was prepared by the general procedure from 2-methylthiobenzyl bromide (0.44 g, 2.0 mmol) and lactone **5b** (50 mg, 0.16 mmol) in 45% yield as a bright yellow solid (31 mg): mp 149−150 °C; ^{1}H NMR ($CDCl_3$) 8.17 (d, J = 7.6, 1H), 7.41 (d, J = 8.3, 1H), 7.35 (dd, J = 9.8 and 2.8, 1H), 7.30−7.17 (m, 3 H), 7.00 (dd, J = 8.8 and 4.8, 1H), 6.83 (td, J = 8.4 and 2.8, 1H), 6.67 (d, J = 8.4, 1H), 6.15 (s, 1H), 5.54 (s, 1H), 4.20 (bs, 1H), 2.39 (s, 3H), 2.16 (s, 3H), and 1.35 (bs, 6H). Anal. ($C_{27}H_{24}$FNOS) C, H, N.

(*Z*)-9-Fluoro-5-(2-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7h). This compound was prepared by the general procedure from 2-fluorobenzyl bromide (0.38 g, 2.0 mmol) and lactone **5b** (50 mg, 0.16 mmol) in 65% yield as a yellow solid (42 mg): mp130−132 °C; ^{1}H NMR ($CDCl_3$) 8.19−8.14 (m, 1H), 7.34 (d, J = 8.4, 1H), 7.28 (dd, J = 9.7 and 3.0, 1H), 7.18−7.08 (m, 2H), 6.99−6.93 (m, 2H), 6.78 (td, J = 8.1 and 3.0, 1H), 6.60 (d, J = 8.4, 1H), 5.84 (s, 1H), 5.47 (s, 1H), 4.12 (s, 1H), 2.06 (s, 3H), and 1.26 (bs, 6H). Anal. ($C_{26}H_{21}F_2NO$) C, H, N.

(*Z*)-9-Fluoro-5-(2-chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7i). This compound was prepared by the general procedure from 2-chlorobenzyl chloride (0.32 g, 2.0 mmol) and lactone **5b** (50 mg, 0.16 mmol) in 45% yield as a yellow solid (30 mg): mp 76−79 °C; ^{1}H NMR ($CDCl_3$) 8.29 (d, J = 7.9, 1H), 7.43 (d, J = 8.4, 1H), 7.40−7.35 (m, 2H), 7.31 (t, J = 7.6, 1H), 7.15 (td, J = 9.0 and 1.5, 1H), 7.04 (dd, J = 8.9 and 4.9, 1H), 6.86 (td, J = 8.5 and 2.9, 1H), 6.69 (d, J = 8.4, 1H), 6.15 (s, 1H), 5.56 (s, 1H), 4.23 (s, 1H), 2.16 (s, 3H), and 1.35 (bs, 6H). Anal. ($C_{26}H_{21}$ClFNO) C, H, N.

(*Z*)-9-Fluoro-5-(2-bromobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7j). This compound was prepared by the general procedure from 2-bromobenzyl bromide (0.50 g, 2.0 mmol) and lactone **5b** (50 mg, 0.16 mmol) in 81% yield as a yellow solid (60 mg): mp 82−84 °C; ^{1}H NMR ($CDCl_3$) 8.31 (dd, J = 8.0 and 1.6, 1H), 7.58 (dd, J = 7.9 and 1.1, 1H), 7.44 (d, J = 8.4, 1H), 7.40−7.31 (m, 2H), 7.12−7.03 (m, 2H), 6.85 (td, J = 8.4 and 2.9, 1H), 6.69 (d, J = 8.4, 1H), 6.15 (s, 1H), 5.56 (s, 1H), 4.23 (s, 1H), 2.16 (s, 3H), and 1.36 (bs, 6H). Anal. ($C_{26}H_{21}$BrFNO) C, H, N.

(*Z*)-9-Fluoro-5-(2-cyanobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7k). To a solution of *o*-tolunitrile (0.23 g, 2.0 mmoL) in THF at −78 °C was added $LiN(SiMe_3)_2$ (1 M in THF, 2.2 mL), and the reaction was stirred at −78 °C for 1 h. A solution of lactone **5b** (0.15 g, 0.40 mmol) in THF (2 mL) was added to give rise a deep red solution, and the reaction was warmed to room temperature and quenched with water. Extraction with EtOAc and removal of solvent afforded crude hemiacetal **6**, which was dehydrated under acidic condition as that described in the general procedure to give **7k** (40 mg, 24%) as yellow solid: mp 100−102 °C; ^{1}H NMR ($CDCl_3$) 8.44 (d, J = 8.1, 1H), 7.65−7.57 (m, 2H), 7.45 (d, J = 8.4, 1H), 7.40 (dd, J = 9.7 and 2.8, 1H), 7.24 (t, J = 7.1, 1H), 7.09 (dd, J = 8.9 and 4.7, 1H), 6.89 (td, J = 8.1 and 3.0, 1H), 6.72 (d, J = 8.4, 1H), 6.15 (s, 1H), 5.12 (s, 1H), 4.27 (s, 1H), 2.15 (s, 3H), and 1.36 (bs, 6H). Anal. ($C_{27}H_{21}FN_2O$) C, H, N.

(*Z*)-9-Fluoro-5-(2-formylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7l). To a solution of compound **7k** (21 mg, 0.050 mmol) in $CHCl_3$ (3 mL) at −78 °C was added DIBAL-H (1.5 M in toluene, 0.05 mL, 0.075 mmol), and the reaction was warmed to room temperature and stirred overnight. The reaction was quenched with water, extracted with EtOAc, and concentrated. Chromatography afforded **7l** as a yellow foam (15 mg, 71%): ^{1}H NMR ($CDCl_3$) 10.21 (s, 1H), 8.00 (d, J = 7.9, 1H), 7.85 (d, J = 6.5, 1H), 7.58 (t, J = 7.6, 1H), 7.42 (d, J = 8.4, 1H), 7−38−7.31 (m, 2H), 6.91 (dd, J = 8.8 and 4.8, 1H), 6.82 (td, J = 8.2 and 2.9, 1H),

6.70 (d, J = 8.4, 1H), 6.48 (s, 1H), 5.55 (s, 1H), 4.25 (bs, 1H), 2.15 (s, 3H), and 1.35 (bs, 6H). Anal. ($C_{27}H_{22}FNO_2 \cdot {}^1/_3H_2O$) C, H, N.

(*Z*)-9-Fluoro-5-(2-trifluoromethoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (7m). This compound was prepared by the general procedure from 2-trifluoromethoxybenzyl bromide (0.51 g, 2.0 mmol) and lactone **5b** (0.10 g, 0.33 mmol) in 77% yield as a yellow solid (0.12 g): mp 147−149 °C; ^{1}H NMR ($CDCl_3$) 8.42 (d, J = 7.4, 1H), 7.42 (d, J = 8.4, 1H), 7.39−7.30 (m, 2H), 7.26−7.20 (m, 2H), 7.07 (dd, J = 8.8 and 4.8, 1H), 6.86 (td, J = 8.0 and 2.8, 1H), 6.68 (d, J = 8.4, 1H), 6.00 (s, 1H), 5.55 (s, 1H), 4.21 (s, 1H), 2.10 (s, 3H), and 1.32 (bs, 6H). Anal. ($C_{27}H_{21}F_4NO_2$) C, H, N.

(*Z*)-9-Fluoro-5-(4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (8a). To a solution of 4-picoline (0.24 g, 2.5 mmol) and TMEDA (0.30 mL, 2.0 mmol) in THF (4 mL) at −78 °C was added n-BuLi (2.4 M in hexane, 0.8 mL, 2.0 mmol), and the resulting orange solution was stirred for 40 min.[21] A solution of lactone **5b** (31 mg, 0.10 mmol) in THF (1 mL) was added, and the reaction mixture was stirred at −70 °C for 30 min. The reaction was quenched with water, extracted, and concentrated. Chromatography afforded hemiacetal **6** (R = 4-pyridyl) as a yellow oil, which was treated with TsOH by the general procedure to give **8a** (35 mg, 91%) as yellow solid: mp 147−149 °C; ^{1}H NMR ($CDCl_3$) 8.56 (dd, J = 4.8 and 1.3, 2H), 7.60 (dd, J = 4.8 and 1.3, 2H), 7.45 (d, J = 8.4, 1H), 7.39 (dd, J = 9.7 and 3.0, 1H), 7.15 (dd, J = 8.9 and 4.8, 1H), 6.91 (td, J = 8.4 and 3.1, 1H), 6.73 (d, J = 8.4, 1H), 5.57 (s, 1H), 5.54 (s, 1H), 4.26 (s, 1H), 2.10 (s, 3H), and 1.37 (bs, 6H). Anal. ($C_{25}H_{21}FN_2O$) C, H, N.

(*Z*)-9-Fluoro-5-(3-methyl-4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (8b). This compound was prepared in a similar fashion as that described in the synthesis of **8a**. Selective lithiation of 3,4-lutidine (0.32 g, 3.0 mmol) followed by addition to lactone **5b** (31 mg, 0.10 mmol) and dehydration afforded **8b** (27 mg, 67%) as a yellow solid: mp 247−249 °C; ^{1}H NMR ($CDCl_3$) 8.46 (d, J = 5.3, 1H), 8.38 (s, 1H), 8.05 (d, J = 5.3, 1H), 7.46 (d, J = 8.4, 1H), 7.38 (dd, J = 9.7 and 2.8, 1H), 7.08 (dd, J = 8.9 and 4.8, 1H), 6.89 (td, J = 8.4 and 2.9, 1H), 6.73 (d, J = 8.4, 1H), 5.84 (s, 1H), 5.55 (s, 1H), 4.27 (s, 1H), 2.24 (s, 3H), 2.14 (s, 3H), and 1.36 (bs, 6H). Anal. ($C_{26}H_{23}FN_2O$) C, H, N.

(*Z*)-9-Fluoro-5-(2-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (8c). This compound was prepared in a similar fashion as that described in the synthesis of **8a**. Lithiation of 2-picoline (0.35 g, 3.8 mmol) followed by addition to lactone **5b** (31 mg, 0.10 mmol) and dehydration afforded **8c** (30 mg, 78%) as a yellow solid: mp 132−134 °C; ^{1}H NMR ($CDCl_3$) 8.57 (d, J = 3.9, 1H), 8.30 (d, J = 8.1, 1H), 7.72 (td, J = 7.9 and 1.7, 1H), 7.44 (d, J = 8.4, 1H), 7.39 (dd, J = 9.8 and 2.9, 1H), 7.14−7.08 (m, 2H), 6.88 (td, J = 8.5 and 2.8, 1H), 6.70 (d, J = 8.4, 1H), 5.95 (s, 1H), 5.54 (s, 1H), 4.23 (s, 1H), 2.15 (s, 3H), and 3.15 (bs, 6H). Anal. ($C_{25}H_{21}FN_2O$) C, H, N.

(*Z*)-9-Fluoro-5-(3-methyl-2-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (8d). This compound was prepared in a similar fashion as that described in the synthesis of **8a**. Selective lithiation of 2,3-lutidine (0.32 g, 3.0 mmol) followed by addition to lactone **5b** (66 mg, 0.21 mmol) and dehydration afforded **8d** (70 mg, 82%) as a yellow solid: mp 194−195 °C; ^{1}H NMR ($CDCl_3$) 8.53 (d, J = 3.8, 1H), 7.48 (d, J = 7.1, 1H), 7.44 (d, J = 8.4, 1H), 7.34 (dd, J = 9.8 and 2.9, 1H), 7.07 (dd, J = 7.7 and 4.8, 1H), 6.95 (dd, J = 8.8 and 4.8, 1H), 6.80 (td, J = 8.5 and 2.8, 1H), 6.70 (d, 1H), 5.94 (s, 1H), 5.53 (s, 1H), 4.22 (s, 1H), 2.31 (s, 3H), 2.26 (s, 3H), and 1.34 (bs, 6H). Anal. ($C_{26}H_{23}FN_2O$) C, H, N.

(*Z*)-5-Benzylidene-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (9a). This compound was prepared by the general procedure from benzylmagnesium chloride (0.4 mL of a 1 M solution in Et_20, 5 equiv) and lactone **5a** (20 mg, 0.065 mmol) in 81% yield as a yellow solid (20 mg): mp 92−94 °C; ^{1}H NMR ($CDCl_3$) 7.87 (d, J = 7.6, 2H), 7.49 (d, J = 8.4, 1H), 7.45 (d, J = 6.4, 1H), 7.39 (t, J = 7.6, 2H), 7.24 (t, J = 7.6, 1H), 6.95 (m, 2H), 6.67 (d, J = 8.4, 1H), 5.68 (s, 1 H), 5.55 (s, 1H), 4.19 (s, 1H), 2.13 (s, 3H), 1.36 (bs, 6H). Anal. ($C_{26}H_{22}FNO$) C, H, N.

(*Z*)-7-Fluoro-5-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (9b). This compound was prepared by the general procedure from 2-fluorobenzyl bromide (189 mg, 1.0 mmol) and **5a** (30 mg, 0.10 mmol) in 54% yield as a bright yellow solid (21 mg): mp 82−84 °C; ^{1}H NMR ($CDCl_3$) 7.73 (dd, J = 9.4 and 1.8, 1H), 7.53 (d, J = 9.1, 1H), 7.51 (d, J = 8.5, 1H), 7.45 (dd, J = 6.5 and 2.3, 1H), 7.32 (td, J = 8.0 and 6.3, 1H), 7.05−6.90 (m, 3H), 6.69 (d, J = 8.5, 1H), 5.65 (s, 1H), 5.55 (s, 1H), 4.20 (bs, 1H), 2.12 (s, 3H), and 1.36 (bs, 6H). Anal. ($C_{26}H_{21}F_2NO$) C, H, N.

(*Z*)-7-Fluoro-5-(4-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (9c). This compound was prepared by the general procedure from 4-fluorobenzyl chloride (0.19 g, 1.0 mmol) and lactone **5a** (20 mg, 0.065 mmol) in 88% yield as a yellow solid (23 mg): mp 160−162 °C; ^{1}H NMR ($CDCl_3$) 7.85 (dd, J = 8.9 and 5.6, 1H), 7.49 (d, J = 8.4, 1H), 7.52 (dd, J = 7.3 and 1.1, 1H), 7.08 (t, J = 8.8, 2H), 7.01−6.93 (m, 2 H), 6.67 (d, J = 8.3, 1H), 5.63 (s, 1H), 5.54 (s, 1H), 4.20 (bs, 1 H), 2.11 (s, 3H), 1.29 (bs, 6H). Anal. ($C_{26}H_{21}F_2NO$) C, H, N.

(*Z*)-7-Fluoro-5-(2-methylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (9d). This compound was prepared by the general procedure from 2-methylbenzyl bromide (185 mg, 1.0 mmol) and lactone **5a** (30 mg, 0.10 mmol) in 50% yield as a yellow solid (20 mg): mp 150−151 °C; ^{1}H NMR ($CDCl_3$) 8.35 (d, J = 7.9, 1H), 7.50 (d, J = 8.4, 1H), 7.45 (t, J = 5.6, 1H), 7.30 (m, 1H), 7.16 (m, 2H), 6.94 (m, 2H), 6.68 (d, J = 8.4, 1H), 5.97 (s, 1H), 5.53 (s, 1H), 4.20 (bs 1H), 2.29 (s, 3H), 2.17 (s, 3H), 1.35 (br s, 6H). Anal. ($C_{27}H_{24}$-FNO) C, H, N.

(*Z*)-9-Fluoro-5-(2-dimethylaminobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (15). To a solution of *N*-methyl-2-toluidine (0.30 g, 2.5 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (1.6 M in hexane, 1.6 mL, 2.6 mmol), and the reaction mixture was warmed to −10 °C and then, saturated with CO_2 gas. The mixture was concentrated under reduced pressure, dissolved in THF (10 mL), and cooled back to −78 °C. Second portion of n-BuLi (1.6 mL) was added, and the resulting orange slurry was stirred at −15 °C for 40 min and then cooled back to −78 °C again. A solution of lactone **5b** (0.10 g, 0.31 mmol) in THF (2 mL) was added, and the reaction mixture was warmed slowly to −40 °C and quenched with water. The mixture was treated with HCl (2 M, 6 mL) to hydrolyze the carbamate and neutralized to pH > 9. Extraction with EtOAc followed by chromatography afforded compound **12** as yellow oil (0.10 g, 93%). To a solution of compound **12** (75 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) were added pyridine (0.5 mL) and methyl chloroformate (0.05 mL, 0.6 mmol), and the reaction was stirred for 10 min. The reaction mixture was extracted with EtOAc, and the organic layer was washed with satd $NaHCO_3$ and brine and concentrated to afford compound **13** as crude mixture. A mixture of compound **13** and satd Na_2CO_3 (5 mL) in MeOH/dioxane (1:1 mixture, 12 mL) was heated at 80 °C for 2 h and extracted with EtOAc. The organic phase was washed with brine and concentrated to provide crude intermediate, which was treated with TsOH in CH_2Cl_2 (5 mL) for 2 h. The reaction was quenched with 2 M $NaHCO_3$ (5 mL) and extracted with EtOAc. Chromatography afforded compound **14** (40 mg, 57%) as a yellow foam: ^{1}H NMR ($CDCl_3$) 8.47 (d, J = 7.5, 1H), 7.43 (d, J = 8.4, 1H), 7.41−7.33 (m, 2H), 7.24 (t, J = 7.4, 1H), 7.12 (d, J = 9.6, 1H), 7.09 (dd, J = 8.9 and 4.8, 1H), 6.87 (td, J = 8.5 and 2.9, 1H), 6.69 (d, J = 8.4, 1H), 5.72 (s, 1H), 5.52 (s, 1H), 4.23 (s, 1H), 3.60 (bs, 3H), 3.10 (bs, 3H), 2.08 (s, 3H), and 1.33 (bs, 6H). To a solution of compound **14** (40 mg, 0.085 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added DIBAL-H (1.5 M in toluene, 0.30 mL), and the reaction was stirred at room temperature for 2 h. The reaction was quenched with water, extracted with EtOAc, and concentrated. Chromatography afforded **15** (22 mg, 60%) as a yellow foam: ^{1}H NMR ($CDCl_3$) 8.24 (dd, J = 7.7 an 1.2, 1H), 7.40 (d, J = 8.3, 1H), 7.33 (dd, J = 9.8 and 2.9, 1H),

7.20 (t, $J = 7.5$, 1H), 7.09 (t, $J = 7.6$, 1H), 7.05−6.96 (m, 2H), 6.81 (t, $J = 5.4$, 1H), 6.66 (d, $J = 8.4$, 1H), 6.09 (s, 1H), 5.49 (s, 1H), 4.20 (bs, 1H), 2.63 (s, 6H), 2.11 (s, 3H), and 1.32 (bs, 6H). Anal. ($C_{28}H_{27}FN_2O \cdot {}^1/_2H_2O$) C, H, N.

9-Fluoro-5-methylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (16). Treatment of lactone **5b** (0.99 g, 3.2 mmol) with Tebbe reagent (0.5 M in toluene, 7 mL) by the literature condition[15] afforded compound **16** in 30% yield as a yellow solid: ^{1}H NMR ($CDCl_3$) 7.39 (d, $J = 8.4$, 1H), 7.33 (dd, $J = 7.5$ and 2.5, 1H), 6.94 (dd, $J = 8.7$ and 4.5, 1H), 6.85 (td, $J = 8.1$ and 2.5, 1H), 6.66 (d, $J = 8.4$, 1H), 5.51 (s, 1H), 5.07 (s, 1H), 4.45 (s, 1H), 2.15 (s, 3H), and 1.30 (s, 6H).

9-Fluoro-5(*Z*)-bromomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (17). Compound **16** (0.10 g, 0.33 mmol) was treated with NBS (30 mg, 0.33 mmol) in DMF (2 mL) at room temperature for 10 min, and standard workup followed by chromatography provided compound **17** (65 mg, 51%) as a yellow foam: ^{1}H NMR ($CDCl_3$) 7.40 (d, $J = 8.4$, 1H), 7.33 (dd, $J = 7.4$ and 2.8, 1H), 7.10 (dd, $J = 8.8$ and 4.8, 1H), 6.86 (td, $J = 8.0$ and 2.8, 1H), 6.67 (d, $J = 8.4$, 1H), 5.52 (s, 1H), 5.45 (s, 1H), 4.19 (s, 1H), 2.08 (s, 3H), and 1.29 (s, 6H).

9-Fluoro-5(*Z*)-(2-trifluoromethylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (18a). To a solution of compound **17** (20 mg, 0.052 mmol) in DME (4 mL) was added $Pd(PPh_3)_4$ (2 mg, 3 mol %), and the mixture was stirred at room temperature for 15 min. A solution of 2-trifluoromethylbenzeneboronic acid (15 mg, 0.078 mmol) in DME (1 mL) and CsF (24 mg, 0.15 mmol) were added to the reaction mixture. The reaction was heated at 80 °C for 2 h, quenched with $NaHCO_3$ (satd aqueous), and extracted with EtOAc. Removal of solvent and chromatography of the crude mixture afforded **18a** (12 mg, 53%) as yellow foam: ^{1}H NMR ($CDCl_3$) 8.52 (d, $J = 8.0$, 1H), 7.64 (d, $J = 8.0$, 1H), 7.58 (t, $J = 8.0$, 1H), 7.43 (d, $J = 8.4$, 1H), 7.37 (dd, $J = 9.0$ and 2.9, 1H), 7.28 (t, $J = 8.0$, 1H), 7.04 (dd, $J = 9.0$ and 4.8, 1H), 6.85 (td, $J = 9.0$ and 2.9, 1H), 6.70 (d, $J = 8.4$, 1H), 6.02 (s, 1H), 5.55 (s, 1H), 4.23 (s, 1H), 2.08 (s, 3H), and 1.33 (bs, 6H). Anal. ($C_{27}H_{21}F_4NO \cdot H_2O$) C, H, N.

9-Fluoro-5(*Z*)−(3-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (18b). This compound was prepared from the coupling reaction of compound **17** (50 mg, 0.13 mmol) and 3-thienylboronic acid (25 mg, 0.20 mmol) as that described in the synthesis of **18a** in 38% yield (19 mg) as orange oil: ^{1}H NMR ($CDCl_3$) 7.61 (d, $J = 2.7$, 1H), 7.49 (dd, $J = 5.0$ and 1.4, 1H), 7.40 (d, $J = 8.4$, 1H), 7.34 (dd, $J = 9.4$ and 2.1, 1H), 7.30 (dd, $J = 4.8$ and 3.0, 1H), 7.08 (dd, $J = 8.7$ and 4.8, 1H), 6.85 (td, $J = 8.1$ and 3.2, 1H), 6.65 (d, $J = 8.4$, 1H), 5.70 (s, 1H), 5.52 (s, 1H), 4.18 (s, 1H), 2.10 (s, 3H), and 1.34 (bs, 6H). Anal. ($C_{24}H_{20}FNOS$) C, H, N.

9-Fluoro-5(*Z*)-(2-furylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (18c). This compound was prepared from the coupling reaction of compound **17** (25 mg, 0.065 mmol) and 2-(tributylstannyl)furan (24 mg, 0.065 mmol) as that described in the synthesis of **18a** in 67% yield (16 mg) as yellow solid: mp 89−91 °C; ^{1}H NMR ($CDCl_3$) 7.40 (d, $J = 8.4$, 1H), 7.36 (d, $J = 1.6$, 1H), 7.34 (dd, $J = 9.6$ and 2.8, 1H), 7.08 (dd, $J = 8.8$ and 4.8, 1H), 6.93 (d, $J = 3.3$, 1H), 6.86 (td, $J = 8.9$ and 2.5, 1H), 6.64 (d, $J = 8.4$, 1H), 6.51 (t, $J = 2.6$, 1H), 5.72 (s, 1H), 5.52 (s, 1H), 4.18 (s, 1H), 2.10 (s, 3H), and 1.33 (bs, 6H). Anal. ($C_{24}H_{20}FNO_2$) C, H, N.

Cotransfection Assays. The function and detailed preparation procedure of the cotransfection assays have been described previously.[10] The agonist activity was determined by examining the LUC expression (normalized response), and the efficacy readout was a relative value to the maximal LUC expression produced by a reference agonist, e.g., progesterone for hPR, dihydrotestosterone (DHT) for hAR, dexamethasone for hGR, aldosterone for hMR, estradiol for hER. All the cotransfection experiments were carried out in 96-well plates by automation (Beckman Biomomek automated workstation).

Receptor Binding Assays. The preparation of receptor binding assays for hPR-A, hGR, and hAR were described previously,[10] and the radioligands used in the competative binding assays are progesterone for hPR-A, DHT for hAR, and dexamethasone for hGR.

Material and Methods for Multiend Point Rat Assay. This assay will be described in greater detail elsewhere, but briefly the assay is a modification as described previously.[22] Briefly, 4-week old female rats were ovariectomized an allowed to recover 1 week prior to dosing for 3 days with either vehicle, estrone (10ug per rat) or estrone plus progestin (0.1, 1, and 10 mg/kg, oral). On the morning of the fourth day, rats were given a single intraperitoneal injection of 5-bromo-2′-deoxyuridine (Brdu), which incorporates into proliferating cells DNA. Animals were sacrificed 2 h later and breast, uterine and vagina tissues isolated and paraffin embedded. The uterine and vagina tissues were sectioned and stained, and the epithelial cell height was measured using ImagePro software. The breast tissue was sectioned, deparaffinized, and subjected to immuno-histochemistry steps which first tags the Brdu within the DNA and second tags the Brdu antibody with a secondary antibody which is fluorescent tagged. The lobular-alveolar buds, which are under progestin control, were identified and the amount of labeled nuclei quantified and expressed as a proliferating index.

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