5-Aryl-1,2-dihydrochromeno[3,4-*f*]quinolines: A Novel Class of Nonsteroidal Human Progesterone Receptor Agonists

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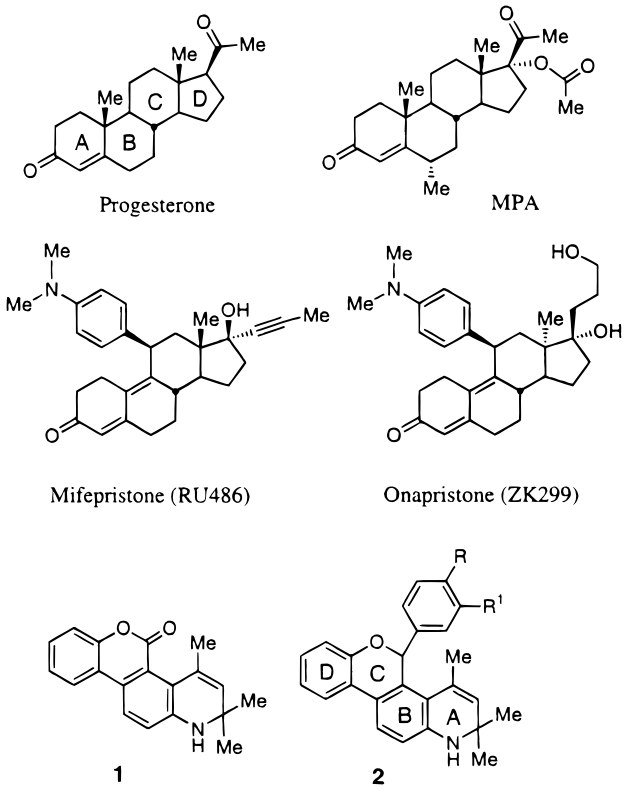
The development of a novel class of nonsteroidal human progesterone receptor (hPR) agonists, 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines **2**, is described. The introduction of a 5-aryl group into the 1,2-dihydrocoumarino[3,4-*f*]quinoline core **1** is the key for progestational activities. The structure−activity relationship (SAR) studies of the 5-aryl substituents generated a series of potent hPR agonists, which exhibited similar biological activity (EC_{50} = 8−30 nM) to the natural hormone progesterone (EC_{50} = 2.9 nM) in cell-based assays with efficacies ranging from 28% to 96%. Most of the analogues displayed similar or greater binding affinity (K_i = 0.41−3.6 nM) than progesterone (K_i = 3.5 nM). Three representative analogues (**13**, **15**, and **24**) demonstrated in vivo activities in mammary gland morphology/uterine wet weight assay in ovariectomized rats.

Introduction

Progesterone (Chart 1) is a unique reproductive hormone, and it plays a trophic role for tissues of female reproduction. Its principal target organs are uterus, breast, and brain.[1] Since the isolation of progesterone in 1934,[1a] development of new progestins and understanding their action have been part of one of the greatest chemical and biological research efforts on a single group of substances (steroids). In the late 1930s and early 1940s, on the basis of animal experiments, several groups reported the idea that progesterone could be used to prevent ovulation in women, but the concept was not realized until the 1950s.[2] Progesterone was originally obtained by an inefficient and expensive extraction from animal ovaries and is rapidly metabolized in vivo,[1b] which prevented the natural hormone from becoming a widely used medicine. In the early 1950s, Djerassi and Rosenkranz[3] of Syntex and Colton[4] of G. D. Searle and Co. reported the synthesis of norethindrone and norethynodrel, respectively. The discovery that these 19-nortestosterones have progestational activity made synthetically modified progestins of tremendous therapeutic importance. It resulted in the successful development of oral contraceptive (OC) agents—"the pill" in the 1960s.[1b] In addition to the primary use as birth control for women, progestins, combined with estrogen, are widely used in hormone replacement therapy (HRT) and have been increasingly prescribed during the last two decades due to the increase of life expectancy for women. It has been reported that addition of a progestin in HRT significantly reduces the risk of endometrial cancer with postmenopausal women who take estrogen.[5,6] Progestins are also used to treat several gynecological disorders:

Chart 1



dysmenorrhea, endometriosis, and dysfunctional uterine bleeding caused by hormonal deficiency or imbalance.[1b]

Like most steroidal drugs, steroidal progestins can have undesirable side effects due to varying degrees of cross-reactivities with the closely related androgen receptor, glucocorticoid receptor, estrogen receptor, and mineralocorticoid receptor and the interactions with GABA (γ-aminobutyric acid) receptor through a nongenomic pathway. Some cross-reactivity with other receptors may occasionally be desirable,[7] requiring inten-

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tional control of the selectivity profile. Development of new generations of progestins to improve the selectivity profile of progestins has been a great challenge.[8] Additionally, exploration of therapeutic applications such as oncology demands progestins with new profiles.[9]

The number of steroid drugs has not substantially increased during the last two decades, but the knowledge of their mechanisms of action has. Since the cloning of the first intracellular receptor (IR) in 1985, more than fifty members of the IR superfamily have been identified.[10] The understanding of the IRs at molecular level makes it possible to devise small-molecule pharmacological agents to modulate gene expression for therapeutic benefit, which opens new opportunities to discover more efficient and more selective orally available small molecules to mimic or block the action of natural hormones.[11] A group of cell-based high-throughput assays, termed cotransfection assays, have been developed[12] and are utilized to detect the interaction of novel small molecules with the IRs to identify individual IR agonists, antagonists, or partial agonists by using cloned human IR cDNAs. These powerful assays can be used to identify novel lead structures[13] and also to profile an existing drug for the purpose of optimization.[14,15] Here we report the results of our endeavor to develop a novel human progesterone receptor (hPR)[16] agonist pharmacophore, 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinoline **2**, and the optimization results of the 5-aryl substituents by using the hPR cotransfection assay as a guide and other IR assays to characterize their selectivity profiles, including human androgen receptor (hAR),[17] human glucocorticoid receptor (hGR),[18] human estrogen receptor (hER),[19] and human mineralocorticoid receptor (hMR).[20]

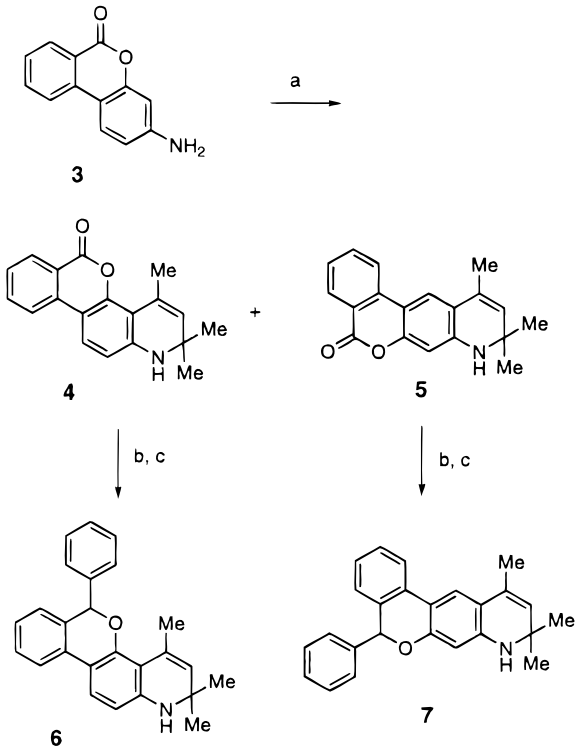
Chemistry

The 1,2-dihydro-2,2,4-trimethylquinoline moiety of the core structure is synthesized by the classic Skraup reaction.[21] Treatment of 3-amino-6*H*-dibenzo[*b*,*d*]pyran-6-one (**3**) with refluxing acetone in the presence of a catalytic amount of iodine provided a 2:1 mixture of two regioisomers of isocoumarinoquinoline (**4** and **5**) in 90% yield. Elevation of reaction temperature in a sealed tube accelerated the Skraup reaction. Scheme 1 shows the synthesis of analogues **6** and **7**. The aryl group was introduced by a nucleophilic addition of phenyllithium to isocoumarinoquinolines **4** and **5** followed by a reduction with triethylsilane in the presence of TFA.

The synthesis of 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines **2** is outlined in Scheme 2, which includes the synthesis of the 1,2-dihydrocoumarino[3,4-*f*]quinoline core **1** and the introduction of the 5-aryl groups. 8-Nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (**10**) was prepared by a modified literature procedure,[22] starting from the controlled double nitration of commercially available 2-biphenylcarboxylic acid (**8**). The first nitration with 70% nitric acid was carried out at room temperature, generating a 2:1 mixture of two compounds favoring 2′-nitration over 4′-nitration. The selectivity, which may arise from the acid coordination with the active nitration species, was not optimized. The second nitration at the 4-position required a higher nitric acid concentration and can be run by two different procedures. The one-pot procedure was performed by adding fuming nitric acid directly to the reaction mixture, requiring a large excess of fuming nitric acid to reach the desired acid concentration. Alternatively, isolation of the 2:1 mixture of the mononitrated products followed by nitration with fuming nitric acid provided a 2:1 mixture of 4,2′-dinitro-2-biphenylcarboxylic acid (**9a**) and the 4,4′-dinitro isomer (**9b**). Formation of the lactone **10** from the mixture of the dinitrated products was completed through an unusual cyclization of the carboxylate onto the nitro phenyl ring at 120 °C in *N*,*N*-dimethylacetamide (DMA).[22] Direct precipitation of the lactone from the water-diluted reaction mixture separated **10** from the undesired 4,4′-dinitro-2-biphenylcarboxylic acid (**9b**). Nitro lactone **10** was reduced by a palladium-catalyzed hydrogenation to afford 8-amino-6*H*-dibenzo[*b*,*d*]pyran-6-one in high yield. The Skraup reaction of the 8-amino compound required 120−130 °C and 15 h in a sealed tube with 40% iodine. However, it regioselectively afforded quinoline **1** in over 50% yield.[23] This practical synthetic route to intermediate **1** provided easy access to a large number of 5-aryl compounds, quickly establishing the structure−activity relationship (SAR) around the 5-aryl group.

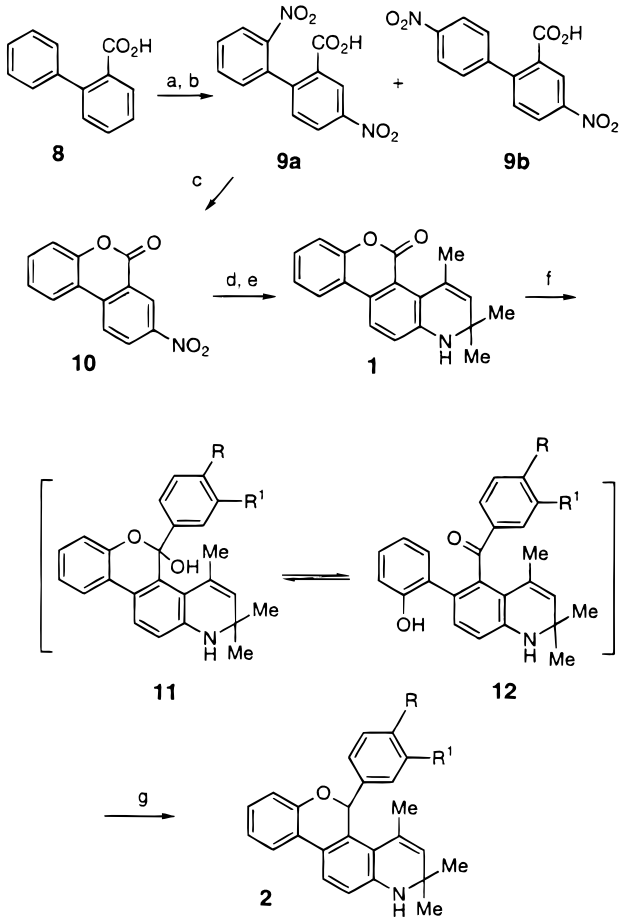
The 5-aryl group was introduced by nucleophilic addition of an aryllithium or aryl Grignard reagent to the 1,2-dihydrocoumarino[3,4-*f*]quinoline **1** followed by reduction with triethylsilane in the presence of a Lewis acid such as TFA or $BF_3{-}OEt_2$.[24] Most of the aryllithium reagents were prepared by treatment of the corresponding aryl bromides with *n*-BuLi at −78 °C in THF. It was found that the disubstituted aryllithium species could not be generated by *n*-BuLi in THF but could be made in diethyl ether[25] (e.g., 3,4-dichlorophenyllithium, 3,5-difluorophenyllithium, and 4-chloro-3-fluorophenyllithium).

Scheme 1[a]



[a] Reagents: (a) acetone, I_2, 100 °C; (b) PhLi, THF, −30 °C; (c) TFA, Et_3SiH, CH_2Cl_2.

Scheme 2[a]



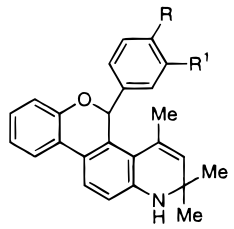
[a] Reagents: (a) 70% HNO_3, rt; (b) fuming HNO_3, rt; (c) DMA, 130 °C; (d) DMF, H_2, 10% Pd/C, rt; (e) acetone, I_2, 130 °C; (f) PhLi or PhMgX, THF or ether, −78 °C to rt; (g) TFA or BF_3−OEt_2, Et_3SiH, CH_2Cl_2, rt.

The aryl adducts presumably are a mixture of two isomers: the cyclic hemiacetal **11** and the open hydroxy ketone **12**. Determination of the ratio of **11** and **12** by NMR spectra was unsuccessful. Peak broadening was observed due to the rapid interconversion between **11** and **12**. In the case of *p*-*N*,*N*-dimethylphenyl adduct, the open form **12** was the only isomer observed, and it was not converted by TFA−Et_3SiH conditions to the 5-aryl product **2** (R′ = H, R = NMe_2). Usually, BF_3−OEt_2 mediated reduction was faster and cleaner than TFA-mediated reduction. However, when the 5-aryl group contains heteroatoms, such as the 5-pyridyl compounds, TFA was superior. In the synthesis of compound **21**, BF_3−OEt_2/Et_3SiH treatment of the corresponding hemiacetal **11** gave the overreduced 5-(4-ethylphenyl) product in high yield. Compounds **13**−**34** in Chart 2 were synthesized from **1** by the method outlined in Scheme 2.

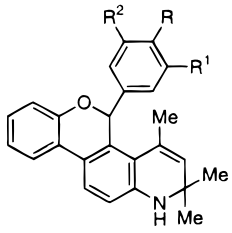
Results and Discussion

Our initial hPR modulator lead, isocoumarinoquinoline **4**, was prepared to mimic the steroid skeleton and showed moderate hPR antagonist activity and moderate binding affinity to PR-A (human A-subtype)[16] (see Table 1). In an effort to develop a novel class of potent PR modulators from this lead, we introduced an aromatic moiety which projects out of the planar structure of lead compound **4**, based on the observation that RU486[26] and ZK98,299[27] (Chart 1), the well-known PR antagonists, were developed by introduction of the 11β-aryl substituent on the relatively planar steroid skeleton. To mimic the known steroidal PR modulators, we synthesized quinoline analogues **6** by introducing an aromatic substituent to lead compound **4**. The binding affinity of compound **6** is stronger than that of the lead compound **4**, but **6** has less hPR antagonist activity in cotransfection assay. A Skraup reaction regioisomer (**5**) of **4** and its 10-phenyl analogue (**7**) were also tested in the similar assays, and **7** is totally inactive. Switching lactone **4** into lactone **1** generated a platform which was used to prepare 5-aryl analogues having more similarity with steroidal antiprogestins. The assay results for 5-phenyl compound **13** were much more promising. Its binding

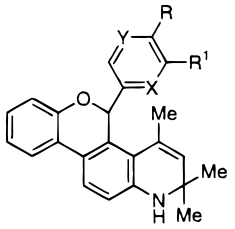
Chart 2



13 R = R^1 = H
14 R = F, R^1 = H
15 R = Cl, R^1 = H
16 R = Br, R^1 = H
17 R = H, R^1 = F
18 R = H, R^1 = Cl
19 R = H, R^1 = Br
20 R = CF_3, R^1 = H
21 R = COMe, R^1 = H
22 R = Me, R^1 = H
23 R = OMe, R^1 = H
24 R = H, R^1 = CF_3



25 R = R^1 = Cl, R^2 = H
26 R = Cl, R^1 = F, R^2 = H
27 R = Cl, R^1 = Me, R^2 = H
28 R = F, R^1 = CF_3, R^2 = H
29 R = Me, R^1 = F, R^2 = H
30 R = H, R^1 = R^2 = Cl
31 R = H, R^1 = Br, R^2 = F
32 R = H, R^1 = Br, R^2 = Me



33 R = Br, R^1 = H, X = C, Y = N
34 R = H, R^1 = Br, X = N, Y = C

Table 1. Cotransfection and Competitive Binding Data for the Quinoline Analogues[a]

	hPR agonist,[b] mean ± SEM		hPR antagonist,[b] mean ± SEM		hPR-A binding K_i (nM), mean ± SEM
compd	eff (%)	pot (EC_{50}, nM)[c]	eff (%)	pot (IC_{50}, nM)[c]	
progesterone	100	2.9 ± 0.9	−[d]	–	3.5 ± 0.2
1	–	–	95	305	669 ± 71
4	–	–	83 ± 6	194 ± 23	119 ± 24
5	–	–	73 ± 7	170 ± 51	274 ± 121
6	–	–	81 ± 4	933 ± 462	80 ± 12
7	–	–	–	–	>1000
13	42 ± 10	156 ± 71	75 ± 4	290 ± 121	3.6 ± 0.7

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations, and values without standard errors represent a single experiment. [b] Agonist efficacies were compared to that of progesterone (100%), and antagonist efficacies were determined as a function (%) of maximal inhibition of progesterone at EC_{50} concentration. [c] All EC_{50} and IC_{50} values were determined from full dose−response curves ranging from 10^{-12} to 10^{-5} M in CV-1 cells. [d] Stands for the efficacy < 20% and potency > 10 000 nM.

Table 2. Cotransfection and Competitive Binding Data for the Quinoline Analogues[a]

compd	hPR agonist,[b] mean ± SEM		hPR antagonist,[b] mean ± SEM		hPR-A binding K_i (nM), mean ± SEM
	eff (%)	pot (EC_{50}, nM)[c]	eff (%)	pot (IC_{50}, nM)[c]	
progesterone	100	2.9 ± 0.9	−[d]	−	3.5 ± 0.2
MPA	80 ± 7	0.15 ± 0.05	−	−	0.34 ± 0.04
13	42 ± 10	156 ± 71	75 ± 4	290 ± 121	3.6 ± 0.7
14	28 ± 4*	8.0 ± 7.0*	77 ± 16	342 ± 175	5.3 ± 1.1
15	77 ± 5	14 ± 2	31	600	0.70 ± 0.14
16	59 ± 7	14 ± 6	42 ± 22*	3138 ± 2272*	0.55 ± 0.21
17	48 ± 13	8.0 ± 3.2	74	150	0.69 ± 0.21
18	76 ± 8	18 ± 5	37	930	0.43 ± 0.11
19	77 ± 11	8.0 ± 3.5	41 ± 10	1136 ± 326	1.1 ± 0.6
20	35 ± 2	33 ± 14	49	150	10.8 ± 1.1
21	−	−	68 ± 19	132 ± 95	8.8 ± 1.2
22	59 ± 5	37 ± 11	38	250	2.3 ± 0.5
23	−	−	65 ± 3	105 ± 40	13.3 ± 1.2
24	96 ± 11	13 ± 2	−	−	2.6 ± 0.2
25	66 ± 7	18 ± 8	42	720	3.4 ± 0.7
26	59 ± 19	17 ± 16	−	−	0.41 ± 0.08
27	68 ± 18	14 ± 8	−	−	1.2 ± 0.2
28	60 ± 13	25 ± 13	56	4600	6.8 ± 0.5
29	83 ± 23	16 ± 10	−	−	1.8 ± 0.8
30	57 ± 7	50 ± 37	−	−	1.7 ± 0.2
31	49 ± 16	27 ± 12	65 ± 8*	1207 ± 269*	2.4 ± 0.4
32	65 ± 24	17 ± 8	31	1100	0.87 ± 0.03
33	24	3900	86 ± 8*	54 ± 15*	3.9 ± 1.4
34	21	1700	86 ± 9	71 ± 18	13.8 ± 4.2

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations, values without standard errors represent a single experiment, and values with an asterisk represent the mean value of two experiments with standard deviation. [b] Agonist efficacies were compared to that of progesterone (100%), and antagonist efficacies were determined as a function (%) of maximal inhibition of progesterone at EC_{50} value. [c] All EC_{50} and IC_{50} values were determined from full dose−response curves ranging from 10^{-12} to 10^{-5} M in CV-1 cells. [d] Stands for efficacy < 20% and potency > 10 000 nM.

affinity (K_i = 3.6 nM) is the same order of magnitude as the natural ligand progesterone (K_i = 3.5 nM).

These preliminary results encouraged us to extensively explore the SAR of the aryl substituent. Preparing analogues in the 5-aryl series (structure **2**) generated a number of interesting compounds that showed nanomolar agonist activity on hPR with efficacies ranging from 28% to 96%. The assay results of the representative 5-aryl analogues in cotransfection assays in both agonist and antagonist modes are summarized in Table 2. The introduction of a chlorine or bromine group into the 5-aryl moiety of parent compound **13** enhanced the agonist activity by about 10-fold with similar or higher efficacy, regardless of the substitution at para or meta positions (compounds **15**, **18** and **16**, **19**). These chloro or bromo 5-aryl compounds represent the most active analogues in this series. Fluorine substitution had a relatively smaller effect at the para position (**14**) and, at the meta position, generated a potent partial agonist (**17**). The *m*-(trifluoromethyl)-phenyl compound **24** showed excellent full agonist activity, while its para analogue **20** only had 35% efficacy. Compounds containing either the electron-withdrawing acetyl group (**21**) or the electron-donating methoxy group (**23**) behaved as hPR antagonists. It appears that the size of the substituents play a greater role than their electronic properties.

These monosubstituted 5-aryl analogues were also examined in the hPR-A binding assay. The EC_{50} value (2.9 nM) of progesterone in the cotransfection assay is the same order of magnitude as its K_i value (3.5 nM) in the binding assay. This is also true for medroxyprogesterone acetate (MPA). However, the K_i values of most analogues in Table 2 are 1 order of magnitude better than their corresponding EC_{50} or IC_{50} values in cellular assays. Similar to the cotransfection assay results, the analogues with best binding affinity (K_i = 0.41−1.8 nM) are those compounds bearing a halogen in the 5-aryl ring (compounds **15**−**19**). The analogues which showed activity in the antagonist mode had slightly lower binding affinities (compounds **21**, **23**, **33**, and **34**).

To study the effect of two substituents on the activities, disubstituted 5-aryl analogues were synthesized and tested (Table 2). The compounds were not substantially more potent than the monosubstituted analogues. Two chlorines were not better than one (compare **25** with **15** and **18**). And in the binding assay, compound **25** was 6−7-fold weaker than the monochloro compounds **15** and **18**. The 3,5-dichlorophenyl analogue **30** also showed weaker activity than the monochloro compound **18** in both binding and cotransfection assays. Compound **26** was less potent than both of its monosubstituted analogues (**15** and **17**) but equally efficacious relative to the parent compounds, although it exhibited similar binding affinity as its parent compound. The activity of **27** was very similar to that of parent compound **15**, which implies that the methyl group in the meta position has little influence on the activity of **15**. The combination of *p*-fluoro and *m*-trifluoromethyl (analogue **28**) did not improve the potency of **24** but resulted in a significant decrease of the efficacy from 96% to 60%. The 3,5-disubstituted analogues **31** and **32** showed similar binding affinity but weaker agonist activity than their corresponding parent compounds. On the basis of the results from the disubstituted analogues, we did not pursue the trisubstituted 5-aryl analogues.

The introduction of a heteroatom into the 5-aryl moiety was accomplished, and the in vitro data of two representative analogues (**33** and **34**) are listed in Table 2. Both of the analogues showed that the nitrogen atom in the 5-aryl ring switched the activity from agonists

Table 3. Cotransfection and Competitive Binding Data for Optically Active 5-Arylquinoline Analogues[a]

compd	optical rotation	hPR agonist,[b] mean ± SEM eff (%)	hPR agonist,[b] mean ± SEM pot (EC_{50}, nM)[c]	hPR-A binding K_i (nM), mean ± SEM
15	±	77 ± 5	14 ± 2	0.70 ± 0.14
35	+	32 ± 2*	165 ± 66*	19.1 ± 2.1
36	−	77 ± 21	7.0 ± 4.3	0.38 ± 0.04
22	±	59 ± 5	37 ± 11	2.3 ± 0.5
37	+	39 ± 5*	192 ± 18*	43.1 ± 7.4
38	−	73 ± 5	22 ± 12	1.4 ± 0.4

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations, and values with an asterisk represent the mean value of two experiments with standard deviations. [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 in CV-1 cells.

(**16** and **19**) to antagonists along with about a 10-fold decrease of the binding affinities.

The 5-arylquinolines **2** contain one stereogenic center. To address the chirality issue, two racemic compounds, one agonist (**15**) and one partial agonist (**22**), were resolved by chiral HPLC, and the assay results of the enantiomers are reported in Table 3. The absolute stereochemistry of these enantiomers has not been determined. The (−)-enantiomers, **36** and **38**, showed superior potency or efficacy relative to their racemic mixtures, **15** and **22**. The (+)-enantiomers, **35** and **37**, showed much less activity in the assays. Theoretically, when one enantiomer contributes to most of the potency, its potency is about twice that of the racemate. This is true for enantiomer **36** versus racemate **15**.

The cross-reactivity profiles of this series of analogues with other steroid hormone receptors were determined in cotransfection assays and receptor binding assays (Tables 4 and 5). None of the nonsteroidal PR agonist analogues showed agonist activity in hAR, hGR, hMR, and hER cotransfection assays, and they showed weak antagonist activities (micromolar IC_{50} values) in the closely related IR assays. Parent compound **13** has moderate antagonist activities with all IRs tested (PR, AR, GR, ER, MR); however, when the PR agonist activity was optimized by introducing substituents at the 5-phenyl position, the cross-reactivities with MR and ER diminished and the selectivity ratio of PR over other IRs significantly increased. In the competitive binding assays, the dihydroquinoline PR agonist series have much less cross-reactivity with AR and GR than progesterone and MPA. The results demonstrate that the cross-reactivities of the dihydroquinoline PR agonist series can be manipulated and potentially could generate more selective progestins.

The in vivo experiments were conducted to define the oral activity of the novel hPR agonist series in two target organs of the rat: the mammary gland and the uterus. The approach used in these experiments has the advantage of simultaneously evaluating the inhibition of estrone-induced uterine wet weight increases and mammary gland differentiation (lobular bud formation) by progestins in the same ovariectomized animal.

As expected uterine wet weight increased after 3 days of treatment by estrone (E) (10 μg/rat) by approximately 4-fold over vehicle-treated animals in all experiments (data not shown). Addition of MPA to E-treated animals significantly ($p < 0.05$, ANOVA) decreased estrogen-induced uterine wet weight 30% compared to E-treated alone animals (Figure 1).[28] Quinoline derivatives **13**, **15**, and **24** were as efficacious as MPA in inhibiting estrogen-induced uterine wet weights in 3.0 mg/animal dose.

Mammary gland differentiation by progestins was observed in the quinoline analogue-treated animals in the ovariectomized rat (Figure 2). MPA and the three tested analogues (3 mg/rat) all significantly ($p < 0.05$, ANOVA) increased the average number of lobular buds when compared to E-treated alone animals. In contrast with the results in uterus, compounds **13**, **15**, and **24** showed different efficacies in stimulating the percentage of lobular bud observed over E-treated alone animals. Compound **13** was surprisingly more efficacious than MPA, while compound **24** was much less efficacious. These results indicate that compound **24** might be a tissue-selective progestin, which has full efficacy in uterus but lower efficacy in breast.

The novel nonsteroidal compounds **2** showed progestational activities in both in vitro and in vivo assays, which inspires a series of questions of how they mimic the steroids to interact with the receptors. No crystal

Table 4. Antagonist Cross-Reactivities with hAR, hGR, hER, and hMR[a]

compd	hAR, mean ± SEM eff (%)[b]	hAR, mean ± SEM IC_{50} (nM)[c]	hGR, mean ± SEM eff (%)	hGR, mean ± SEM IC_{50} (nM)[c]	hMR, mean ± SEM eff (%)	hMR, mean ± SEM IC_{50} (nM)[c]	hER, mean ± SEM eff (%)	hER, mean ± SEM IC_{50} (nM)[c]
progesterone	46 ± 7	37 ± 2	39 ± 8	>1000	83 ± 6	14 ± 4	−[d]	−
MPA	(159 ± 10	6.1 ± 1.0	157 ± 22	10 ± 1)[e]	67 ± 10	1197 ± 852	(46 ± 5	924 ± 203)[e]
13	78 ± 5*	745 ± 285*	98 ± 2	226 ± 55	90 ± 1	354 ± 85	89 ± 7	299 ± 85
15	85 ± 1*	1550 ± 538*	97 ± 2	339 ± 154	73 ± 3	1525 ± 504	43 ± 23	1803 ± 385
16	90 ± 3	481 ± 127	98 ± 0*	115 ± 27*	76 ± 5*	977 ± 706*	−	−
18	88 ± 8	253 ± 156	98 ± 2	136 ± 52	80 ± 6	748 ± 580	76 ± 10	1480 ± 691
19	90 ± 7	401 ± 13	99 ± 1	266 ± 103	72 ± 9	1068 ± 406	73 ± 16	1095 ± 394
22	89 ± 5	1239 ± 314	97 ± 2	294 ± 161	70 ± 8	1592 ± 460	53 ± 12*	2395 ± 1081*
24	90 ± 5	315 ± 42	96 ± 3	505 ± 320	70 ± 16	2219 ± 644	44 ± 22	1537 ± 185
25	90 ± 4	946 ± 419	99 ± 11	80 ± 45	70 ± 5	1062 ± 945	52 ± 18	2632 ± 781
26	77 ± 10	2205 ± 925	99 ± 1	171 ± 39	70 ± 12	1358 ± 299	52 ± 14	1449 ± 382
27	88 ± 6	1426 ± 187	99 ± 1	275 ± 63	58 ± 7	2035 ± 1023	58 ± 7	1220 ± 491
29	82 ± 4	1220 ± 296	98 ± 1	185 ± 74	56 ± 4	1000 ± 390	54 ± 3	1449 ± 194
30	83 ± 8	1089 ± 351	91 ± 4	225 ± 84	−	−	−	−
32	84 ± 9	1236 ± 603	97	166	−	−	49	1037

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations, and values with an asterisk represent the mean value of two experiments with standard deviation. [b] Antagonist efficacies were determined as a function (%) of maximal inhibition of an agonist. [c] All IC_{50} values were determined from full dose−response curves ranging from 10^{-12} to 10^{-5} M in CV-1 cells. [d] Stands for efficacy < 20% and potency > 10 000 nM. [e] Agonist efficacy, EC_{50} (nM).

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

	K_i (nM), mean ± SEM		
compd	hPR	hAR	hGR
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
13	3.6 ± 0.7	1856 ± 251	154 ± 16
15	0.70 ± 0.14	2685 ± 312	152 ± 16
16	0.55 ± 0.21	>10000	67 ± 3
18	0.43 ± 0.11	1526 ± 360	58 ± 21
19	1.1 ± 0.6	2138 ± 341	34 ± 4
22	2.3 ± 0.5	2330 ± 166	80 ± 36
24	2.6 ± 0.2	795 ± 95	44 ± 12
25	3.4 ± 0.7	5831 ± 4168	59 ± 22
26	0.41 ± 0.08	1457 ± 611	39 ± 8
27	1.2 ± 0.2	1860 ± 364	147 ± 52
29	1.8 ± 0.8	1581 ± 602	60 ± 22
30	1.7 ± 0.2	2584 ± 22	100 ± 16
32	0.87 ± 0.03	3499 ± 451	42 ± 7

[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.

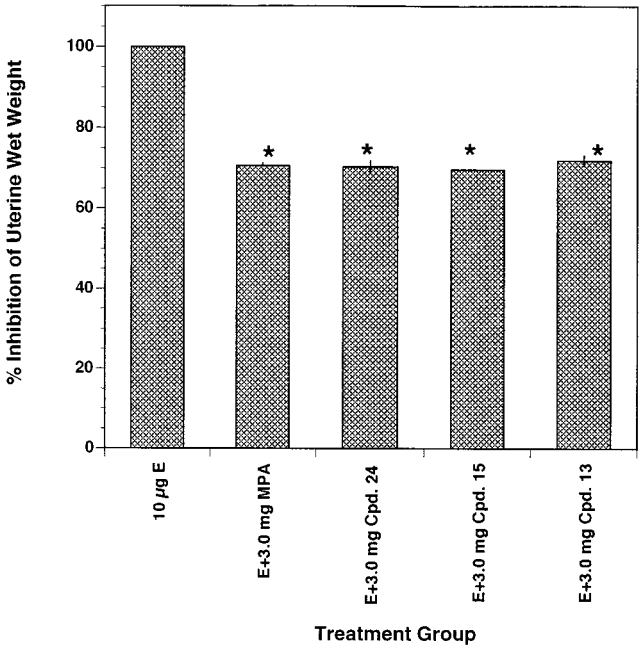


Figure 1. Inhibition of estrone-induced uterine wet weight in the ovariectomized rat by quinoline derivatives or MPA (3.0 mg/rat, $n = 4$). All values represent the mean percent change ± SEM of uterine wet weight from animals treated with E alone (*$p < 0.05$ vs E ANOVA).

structure of the ligand-binding domain exists for PR; consequently, other less direct methods must be employed to delineate the physical alignment between the steroidal and nonsteroidal progesterone agonists. One method to gain possible insight into the correlation of molecular structure with the biological response is CoMFA.[29] CoMFA correlates a three-dimensional grid of steric and electrostatic interaction energies between a series of overlapped molecules and two probe atoms, an sp^3 carbon atom and a proton. The results of the CoMFA modeling will be discussed in a subsequent paper.[30] However to force a physically meaningful alignment of the nonsteroidal PR compounds, a CoMFA model of six steroidal PR agonists including progesterone was developed. When the predictive ability of that CoMFA model was verified, the steric and electrostatic

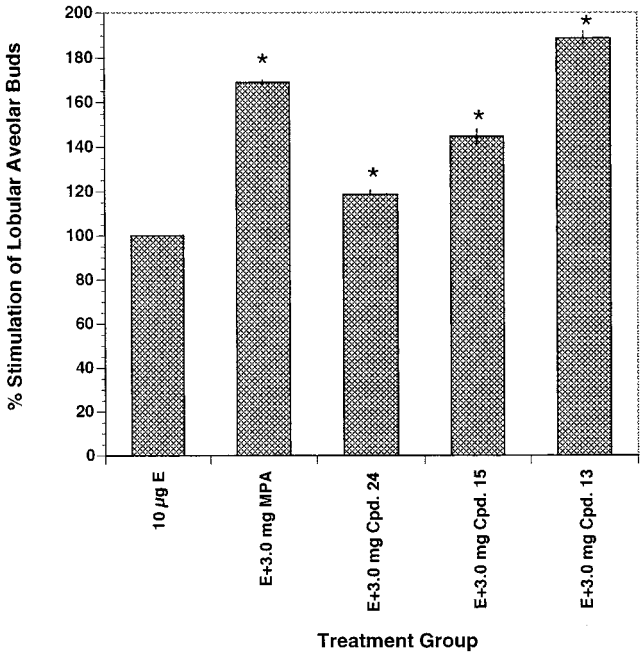


Figure 2. Stimulation of lobular alveolar bud formation in the ovariectomized rat by quinoline derivatives or MPA (3.0 mg/rat, $n = 4$). All values represent the mean percent change ± SEM of lobular alveolar buds from animals treated with E alone (*$p < 0.05$ vs E ANOVA).

fields of progesterone were used as a template to fit alignment.

In attempting to understand the relationship of these compounds with their steroidal counterparts, it was decided to use a predictive cross-validated r^2 in a CoMFA analysis of a set of steroidal and nonsteroidal progesterone agonists as the criteria for judging the validity of these overlaps. Attempts to manually overlap isosteric moieties were performed, and none of these produced an alignment which led to a favorable cross-validated r^2. Manual attempts were made to overlap these structures with progesterone and other steroidal progesterone agonists. None of these produced significant correlation with the cotransfection EC_{50} values in a CoMFA study. When the alignment generated from the CoMFA field of progesterone was used, the cross-validated r^2 obtained was predictive and correlative.[31] The modeling results can be understood by the alignments shown in Figure 3. Progesterone can be seen in its alignment with **2**. The quinoline ring overlays with the steroid D-ring, and the aromatic D-ring of the quinoline **2** overlays with the steroid A-ring. By the modeling alignment, the 5-position of quinoline **2** overlays with the 7-position of the steroid skeleton rather than the 11-position. Figure 3 represents a possible explanation of the orientation of our nonsteroidal agonists with respect to the native hormone.

Conclusion

A novel series of nonsteroidal hPR agonists, 5-aryl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinolines **2**, was developed by using cotransfection and binding assays as guides. This 5-aryl series exhibits biological activity ($EC_{50} = 8-30$ nM) similar to that of the natural hormone progesterone ($EC_{50} = 2.9$ nM) in cotransfection assays with efficacies ranging from 28%

Figure 3. Top and side views of progesterone and **13** showing the alignment rule. All other compounds overlap with the same rule.

to 96%. Most analogues of the series have the same or greater binding affinity (K_i = 0.41−3.6 nM) than progesterone (K_i = 3.5 nM), including 5-chloro- and 5-bromophenyl compounds (**15**, **16**, **18**, and **19**). The novel pharmacophore of the 5*H*-chromeno[3,4-*f*]quinoline provides a number of opportunities for further optimization. The results of the D-ring modifications of the agonist series will be published in a separate report.[32] The novel structure of 5-arylquinoline **2** is quite distinct from the structure of the steroidal PR agonists. Our molecular modeling results suggest a possible overlap of the quinoline A-ring in **2** with the steroid D-ring, which may be how they mimic steroidal interaction with the receptors.

Experimental Section

General Experimental Methods. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC400 spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$ as solvent and TMS (0.00 ppm ^{1}H, 0.00 ppm ^{13}C) or $CHCl_3$ (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as internal standards, unless otherwise noted. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in hertz (Hz). Selected data are reported in the following order: chemical shift, coupling constants, and assignment. Infrared (IR) spectra were recorded on a Mattson Galaxy Series 3000 FT infrared spectrometer. Liquid samples were measured as neat films on NaCl plates; solid samples were measured as KBr pellets. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 70−100%), m (medium, 40−70%), w (weak, 20−40%), br (broad). Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY, or Galbraith Laboratories, Inc., Knoxville, TN. Melting points were taken on an Electrothermal IA9100 digital apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter and are reported as follows: $[\alpha]^{temp}_{wavelength}$ (concentration in g/100 mL, solvent). Flash column chromatography refers to the method of Still[33] using Merck 230−400 mesh silica gel. Analytical thin-layer chromatography (TLC) was performed using Merck 60-F-254 0.25-mm precoated silica gel plates. Preparative thin-layer chromatography (PTLC) was performed using Merck 60-F-254, 0.50- or 1.00-mm precoated silica gel plates. Analytical HPLC was performed on a Beckman System Gold HPLC system. Preparative HPLC was performed on a Waters Delta Prep 4000. The detector wavelength was set to 254 nm. Ethyl ether and tetrahydrofuran were distilled directly prior to use from sodium/benzophenone. Dichloromethane (CH_2Cl_2), benzene, and toluene were stored under nitrogen over 4-Å molecular sieves. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of common inorganic salts used in workups are aqueous solutions. Reactions were conducted under a nitrogen atmosphere unless otherwise noted. Reported yields are not optimized.

1,2-Dihydro-2,2,4-trimethyl-10-isocoumarino[3,4-*f*]quinoline (4) and 1,2-Dihydro-2,2,4-trimethyl-10-isocoumarino-[4,3-*g*]quinoline (5). A solution of 3-amino-6*H*-dibenzo[*b*,*d*]-pyran-6-one (**3**) (185 mg, 0.87 mmol) and iodine (25 mg, 0.10 mmol, 11 mol %) in acetone (20 mL) was heated at 100 °C in a sealed tube for 15 h. The mixture was concentrated, and chromatography (30- × 150-mm column, hexane−EtOAc, 10:1 to 2:1 gradient) afforded **4** (150 mg, 60%) and **5** (75 mg, 30%) as yellow solids. Data for **4**: mp 197−199 °C; ^{1}H NMR (400 MHz, acetone-d_6) 8.20 (d, J = 7.6, H_7), 8.10 (d, J = 7.6, H_{11}), 7.83 (d, J = 8.6, H_{12}), 7.77 (t, J = 7.6, H_9), 7.44 (t, J = 7.6, H_8), 6.64 (d, J = 8.6, H_{10}), 5.88 (br s, NH), 5.38 (s, H_3), 2.39 (s, 3 × H_{4a}), 1.29 (s, 6 × H_{2a}); ^{13}C NMR (100 MHz, $CDCl_3$) 161.5, 149.6, 146.9, 136.6, 134.8, 130.4, 128.3, 126.6, 122.8, 120.8, 119.0, 111.1, 109.6, 108.6, 51.7, 30.4, 23.6; IR (KBr) 3350 br, 2960 m, 1711 s, 1608 s, 1566 m, 1468 m, 1311 m. Anal. ($C_{19}H_{17}NO_2$) C, H, N. Data for **5**: mp 246−248 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.30 (d, J = 7.6, H_9), 7.93 (d, J = 7.6, H_6), 7.72 (t, J = 7.6, H_7), 7.63 (s, H_5), 7.41 (t, J = 7.6, H_8), 6.36 (s, H_{12}), 5.40 (s, H_3), 4.13 (br s, NH), 2.10 (s, 3 × H_{4a}), 1.33 (s, 6 × H_{2a}); ^{13}C NMR (100 MHz, $CDCl_3$) 162.2, 152.7, 146.1, 136.4, 134.9, 130.7, 129.1, 127.2, 126.5, 120.5, 119.4, 119.0, 117.8, 107.6, 99.8, 52.7, 31.8, 19.0. Anal. ($C_{19}H_{17}NO_2$) C, H, N.

1,2-Dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (1). The intermediate 8-nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (**10**) was prepared by a modified literature procedure.[23] To a 50-mL round-bottom flask charged with 2-biphenylcarboxylic acid (**8**) (5.0 g, 25 mmol) was added 10 mL of 70% nitric acid, and the resulting yellow slurry was stirred at room temperature (rt) for 30 min.[34] The second nitration was performed in two procedures (A and B). For the one-pot operation, procedure A, 25 mL of fuming nitric acid was directly introduced to the above reaction mixture dropwise in 20 min, giving rise to a clear yellow solution. The reaction mixture was stirred at rt for 15 h and was poured into ice water (100 mL). The crude mixture was extracted with ethyl acetate (EtOAc) (3 × 60 mL), and the combined extract was washed with water (2 × 20 mL) and brine (2 × 20 mL). Removal of solvent under reduced pressure afforded a crude yellow solid, which was a 2:1 mixture of two regioisomers, 4,2′-dinitrobiphenyl-2-carboxylic acid (**9a**) and 4,4′-dinitrobiphenyl-2-carboxylic acid (**9b**). For the alternative procedure B, the mixture of the first nitration was poured into ice water (50 mL) and the products were precipitated out from the solution. Filtration of the mixture afforded the mononitrated products as a white solid, which was then treated with fuming nitric acid (10 mL) at rt for 6 h followed by the same workup procedure as described in procedure A to afford the same ratio mixture of dinitrated products **9a**,**b** in quantitative yield.

The mixture of the dinitrobiphenylcarboxylic acid was dissolved in DMA (80 mL), and the solution was heated at reflux for 12 h. The reaction mixture was cooled to rt and diluted with water (20 mL). The desired product was precipitated out from the solution upon standing at rt overnight. Filtration of the mixture afforded the product (2.9 g, 50%) as a brown solid, which was directly used in the next step without

further purification. In a 1-L round-bottom flask, a solution of 8-nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (**10**) (2.9 g, 12 mmol) in EtOAc (600 mL) was treated with 10% Pd/C (1.0 g, 0.94 mmol, 7.8 mol %) under hydrogen balloon for 24 h. Filtration from the catalyst and removal of solvent afforded 2.2 g of 8-amino-6*H*-dibenzo[*b*,*d*]pyran-6-one (86%) as a yellowish solid. A 210-mL Ace-Thred pressure tube charged with the amino compound (2.2 g, 10.4 mmol), iodine (1.1 g, 4.3 mmol, 41 mol %), and acetone (150 mL) was sealed with the thred cap at rt. The tube was heated in an oil bath at 110−130 °C for 24 h. The dark reaction mixture was concentrated, and purification by flash chromatography (40- × 200-mm column, hexane−EtOAc, 9:1 to 2:1 gradient) afforded 1.5 g of the title compound **1** (50%) as a yellow solid: mp 190−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.90 (d, J = 7.8, H_{10}), 7.78 (d, J = 8.4, H_{11}), 7.38−7.22 (m, H_7, H_8, H_9), 7.01 (d, J = 8.4, H_{12}), 5.58 (s, H_3), 4.31 (br s, NH), 2.12 (s, 3 × H_{4a}), 1.33 (s, 6 × H_{2a}); ^{13}C NMR (100 MHz, $CDCl_3$) 160.3, 150.5, 145.7, 132.4, 131.6, 128.4, 124.2, 122.0, 121.4, 121.2, 119.3, 118.4, 117.2, 50.8, 29.9, 28.6; IR (KBr) 3352 br, 2966 s, 2924 m, 1712 s, 1626 m, 1450 m, 1356 m, 1251 m, 1205 m, 740 m. Anal. ($C_{19}H_{17}NO_2$) C, H, N.

General Procedure for Preparing 5-Aryl Compounds from the Lactone 1. This transformation was a two-step sequence: an addition of a nucleophile either from a commercial reagent or prepared in situ from a metal−halogen-exchange reaction and a reduction of the resulting cyclic hemiacetal. To a solution of a bromo compound in THF or diethyl ether (0.1−0.3 M) at − 78 °C was added *n*-BuLi (1.6 M solution in hexane, 1.1 equiv) slowly, and the resulting reaction mixture was allowed to stir at − 78 °C until the anion was formed. A yellow solution (0.2−0.5 M) of **1** in THF was added via cannula to the above solution, and the resulting dark-red mixture was slowly warmed. As soon as the red color faded (around − 30 °C), the reaction was quenched immediately with water to give a light-yellow solution (with aryl Grignard reagents the addition reaction took hours at room temperature). The reaction mixture was extracted with EtOAc (2×), and the combined extracts were washed with brine and concentrated. Purification by flash chromatography (hexane−EtOAc, 10:1 to 2:1 gradient) afforded the hemiacetal intermediate as a yellow oil. To a solution of the intermediate in dichloromethane (0.10 M) at − 78 °C were added triethylsilane (5.0 equiv) and either trifluoroacetic acid (1.1 equiv) or BF_3−OEt_2 (0.20 equiv), and the resulting slurry was warmed to rt, giving rise to a dark-green solution. The mixture was allowed to stir at rt or reflux in some cases until the reaction went to completion. The reaction then was quenched with 5% NaOH aqueous solution and extracted with ethyl acetate. The combined extracts were washed with brine and concentrated. Purification by flash chromatography (hexane−EtOAc, 10:1 to 2:1 gradient) afforded the 5-aryl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline in moderate to good yield. A second flash chromatography might be needed to remove the silane oxide and the byproduct using a 1:2 mixture of dichloromethane and hexane as eluents.

(*R*,*S*)-1,2-Dihydro-2,2,4-trimethyl-6-phenyl-6*H*-isochromeno[3,4-*f*]quinoline (6). This compound was prepared by a similar addition−reduction sequence as described in the general procedure from bromobenzene (157 mg, 1.0 mmol, 4.7 equiv) and lactone **4** (60 mg, 0.21 mmol) in a 85% two-step yield as a colorless oil (60 mg): ^{1}H NMR (400 MHz, $CDCl_3$) 7.60 (d, J = 7.7, H_7), 7.46−7.30 (m, -C_6H_5, H_8, H_{11}), 7.09 (t, J = 7.7, H_9), 6.73 (d, J = 7.7, H_{12}), 6.26 (d, J = 8.2, H_{10}), 6.04 (s, H_6), 5.22 (s, H_3), 3.86 (br s, NH), 2.11 (s, 3 × H_{4a}), 1.26 (s, 3 × H_{2ab}), 1.23 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, $CDCl_3$) 152.0, 146.3, 145.2, 139.6, 132.9, 131.6, 129.3, 128.5, 128.4, 125.9, 125.6, 123.5, 121.2, 113.9, 111.2, 108.5, 80.1, 51.4, 30.2, 30.1, 23.5. Anal. ($C_{25}H_{23}NO$) C, H, N.

(*R*,*S*)-1,2-Dihydro-2,2,4-trimethyl-10-phenyl-10*H*-isocoumarino[4,3-*g*]quinoline (7). This compound was prepared by a similar addition−reduction sequence as described in the general procedure from bromobenzene (157 mg, 1.0 mmol) and quinoline **5** (100 mg, 0.34 mmol) in 83% yield as a white solid (110 mg): mp 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.64 (d, J = 7.8, H_9), 7.42 (s, H_5), 7.39−7.31 (m, H_8, -C_6H_5), 7.10 (t, J = 7.8, H_7), 6.79 (d, J = 7.8, H_6), 6.09 (s, H_{10}), 6.08 (s, H_{12}), 5.26 (s, H_3), 3.81 (br s, NH), 2.06 (s, 3 × H_{4a}), 1.28 (s, 3 × H_{2ab}), 1.27 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, $CDCl_3$) 154.7, 145.4, 140.2, 132.4, 131.2, 128.7, 128.5, 128.4, 128.3, 128.2, 127.0, 126.3, 125.7, 120.7, 118.6, 116.6, 112.2, 101.2, 80.0, 52.3, 31.6, 31.5, 19.0. Anal. ($C_{25}H_{23}NO$) C, H, N.

(*R*,*S*)-1,2-Dihydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno[3,4-*f*]quinoline (13). This compound was prepared by the general procedure from bromobenzene (0.15 mL, 1.4 mmol, 2.8 equiv) and compound **1** (150 mg, 0.50 mmol) in 68% yield as a white solid (120 mg): mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (d, J = 7.8, H_{10}), 7.50 (d, J = 8.2, H_{11}), 7.22−7.12 (m, -C_6H_5), 7.00 (t, J = 7.8, H_8), 6.92 (s, H_5), 6.88 (t, J = 7.8, H_9), 6.83 (d, J = 7.8, H_7), 6.69 (d, J = 8.2, H_{12}), 5.46 (s, H_3), 3.92 (br s, NH), 1.99 (s, 3 × H_{4a}), 1.29 (s, 3 × H_{2ab}), 1.26 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.5, 147.0, 141.1, 134.4, 134.3, 130.3, 129.1, 129.0, 128.8, 128.5, 127.9, 125.7, 124.3, 122.6, 122.5, 120.7, 119.6, 118.1, 115.8, 115.7, 76.1, 51.0, 29.1, 29.0, 24.0; IR (neat) 3364 br, 2962 m, 1705 m, 1635 m, 1593 m, 1470 s, 1435 m, 1167 m. Anal. ($C_{25}H_{23}NO\cdot{}^1/_8H_2O$) C, H, N.

(*R*,*S*)-5-(4-Fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (14). This compound was prepared by the general procedure from 4-fluorobromobenzene (175 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.068 mmol) in 59% yield as a white solid (15 mg): mp 85−87 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.60 (d, J = 7.8, H_{10}), 7.56 (d, J = 8.3, H_{11}), 7.26 (dd, J = 8.7, 5.7, $H_{2'}$, $H_{6'}$), 6.98 (t, J = 8.7, $H_{3'}$, $H_{5'}$), 6.97 (t, J = 7.8, H_8), 6.92 (s, H_5), 6.87 (t, J = 7.8, H_9), 6.83 (d, J = 8.3, H_{12}), 6.76 (d, J = 7.8, H_7), 5.54 (br s, NH), 5.47 (s, H_3), 1.99 (s, 3 × H_{4a}), 1.26 (s, 3 × H_{2ab}), 1.24 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, $CDCl_3$) 163.0 (d, J = 245, $C_{4'}$), 151.3, 147.1, 137.2, 134.4, 131.3, 131.2, 130.2, 129.0, 128.0, 125.7, 124.4, 122.7, 120.6, 119.5, 118.2, 115.9, 115.5 (d, J = 22, $C_{3',5'}$), 75.5, 51.0, 29.7, 29.1, 24.0; IR (KBr) 3360 br, 2962 m, 1707 m, 1601 m, 1506 s, 1469 s, 1221 m, 1157 m. Anal. ($C_{25}H_{22}FNO\cdot{}^1/_4H_2O$) C, H, N.

(*R*,*S*)-5-(4-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (15). This compound was prepared by the general procedure from 4-bromochlorobenzene (1.4 g, 7 mmol, 4.1 equiv) and compound **1** (0.50 g, 1.7 mmol) in 40% yield as a white solid (264 mg): mp 139−140 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.59 (d, J = 7.8, H_{10}), 7.56 (d, J = 8.4, H_{11}), 7.24 (d, J = 9.1, $H_{3'}$, $H_{5'}$), 7.21 (d, J = 9.1, $H_{2'}$, $H_{6'}$), 6.98 (t, J = 7.8, H_8), 6.92 (s, H_5), 6.86 (t, J = 7.8, H_9), 6.83 (d, J = 8.4, H_7), 6.77 (d, J = 7.8, H_{12}), 5.54 (br s, NH), 5.48 (s, H_3), 1.99 (s, 3 × H_{4a}), 1.26 (s, 3 × H_{2ab}), 1.24 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, $CDCl_3$) 137.8, 134.5, 131.0, 129.8, 128.2, 124.5, 75.6, 61.1, 27.9, 22.5, 14.2; IR (KBr) 3371 br, 2964 m, 1593 m, 1469 m, 1435 m. Anal. ($C_{25}H_{22}ClNO$) C, H, N.

(*R*,*S*)-5-(4-Bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (16). This compound was prepared by the general procedure from 1,4-dibromobenzene (250 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 54% yield as a white solid (16 mg): mp 97−99 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.58 (d, J = 7.8, H_{10}), 7.55 (d, J = 8.4, H_{11}), 7.39 (d, J = 8.5, $H_{3'}$, $H_{5'}$), 7.16 (d, J = 8.5, $H_{2'}$, $H_{6'}$), 6.98 (t, J = 7.8, H_8), 6.90 (s, H_5), 6.86 (t, J = 7.8, H_9), 6.83 (d, J = 8.4, H_{12}), 6.77 (d, J = 7.8, H_7), 5.54 (br s, NH), 5.47 (s, H_3), 1.99 (s, 3 × H_{4a}), 1.26 (s, 3 × H_{2ab}), 1.23 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.4, 147.2, 140.7, 134.6, 132.0, 131.9, 131.4, 129.9, 129.0, 128.1, 125.7, 124.5, 122.8, 122.3, 120.6, 119.6, 118.2, 116.1, 75.6, 51.1, 29.8, 29.2, 24.1; IR (neat) 3364 br, 2962 m, 1699 m, 1593 m, 1574 m, 1483 s, 1469 m, 1435 m, 1249 m, 1213 m, 1167 m, 1010 m. Anal. ($C_{25}H_{22}BrNO$) C, H, N.

(*R*,*S*)-5-(3-Fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (17). This compound was prepared by the general procedure from 1-bromo-3-fluorobenzene (175 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 47% yield as a white solid (12 mg): mp 78−80 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.60 (d, J = 7.9, H_{10}), 7.57 (d, J = 8.4, H_{11}), 7.26 (td, J = 7.6, 5.9, $H_{5'}$), 7.06 (d, J = 7.6,

$H_{6'}$), 7.01−6.81 (m, H_7, H_8, H_9, H_{12}, $H_{2'}$, $H_{4'}$), 6.95 (s, H_5), 5.58 (br s, H_3), 5.49 (s, H_3), 2.02 (s, 3 × H_{4a}), 1.27 (s, 3 × H_{2ab}), 1.25 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 163.5 (d, J = 245, $C_{3'}$), 151.4, 147.2, 144.3, 134.7, 130.7, 129.9, 128.9, 128.2, 125.6, 125.2, 124.5, 122.8, 120.6, 119.6, 118.3, 116.0, 115.8, 115.6, 115.3, 75.5, 51.1, 29.6, 24.0; IR (neat) 3369 br, 2964 m, 1699 m, 1633 s, 1581 s, 1498 s, 1342 m, 1253 m, 1167 m. Anal. ($C_{25}H_{22}FNO\cdot{}^1/_8H_2O$) C, H, N.

(*R*,*S*)-5-(3-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (18). This compound was prepared by the general procedure from 3-bromochlorobenzene (195 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 52% yield as a white solid (14 mg): mp 122−124 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.61 (d, J = 7.8, H_{10}), 7.57 (d, J = 8.4, H_{11}), 7.28−7.18 (m, H_8, $H_{2'}$, $H_{4'}$, $H_{5'}$), 7.00 (t, J = 7.8, H_9), 6.95 (s, H_5), 6.89 (d, J = 7.8, H_7), 6.84 (d, J = 8.4, H_{12}), 6.82 (d, J = 8.1, $H_{6'}$), 5.58 (br s, NH), 5.49 (s, H_3), 2.01 (s, 3 × H_{4a}), 1.27 (s, 3 × H_{2ab}), 1.25 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.3, 143.7, 134.7, 134.4, 130.6, 129.7, 129.0, 128.9, 128.7, 128.3, 128.1, 127.7, 124.4, 122.8, 122.7, 120.5, 119.6, 118.2, 116.1, 75.4, 51.0, 30.6, 24.0; IR (neat) 3366 m, 2968 m, 1591 m, 1572 m, 1468 s, 1433 s, 1259 m, 1207 m, 1167 m, 754 m. Anal. ($C_{25}H_{22}ClNO$) C, H, N.

(*R*,*S*)-5-(3-Bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (19). This compound was prepared by the general procedure from 1,3-dibromobenzene (250 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 83% yield as a white solid (25 mg): mp 87−89 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.61 (d, J = 7.8, H_{10}), 7.57 (d, J = 8.4, H_{11}), 7.38 (s, $H_{2'}$), 7.36 (d, J = 7.8, $H_{4'}$), 7.26 (d, J = 7.8, $H_{6'}$), 7.19 (t, J = 7.8, $H_{5'}$), 7.00 (t, J = 8.3, H_8), 6.98 (s, H_5), 6.81−6.90 (m, H_7, H_9, H_{12}), 5.60 (br s, NH), 5.50 (s, H_3), 2.01 (s, 3 × H_{4a}), 1.27 (s, 3 × H_{2ab}), 1.25 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.2, 147.1, 144.0, 134.7, 131.9, 131.6, 130.9, 129.6, 128.8, 128.1, 128.0, 125.4, 124.4, 122.8, 122.7, 122.6, 120.4, 119.6, 118.2, 116.1, 75.3, 51.1, 29.5, 24.0; IR (neat) 3364 br, 2962 m, 1699 m, 1591 m, 1469 s, 1437 m. Anal. ($C_{25}H_{22}BrNO$) C, H, N.

(*R*,*S*)-1,2-Dihydro-2,2,4-trimethyl-5-[4-(trifluoromethyl)phenyl]-5*H*-chromeno[3,4-*f*]quinoline (20). This compound was prepared by the general procedure from 4-bromo-(trifluoromethyl)benzene (130 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 35% yield as a white solid (10 mg): mp 79−81 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.61−7.56 (m, H_{10}, H_{11}, $H_{3'}$, $H_{5'}$), 7.45 (d, J = 8.3, $H_{2'}$, $H_{6'}$), 7.01 (s, H_5), 6.97 (t, J = 7.7, H_8), 6.86 (t, J = 7.7, H_9), 6.85 (d, J = 8.4, H_{12}), 6.81 (d, J = 7.7, H_7), 5.57 (br s, NH), 5.49 (s, H_3), 1.99 (s, 3 × H_{4a}), 1.27 (s, 3 × H_{2ab}), 1.25 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.2, 147.1, 134.7, 129.8, 129.5, 128.8, 128.1, 125.7, 125.5, 124.5, 122.9, 122.8, 120.5, 119.6, 118.1, 116.1, 116.0, 75.5, 51.0, 29.1, 24.0; IR (neat) 2964 br, 1469 m, 1325 s, 1165 m, 1124 m, 1056 m. Anal. ($C_{26}H_{22}F_3NO$) C, H, N.

(*R*,*S*)-5-(4-Acetylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (21). This compound was prepared by the general procedure from 2-(4-bromophenyl)-2-methyl-1,3-dioxane (219 mg, 1.0 mmol, 9.7 equiv) and compound **1** (30 mg, 0.10 mmol) in 30% yield as a colorless oil (12 mg): ^{1}H NMR (400 MHz, acetone-d_6) 7.83 (d, J = 8.3, $H_{2'}$, $H_{6'}$), 7.60 (d, J = 7.6, H_{10}), 7.57 (d, J = 8.4, H_{11}), 7.36 (d, J = 8.3, $H_{3'}$, $H_{5'}$), 6.99 (s, H_5), 6.98 (t, J = 7.6, H_9), 6.89−6.79 (m, H_7, H_8, H_{12}), 5.56 (br s, NH), 5.50 (s, H_3), 2.49 (s, COCH_3), 2.00 (s, 3 × H_{4a}), 1.28 (s, 3 × H_{2aa}), 1.25 (s, 3 × H_{2ab}). Anal. ($C_{27}H_{25}NO_2$) C, H, N.

(*R*,*S*)-1,2-Dihydro-2,2,4-trimethyl-5-(4-methylphenyl)-5*H*-chromeno[3,4-*f*]quinoline (22). This compound was prepared by the general procedure from 4-bromotoluene (171 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 58% yield as a white solid (15 mg): mp 83−85 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.58 (d, J = 7.9, H_{10}), 7.54 (d, J = 8.5, H_{11}), 7.10 (d, J = 8.0, $H_{2'}$, $H_{6'}$), 7.00 (d, J = 8.0, $H_{3'}$, $H_{5'}$), 6.97 (t, J = 7.9, H_8), 6.89 (s, H_5), 6.84 (d, J = 7.9, H_9), 6.81 (d, J = 8.5, H_{12}), 6.75 (d, J = 7.9, H_7), 5.47 (br s, NH), 5.45 (s, H_3), 2.19 (s, 3 × $H_{4'a}$), 1.99 (s, 3 × H_{4a}), 1.25 (s, 3 × H_{2ab}), 1.23 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.6, 147.0, 138.1, 138.0, 134.3, 130.6, 129.4, 129.2, 127.9, 125.7, 124.2, 122.6, 122.4, 120.7, 119.5, 118.1, 115.8, 115.7, 76.1, 50.9, 24.0, 20.9; IR (KBr) 3362 br, 2964 m, 1707 m, 1593 m, 1469 s, 1437 m, 1259 m, 1169 m. Anal. ($C_{26}H_{25}NO$) C, H, N.

(*R*,*S*)-1,2-Dihydro-5-(4-methoxyphenyl)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (23). This compound was prepared by the general procedure from 4-bromoanisole (187 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 48% yield as a colorless oil (13 mg); ^{1}H NMR (400 MHz, acetone-d_6) 7.59 (d, J = 7.7, H_{10}), 7.54 (d, J = 8.4, H_{11}), 7.13 (d, J = 8.7, $H_{2'}$, $H_{6'}$), 6.95 (t, J = 7.7, H_8), 6.87 (s, H_5), 6.85 (t, J = 7.7, H_9), 6.81 (d, J = 8.4, H_{12}), 6.75 (d, J = 8.7, $H_{3'}$, $H_{5'}$), 6.74 (d, J = 7.7, H_7), 5.47 (br s, NH), 5.45 (s, H_3), 3.69 (s, OCH_3), 1.99 (s, 3 × H_{4a}), 1.25 (s, 3 × H_{2ab}), 1.23 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 160.1, 151.6, 147.0, 134.2, 132.9, 130.5, 127.9, 125.8, 124.2, 122.6, 122.4, 120.7, 119.4, 118.1, 115.7, 114.3, 114.1, 76.0, 55.3, 50.9, 29.7, 24.0; IR (neat) 3366 br, 2960 m, 1608 m, 1510 m, 1469 s, 1249 s, 1168 m. Anal. ($C_{26}H_{25}NO_2$) C, H, N.

(*R*,*S*)-1,2-Dihydro-2,2,4-trimethyl-5-[3-(trifluoromethyl)phenyl]-5*H*-chromeno[3,4-*f*]quinoline (24). This compound was prepared by the general procedure from 1-bromo-3-(trifluoromethyl)benzene (450 mg, 2.0 mmol, 4 equiv) and compound **1** (146 mg, 0.50 mmol) in 57% yield as a pale-white solid (120 mg): mp 75−77 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.61 (d, J = 7.6, H_{10}), 7.60 (d, J = 9.0, H_{11}), 7.56−7.45 (m, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.04 (s, H_5), 6.98 (t, J = 7.6, H_8), 6.89−6.83 (m, H_7, H_9, H_{12}), 5.60 (br s, NH), 5.55 (s, H_3), 2.02 (s, 3 × H_{4a}), 1.27 (s, 6 × H_{2a}); ^{13}C NMR (100 MHz, $CDCl_3$) 150.5, 145.3, 141.3, 134.3, 131.7, 129.1, 128.7, 128.6, 128.0, 125.2, 124.9, 124.8, 124.5, 124.0, 122.3, 121.3, 120.0, 117.8, 115.7, 75.1, 50.9, 29.5, 29.2, 24.0; IR (neat) 2966 m, 1593 m, 1469 m, 1435 m, 1330 s, 1165 s, 1126 s. Anal. ($C_{26}H_{22}F_3NO\cdot{}^1/_8H_2O$) C, H, N.

(*R*,*S*)-5-(3,4-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (25). This compound was prepared by the general procedure from 1-bromo-3,4-dichlorobenzene (226 mg, 1.0 mmol, 7.3 equiv) and compound **1** (40 mg, 0.13 mmol) in 56% yield as a pale-white solid (31 mg): mp 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (d, J = 7.8, H_{10}), 7.50 (d, J = 8.3, H_{11}), 7.29 (s, $H_{2'}$), 7.23 (d, J = 8.0, $H_{5'}$), 7.09 (d, J = 8.0, $H_{6'}$), 7.04 (t, J = 7.5, H_8), 6.92 (t, J = 7.5, H_9), 6.85 (d, J = 8.2, H_7), 6.83 (s, H_5), 6.71 (d, J = 8.4, H_{12}), 5.48 (s, H_3), 4.0 (br s, NH), 1.97 (s, 3 × H_{4a}), 1.30 (s, 3 × H_{2ab}), 1.26 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, $CDCl_3$) 150.4, 145.3, 140.7, 134.3, 132.6, 132.1, 130.5, 130.3, 128.8, 128.6, 128.0, 127.9, 124.5, 124.0, 122.5, 122.4, 121.2, 119.9, 117.8, 115.8, 74.6, 50.9, 29.8, 29.0, 24.0; IR (KBr) 3377 br, 2962 m, 1467 s, 1435 m, 1257, 816 m, 755 m. Anal. ($C_{25}H_{21}Cl_2NO\cdot{}^1/_4H_2O$) C, H, N.

(*R*,*S*)-5-(4-Chloro-3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (26). This compound was prepared by the general procedure from 2-chloro-5-bromofluorobenzene (209 mg, 1.0 mmol, 19 equiv) and compound **1** (15 mg, 0.051 mmol) in 64% yield as a colorless oil (13 mg): ^{1}H NMR (400 MHz, acetone-d_6) 7.61 (dd, J = 7.7, 1.4, H_{10}), 7.57 (d, J = 8.3, H_{11}), 7.38 (t, J = 7.9, $H_{5'}$), 7.13 (dd, J = 10.3, 1.8, $H_{2'}$), 7.05 (td, J = 7.7, 1.4, H_8), 7.00 (dd, J = 7.9, 1.8, $H_{6'}$), 6.93 (s, H_5), 6.89 (td, J = 7.7, 1.4, H_9), 6.86 (d, J = 8.3, H_{12}), 6.83 (dd, J = 7.7, 1.4, H_7), 5.62 (br s, NH), 5.50 (s, H_3), 2.02 (s, 3 × H_{4a}), 1.27 (s, 3 × H_{2ab}), 1.25 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 157.1 (d, J = 247.2, $C_{3'}$), 150.3, 146.4, 142.3 (d, J = 6.5), 133.9, 130.3, 128.6, 128.0, 127.4, 125.4, 124.6, 123.7, 122.2, 122.0, 119.6, 118.8, 117.4, 116.5 (d, J = 22.4), 115.4, 74.2, 50.2, 28.3, 23.2; IR (neat) 3371 br, 2964 m, 1581 m, 1469 s, 1242 m. Anal. ($C_{25}H_{21}ClFNO\cdot{}^1/_4H_2O$) C, H, N.

(*R*,*S*)-5-(4-Chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (27). This compound was prepared by the general procedure from 5-bromo-2-chlorotoluene (206 mg, 1.0 mmol, 14 equiv) and **1** (20 mg, 0.069 mmol) in 82% yield as a pale-white solid (22 mg): mp 89−91 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.60 (d, J = 7.7, H_{10}), 7.55 (d, J = 8.4, H_{11}), 7.21 (d, J = 7.9, $H_{5'}$), 7.20 (s, $H_{2'}$), 7.01 (d, J = 7.9, $H_{6'}$), 6.98 (t, J = 7.7, H_8), 6.89 (s, H_5), 6.87 (t, J = 7.7, H_9), 6.83 (d, J = 8.4, H_{12}), 6.78 (d, J = 7.7, H_7), 5.55

(br s, NH), 5.48 (s, H_3), 2.22 (s, 3 × $H_{3'a}$), 2.00 (s, 3 × H_{4a}), 1.26 (s, 3 × H_{2ab}), 1.24 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.5, 147.2, 140.3, 136.2, 134.6, 134.2, 132.0, 130.1, 129.4, 129.1, 128.4, 128.1, 125.7, 124.5, 122.8, 120.6, 119.7, 118.3, 116.1, 116.0, 75.6, 51.1, 29.6, 29.2, 24.1, 20.1; IR (KBr) 3369 br, 2960 m, 1593 m, 1467 s, 1435 s, 1323 m, 1257 m, 1047 m, 762 m. Anal. ($C_{26}H_{24}ClNO$) C, H, N.

(*R*,*S*)-5-[4-Fluoro-3-(trifluoromethyl)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (28). This compound was prepared by the general procedure from 5-bromo-2-fluorobenzotrifluoride (243 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 61% yield as a pale-white solid (18 mg): mp 74−76 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.62 (d, J = 7.7, H_{10}), 7.61 (d, J = 8.3, H_{11}), 7.61−7.53 (m, $H_{2'}$, $H_{6'}$), 7.27 (t, J = 7.7, $H_{5'}$), 7.04 (s, H_5), 7.02 (t, J = 7.7, H_8), 6.89 (t, J = 7.7, H_9), 6.86 (d, J = 8.3, H_{12}), 6.83 (d, J = 7.7, H_7), 5.62 (br s, NH), 5.51 (s, H_3), 2.02 (s, 3 × H_{4a}), 1.26 (s, 6 × H_{2a}); ^{13}C NMR (100 MHz, acetone-d_6) 159.7 (d, J = 255), 151.0, 147.3, 138.3 (d, J = 4.0), 135.5 (d, J = 8.9), 134.9 (d, J = 4.0), 129.3, 128.8, 128.3, 127.7 (d, J = 4.0), 125.4, 124.6, 123.1, 122.9, 122.8 (q, J = 272), 120.4, 119.6, 118.2, 117.8, 117.6, 116.3 (d, J = 5.0), 74.8, 51.1, 29.4, 29.3, 24.0; IR (KBr) 3371 br, 2966 m, 1595 m, 1502 s, 1467 s, 1323 m, 1163 m. Anal. ($C_{26}H_{21}F_4NO$) C, H, N.

(*R*,*S*)-5-(3-Fluoro-4-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (29). This compound was prepared by the general procedure from 4-bromo-2-fluorotoluene (189 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 56% yield as a colorless oil (15 mg): ^{1}H NMR (400 MHz, acetone-d_6) 7.60 (d, J = 7.8, H_{10}), 7.56 (d, J = 8.4, H_{11}), 7.08 (t, J = 7.9, $H_{5'}$), 6.98 (t, J = 7.8, H_8), 6.94 (d, J = 8.0, $H_{2'}$), 6.91 (s, H_5), 6.90−6.80 (m, H_7, H_9, H_{12}, $H_{6'}$), 5.55 (br s, NH), 5.48 (s, H_3), 2.12 (s, 3 × $H_{4'a}$), 2.01 (s, 3 × H_{4a}), 1.26 (s, 3 × H_{2ab}), 1.24 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 161.9 (d, J = 235), 151.4, 147.1, 141.3, 134.5, 132.0, 131.9, 130.0, 129.0, 128.0, 125.6, 125.0, 124.9, 124.4, 122.7, 120.5, 119.5, 118.2, 115.9, 115.5 (d, J = 23), 75.4, 50.9, 29.5, 24.0, 14.1; IR (KBr) 3369 br, 2962 m, 1593 m, 1575 m, 1467 s, 1259 m, 815 m, 754 m. Anal. ($C_{26}H_{24}FNO$) C, H, N.

(*R*,*S*)-5-(3,5-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (30). This compound was prepared by the general procedure from 1-bromo-3,5-dichlorobenzene (226 mg, 1.0 mmol, 19 equiv) and **1** (15 mg, 0.051 mmol) in 95% yield as a white solid (20 mg): mp 100−102 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.63 (d, J = 7.7, H_{10}), 7.58 (d, J = 8.4, H_{11}), 7.29 (t, J = 1.9, $H_{4'}$), 7.20 (d, J = 1.9, $H_{2'}$, $H_{6'}$), 7.03 (t, J = 7.7, H_8), 6.97 (s, H_5), 6.93−6.85 (m, H_7, H_9, H_{12}), 5.63 (br s, NH), 5.53 (s, H_3), 2.04 (s, 3 × H_{4a}), 1.28 (s, 3 × H_{2ab}), 1.27 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.0, 147.3, 145.7, 135.5, 135.1, 135.0, 129.0, 128.8, 128.6, 128.4, 127.8, 125.3, 124.6, 123.2, 123.0, 120.3, 119.7, 118.3, 116.4, 116.3, 74.9, 51.2, 24.0; IR (neat) 3350 br, 2940 m, 1690 m, 1590 m, 1480 s, 1070 m. Anal. ($C_{25}H_{21}Cl_2NO\cdot{}^1/_2H_2O$) C, H, N.

(*R*,*S*)-5-(3-Bromo-5-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (31). This compound was prepared by the general procedure from 1,3-dibromo-5-fluorobenzene (254 mg, 1.0 mmol, 4.7 equiv) and compound **1** (60 mg, 0.21 mmol) in 63% yield as a white powder (60 mg): mp 82−84 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.63 (d, J = 7.7, H_{10}), 7.58 (d, J = 8.4, H_{11}), 7.23 (d, J = 5.2, $H_{4'}$), 7.20 (s, $H_{2'}$), 7.08−7.02 (m, H_8, $H_{6'}$), 6.97 (s, H_5), 6.94−6.85 (m, H_7, H_9, H_{12}), 5.64 (br s, NH), 5.53 (s, H_3), 2.04 (s, 3 × H_{4a}), 1.28 (s, 3 × H_{2ab}), 1.27 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 163.4 (d, J = 250), 151.1, 147.3, 146.4 (d, J = 7.0), 135.0, 129.1, 128.8, 128.4, 128.3, 125.3, 124.6, 123.2, 123.0, 122.9, 120.4, 119.7, 119.2 (d, J = 24.8), 118.3, 116.4, 115.2 (d, J = 22.2), 74.9, 51.2, 29.4, 24.0; IR (neat) 3367 br, 1699 m, 1595 s, 1581 s, 1469 s, 1435 s, 1251 s. Anal. ($C_{25}H_{21}BrFNO$) C, H, N.

(*R*,*S*)-5-(3-Bromo-5-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (32). This compound was prepared by the general procedure from 3,5-dibromotoluene (250 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 52% yield as a white solid (16 mg): mp 87−89 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.61 (d, J = 7.7, H_{10}), 7.56 (d, J = 8.4, H_{11}), 7.17 (s, $H_{2'}$), 7.14 (s, $H_{4'}$), 7.10 (s, $H_{6'}$), 7.01 (t, J = 7.7, H_8), 6.91 (s, H_5), 6.90−6.82 (m, H_7, H_9, H_{12}), 5.58 (br s, NH), 5.50 (s, H_3), 2.21 (s, 3 × $H_{5'a}$), 2.02 (s, 3 × H_{4a}), 1.27 (s, 3 × H_{2ab}), 1.26 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 151.4, 147.2, 143.9, 141.1, 134.8, 132.2, 129.8, 129.2, 129.1, 128.8, 128.2, 125.5, 124.5, 122.9, 122.8, 122.6, 120.6, 119.8, 118.3, 116.2, 75.4, 51.1, 24.0, 21.1; IR (neat) 3367 br, 2960 m, 1699 m, 1469 s, 1253 m. Anal. ($C_{26}H_{24}BrNO$) C, H, N.

(*R*,*S*)-5-(4-Bromo-3-pyridyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (33). This compound was prepared by the general procedure from 2,5-dibromopyridine (237 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 46% yield as a colorless oil (14 mg): ^{1}H NMR (400 MHz, acetone-d_6) 8.24 (d, J = 5.2, $H_{5'}$), 7.62 (dd, J = 7.7, 1.3, H_{10}), 7.57 (d, J = 8.4, H_{11}), 7.34 (s, $H_{2'}$), 7.27 (d, J = 6.5, $H_{6'}$), 7.06 (td, J = 7.7, 1.3, H_8), 6.97 (s, H_5), 6.94−6.88 (m, H_7, H_9), 6.86 (d, J = 8.4, H_{12}), 5.68 (br s, NH), 5.55 (s, H_3), 2.06 (s, 3 × H_{4a}), 1.29 (s, 3 × H_{2ab}), 1.28 (s, 3 × H_{2aa}); IR (neat) 3373 br, 2962 m, 1593 s, 1574 s, 1467 s, 1429 s, 1120 m. Anal. ($C_{24}H_{21}BrN_2O\cdot{}^1/_8H_2O$) C, H, N.

(*R*,*S*)-5-(3-Bromo-2-pyridyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (34). This compound was prepared by the general procedure from 2,6-dibromopyridine (237 mg, 1.0 mmol, 14 equiv) and compound **1** (20 mg, 0.069 mmol) in 67% yield as a white solid (20 mg): mp 89−91 °C; ^{1}H NMR (400 MHz, acetone-d_6) 7.63 (dd, J = 7.8, 1.5, H_{10}), 7.54 (d, J = 8.5, H_{11}), 7.53 (t, J = 7.8, $H_{5'}$), 7.39 (d, J = 7.9, $H_{6'}$), 7.13 (d, J = 7.6, $H_{4'}$), 7.03 (t, J = 7.6, H_8), 6.91 (t, J = 7.6, H_9), 6.90 (s, H_5), 6.83 (d, J = 7.6, H_7), 6.81 (d, J = 8.5, H_{12}), 5.52 (br s, NH), 5.48 (s, H_3), 2.03 (s, 3 × H_{4a}), 1.25 (s, 3 × H_{2ab}), 1.24 (s, 3 × H_{2aa}); ^{13}C NMR (100 MHz, acetone-d_6) 161.7, 151.3, 147.4, 142.2, 140.1, 134.4, 129.4, 129.2, 128.7, 128.2, 128.0, 125.4, 124.2, 123.0, 122.9, 122.8, 120.3, 118.1, 116.2, 77.0, 51.1, 29.2, 24.3; IR (neat) 3360 br, 2964 m, 1710 s, 1574 m, 1469 m, 1429 m, 1221 m, 1120 m. Anal. ($C_{24}H_{21}BrN_2O$) C, H, N.

(+)-5-(4-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (35) and (−)-5-(4-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (36). These compounds were prepared by a HPLC separation of racemic compound **15** by a chiral column, Chiracel OD-R, using a 9:1 mixture of methanol and water as mobile phase. The optical purity of **35** was determined by HPLC: >97% ee; $[\alpha]^{20}_D$ = +277 (MeOH). The optical purity of **36** was determined by HPLC: >99% ee; $[\alpha]^{20}_D$ = −254 (MeOH).

(+)-1,2-Dihydro-2,2,4-trimethyl-5-(4-methylphenyl)-5*H*-chromeno[3,4-*f*]quinoline (37) and (−)-1,2-Dihydro-2,2,4-trimethyl-5-(4-methylphenyl)-5*H*-chromeno[3,4-*f*]quinoline (38). These compounds were prepared by a HPLC separation of racemic compound **22** by a chiral column, Chiracel OD-R, using a 9:1 mixture of methanol and water as mobile phase. The optical purity of **37** was determined by HPLC: >93% ee; $[\alpha]^{20}_D$ = +235 (MeOH). The optical purity of **38** was determined by HPLC: >99% ee; $[\alpha]^{20}_D$ = −246 (MeOH).

Cotransfection Assays. The function and detailed preparation procedure of the cotransfection assays have been described previously.[13] Briefly, the cotransfection assays were carried out in CV-1 cells (African green monkey kidney fibroblasts), which were transiently transfected, by the standard calcium phosphate coprecipitation procedure,[12] with the plasmid-containing receptor, MTV-LUC reporter, pRS-β-Gal, and filler DNA (Rous sarcoma virus chloramphenical acetyltransferase). 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 was described

previously,[13] and the K_i values for the analogues were determined by application of the Cheng−Prusoff equation.[35] The radioligands used in the competitive binding assays were progesterone for hPR-A, DHT for hAR, and dexamethasone for hGR.

Alignment Rule Generation. The CoMFA fields from which the overlap was derived was developed by minimizing all structures to a minimum gradient of 10^{-6} using the Tripos force field and the BFGS minimizer internal to SYBYL.[27] Charges were Mullikan charges taken from MOPAC 5.0 single points computed with the MNDO model Hamiltonian.[36] The steric and electrostatic fields were projected for progesterone and used to rms fit our molecules. All alignments were as depicted in Figure 3. The steric and electrostatic fields of ketodesgestrel and ICI 182780 were projected and used to generate alignment rules as well. The alignments were identical with those developed from progesterone.

Material and Methods for Mammary Gland Morphology/Uterine Wet Weight Assay in the Ovariectomized Rat. Inhibitory effects of progestins on estrogen-induced uterine wet weight and stimulation of mammary alveolar bud formation were evaluated using a modification of previously described methods.[37−39] Four- to five-week-old ovariectomized Sprague−Dawley rats were obtained 1 week after surgery and allowed to acclimate for an additional week after shipment. The tested compounds, MPA and estrone, were dissolved in purified sesame oil. Animals were randomized into treatment groups (4 rats/group) and administered either MPA or quinoline derivatives 3.0 mg/rat, 0.5-mL volumes, per os (po), QD for 3 days in the presence of 10 μg/day, subcutaneous (sc) estrone. MPA (po, QD) was used as the progestin standard in all assays. Additional groups of rats, administered estrone (10 μg/day, sc) or vehicle alone for 3 days, were included as both positive and negative controls, respectively. Animals were sacrificed on the fourth day of the experiment. Upon necropsy, mammary glands were excised, fixed in acetone, and stained in Gill's #2 for 6−8 h. Mammary glands were mounted in Permount and quantified by counting buds in four 1-mm^2 microscopic fields, per gland. Uteri were also excised, blotted on filter paper, and weighed. Statistical analyses of the resulting data were performed using ANOVA followed by a modified Fisher's test.

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