5-Aryl-1,2,3,4-tetrahydrochromeno[3,4-*f*]quinolin-3-ones as a Novel Class of Nonsteroidal Progesterone Receptor Agonists: Effect of A-Ring Modification

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Optimization of the 1,2-dihydroquinoline A-ring of a nonsteroidal human progesterone receptor (hPR) agonist pharmacophore (**1**) was performed by using the cotransfection and receptor binding assays as guides. The 3-keto group was discovered to regain the potent agonist activity which was lost upon removal of the 3,4-olefin, and it led to a novel hPR agonist series, 5-aryl-1,2,3,4-tetrahydrochromeno[3,4-*f*]quinolin-3-ones. The new progestins demonstrated potent hPR agonist activity in the cotransfection assay and high binding affinity similar to progesterone. T47D human breast cancer cell line was employed for further characterization of the new progestins and a number of reference analogues. It was found that the new 3-keto analogues showed full agonist activity in the T47D assay, while the reference compounds from other related nonsteroidal hPR agonist series exhibited only partial agonist activity.

Introduction

Several reports from our laboratory have described the development of potent human progesterone receptor (hPR) agonists based on a novel nonsteroidal pharmacophore, 5-substituted 1,2-dihydro-5*H*-chromeno[3,4-*f*]-quinoline. Three separate series, 5-aryl (**1**),[1] 5-benzylidene (**2**),[2] and 5-alkyl (**3**)[3] (Figure 1), have been optimized by using the cell-based cotransfection assays[4] to measure the modulated transcriptional activities of hPR and the binding assay to detect the receptor/ligand interaction. A number of analogues have demonstrated potent hPR agonist activity in rodent models via oral administration. Additionally, the 9-substituents were shown to have a significant enhancement effect on the agonist activity,[5] and certain numbers of this class of selective progesterone receptor modulators (**4**)[6] display encouraging and potentially useful tissue-selective effects. In addition to our hPR agonist series, the 1,2-dihydro-2,2,4-trimethylquinoline motif contributed to other nonsteroidal small molecules that interact with hPR and hAR (human androgen receptor) as antagonists.[7] In this paper we describe a new 3-quinolinone hPR agonist series (**5**), which was discovered during the A-ring optimization of the 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinoline pharmacophore for hPR agonist activity.

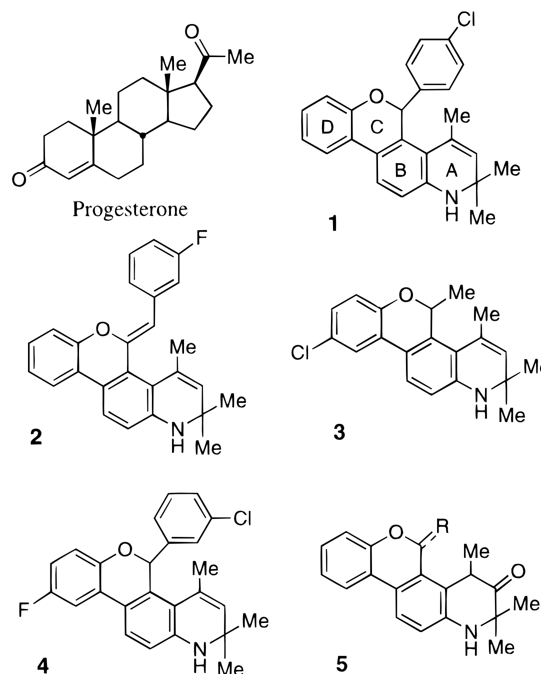

Figure 1. Progesterone and 5-substituted dihydrochromeno-[3,4-*f*]quinoline structures: 5-aryl compound **1**, 5-benzylidene compound **2**, 5-alkyl compound **3**, LG120746 (**4**), and the new 3-keto general structure **5**.

Chemistry

The 4-methylidene compound **7** was isolated as a byproduct from a previously described method[1] of preparing compound **1** from latone **6** (Scheme 1). Compounds **8** and **9** were obtained in a 5:1 ratio from a palladium-catalyzed hydrogenation of the parent compound **1**. The 4-quinolinone analogue **10** was prepared from ozonolysis of N-*t*-Boc-protected compound **7** in good yield. Reduction of compound **10** followed by acid-catalyzed elimination provided 4-desmethylquinoline **11**.

The 3-quinolinones **5** (R = aryl) were synthesized from the corresponding 1,2-dihydroquinolines reported previously (**1**, **12**−**14**) (Scheme 2). The general procedure started from the protection of the quinoline nitrogen by *tert*-butoxycarbonyl followed by a standard hydrobora-

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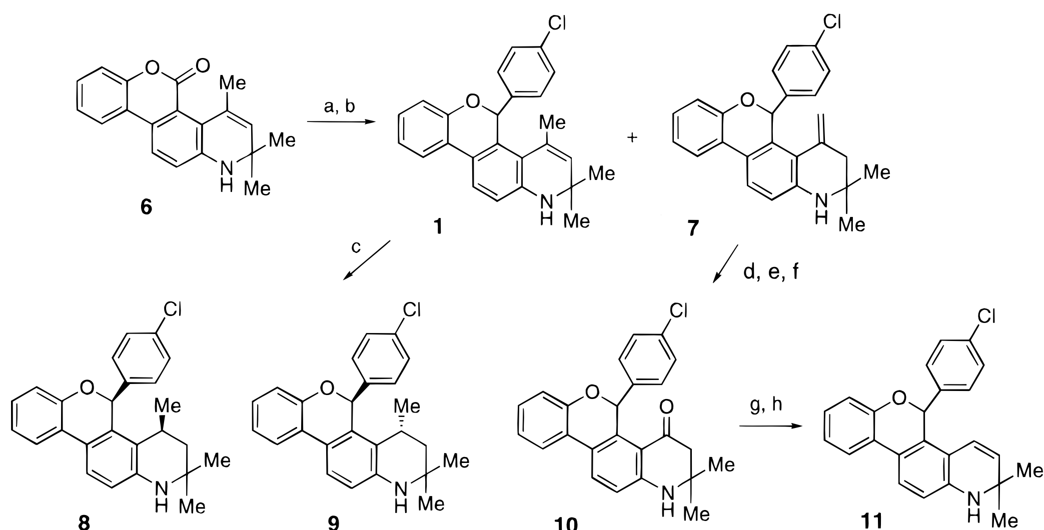
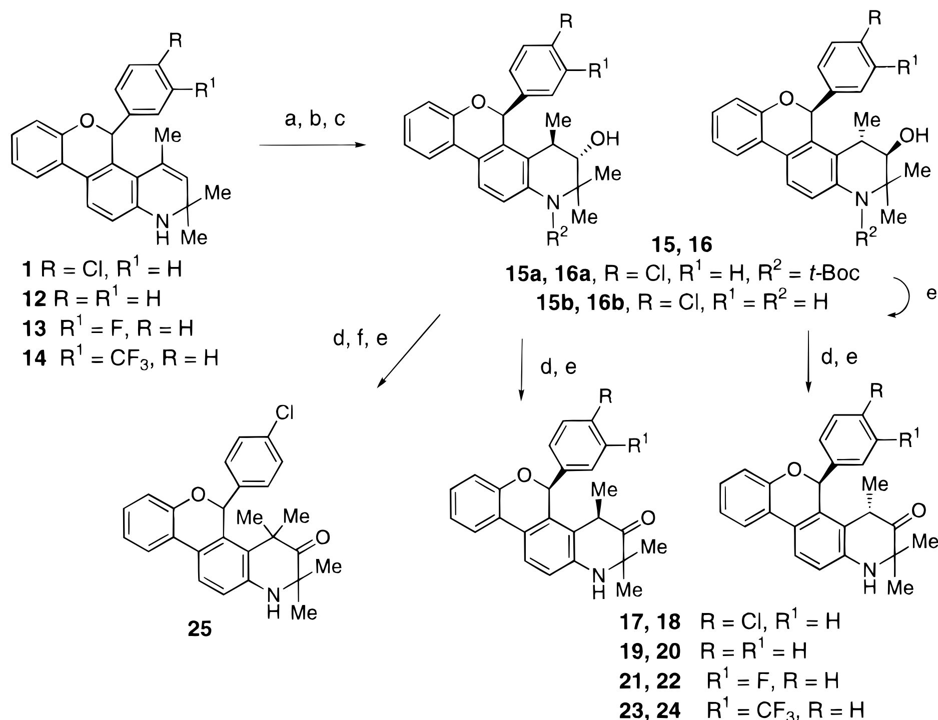
Scheme 1[a]



[a] Reagents: (a) 4-ClPhLi, THF, −30 °C; (b) TFA, Et_3SiH, CH_2Cl_2, rt; (c) H_2, 10% Pd/C, EtOAc, rt; (d) *n*-BuLi, *t*-Boc_2O, THF, −78 °C to rt; (e) O_3, MeOH, −78 °C; (f) TFA, CH_2Cl_2, rt; (g) DIBAL-H, toluene, rt; (h) TsOH, CH_2Cl_2, rt.

Scheme 2[a]



[a] Reagents: (a) *n*-BuLi, *t*-Boc_2O, THF, −78 °C to rt; (b) BH_3−THF, THF, rt; (c) H_2O_2, THF, rt; (d) PCC, CH_2Cl_2, rt; (e) TFA, CH_2Cl_2, rt; (f) NaH, MeI, THF, rt.

tion procedure using borane-tetrahydrofuran complex and hydrogen peroxide as reagents to afford a diastereomeric mixture of two 3-hydroxy products (**15** and **16**). Each of the isomers (**15** or **16**) was treated with pyridinium chlorochromate (PCC) followed by TFA to remove the protection group to give the corresponding 3-quinolinones **17**−**24** in moderate yield.[8] A couple of 3-hydroxy intermediates (**15b** and **16b**, $R = Cl$, $R^1 = R^2 = H$) were prepared by hydrolysis of **15a** and **16a** directly with TFA. Tetramethylquinolinone **25** was prepared from 3-hydroxyquinoline **15a** by oxidation with PCC followed by methylation with iodomethane in the presence of sodium hydride and then hydrolysis of the Boc protection with TFA.

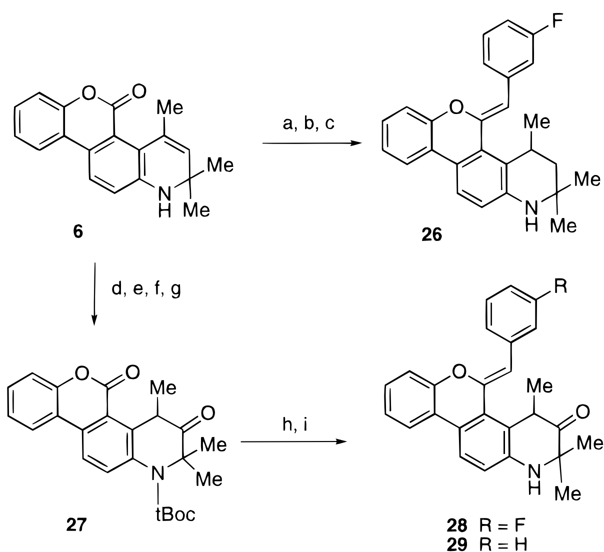
Scheme 3 describes the synthesis of 5-benzylidene analogues with the modified A-ring. Compound **26** was prepared by the addition of benzyl Grignard reagent to the hydrogenated lactone **6** followed by an acid-catalyzed elimination. The 3-quinolinones **28** and **29** were prepared by a different route from the 3-keto-5-aryl analogue synthesis since the benzylidene moiety was incompatible with the hydroboration procedure. Lactone **6** was converted to intermediate **27** by the standard hydroboration procedure, which included N-Boc formation, hydroboration, and PCC oxidation. The addition of 2 equiv of the benzylmagnesium bromide gave the lactone adduct selectively without touching the 3-ketone. Treatment of the adduct with TFA provided

Table 1. Cotransfection and Competitive Binding Data for Reference Compounds and the New Analogues[a]

compd	hPR agonist[b] (mean ± SEM)		hPR antagonist[b] (mean ± SEM)		hPR-A binding
	eff (%)	EC_{50} (nM)[c]	eff (%)	IC_{50} (nM)[c]	K_i (nM) (mean ± SEM)
Prog	100 ± 0	2.9 ± 0.9	–[d]	–	3.5 ± 0.2
MPA	80 ± 7	0.15 ± 0.05	–	–	0.34 ± 0.04
1	77 ± 5	14 ± 2	31	600	0.70 ± 0.14
2	132 ± 17	7.6 ± 3.7	–	–	0.83 ± 0.04
3	138 ± 12	3.2 ± 0.9	–	–	0.44 ± 0.03
4	117 ± 7	2.8 ± 0.7	–	–	0.32 ± 0.11
7	30 ± 5	124 ± 54	81 ± 12	1755 ± 742	11.6 ± 2.1
8	39 ± 4	39 ± 13	–	–	10.1 ± 2.1
9	58 ± 18	48 ± 28	56	3100	91 ± 11
10	–	–	84 ± 4	376 ± 201	24.6 ± 1.1
11	28	1300	50	140	10.5 ± 1.2
15b	–	–	69	3200	>500
16b	–	–	91	460	>500
17	102 ± 24	5.3 ± 2.1	–	–	21.3 ± 3.7
18	122 ± 26	4.5 ± 1.3	–	–	1.3 ± 0.1
25	36 ± 21	9.8 ± 6.9	–	–	5.3 ± 0.1

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations; values without standard deviations 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 the 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] A dash indicates an efficacy of <20% and a potency of >10 000 nM.

Scheme 3[a]



[a] Reagents: (a) H_2, 10% Pd/C, EtOAc, rt; (b) 3-FPhCH_2MgBr, ether, rt; (c) TsOH, CH_2Cl_2, rt; (d) *n*-BuLi, *t*-Boc_2O, THF, −78 °C to rt; (e) BH_3–THF, THF, rt; (f) H_2O_2, THF/H_2O, rt; (g) PCC, CH_2Cl_2, rt; (h) RPhCH_2MgBr, ether, rt; (i) TFA, CH_2Cl_2, rt.

the eliminated benzylidene moiety and at the same time mediated the hydrolysis of the Boc protection to afford **28** and **29** in good yields.[9]

Biological Results and Discussion

The structure–activity relationship (SAR) study of the A-ring modification was guided by the cotransfection assay to measure ligand-induced agonistic or antagonistic transcriptional responses of hPR in CV-1 cells (African green monkey kidney fibroblasts) and by the competitive binding assay of baculovirus-expressed hPR-A to record the ligand binding affinity as previously reported.[1] Progesterone (Prog) and medroxyprogesterone acetate (MPA) were used as progestin standards.

Our initial effort was to investigate the necessity of the 3,4-olefin and 4-methyl group at the A-ring by simply modifying compound **1**. Shifting the 3,4-double bond to an external olefin at C4 generated compound **7**, saturation of the olefin provided a mixture of two diastereomers **8** and **9**, and removal of the 4-methyl afforded compound **11**. These changes made no improvement of any kind over parent compound **1** in cotransfection or binding assays (see Table 1). In comparison of our nonsteroidal compounds with the typical steroidal progestins, it was noticeable that the new structures might lack a polar functional group to interact with the steroidal receptor. To test this hypothesis, we introduced a hydroxy or carbonyl group to the A-ring. The 3-quinolinone analogues **17** and **18** exhibited significant potency and efficacy improvement not only over the parent compounds **8** and **9** but also over the corresponding dihydroquinoline counterpart **1** in the cotransfection assay. The added methyl group at C4 (**25**) diminished the K_i and efficacy versus **18**. The tetrahydro-4-quinolinone **10** and 3-hydroxy analogues **15b** and **16b** showed no activity as hPR agonists.

Four pairs of 5-aryl-3-quinolinone analogues were synthesized, and their in vitro activities are listed in Table 2. It was noticed that both stereoisomers showed similar activity in the cotransfection assay but with quite different binding affinity to hPR-A. The *trans*-isomers (**18**, **20**, **22**, and **24**) bind 5–10-fold better than their *cis*-counterparts (**17**, **19**, **21**, and **23**), which implies that the *trans*-isomer should be more active than the *cis*-isomer and the cell media might cause an epimerization at C4 during the cotransfection assay process. Two 5-benzylidene-3-quinolinone analogues (**28** and **29**) were also prepared and evaluated in the assays. Compound **28** exhibited improved potency over the 3-methylene analogue **26** but no difference with the corresponding 1,2-dihydroquinoline analogue **2**.

The cross-reactivities of the new compounds were monitored by the competitive binding assays of baculovirus-expressed human androgen receptor (hAR) and glucocorticoid receptor (hGR). As observed with other related nonsteroidal series, these new structures have much less cross-reactivities than those of the steroidal progestins (see Table 2).

In comparison of hPR agonist activity of the new 3-quinolinone analogues as a group with that of the 1,2-

Table 2. Cotransfection and Competitive Binding Data for the 3-Quinolinone Analogues[a]

compd	hPR agonist[b] (mean ± SEM) eff (%)	hPR agonist[b] (mean ± SEM) EC_{50} (nM)[c]	binding K_i (nM) (mean ± SEM) hPR-A	binding K_i (nM) (mean ± SEM) hAR	binding K_i (nM) (mean ± SEM) hGR
Prog	100 ± 0	2.9 ± 0.9	3.5 ± 0.2	8.5 ± 3.1	30.5 ± 1.9
MPA	80 ± 7	0.15 ± 0.05	0.34 ± 0.04	2.9 ± 0.2	13.2 ± 1.8
17	102 ± 24	5.3 ± 2.1	21.3 ± 3.7	698 ± 114	913 ± 211
18	122 ± 26	4.5 ± 1.3	1.3 ± 0.1	1177 ± 170	331 ± 31
19	103 ± 31	9.0 ± 3.5	28.6 ± 3.3	1075 ± 227	909 ± 248
20	92 ± 10	10 ± 6	6.6 ± 1.0	732 ± 18	249 ± 157
21	114 ± 22	8.7 ± 1.5	28 ± 6	504 ±186	864 ± 121
22	106 ± 10	6.3 ± 3.1	2.6 ± 0.2	620 ± 112	193 ± 55
23	66 ± 7	16 ± 5	123 ± 19	807 ± 212	250 ± 170
24	93 ± 38	14 ± 8	16.6 ± 4.4	1091 ± 40	257 ± 96
26	114 ± 49	47 ± 13	6.3 ± 0.1	na[d]	na
28	155 ± 29	8.7 ± 5.5	3.5 ± 1.7	560 ± 196	4728 ± 4272
29	133 ± 38	17 ± 6	4.9 ± 1.3	1196 ± 76	680 ± 270

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations. [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. [d] na indicates the data is not available.

Table 3. T47D and CV-1 Cell Line Data for Reference Compounds and the New Analogues[a]

compd	hPR agonist[b] (mean ± SEM) T47D cells eff (%)	T47D cells EC_{50} (nM)[c]	CV-1 cells eff (%)	CV-1 cells EC_{50} (nM)[c]
Prog	100 ± 0	1.8 ± 0.3	100 ± 0	2.9 ± 0.9
MPA	90 ± 15	0.33 ± 0.05	80 ± 7	0.15 ± 0.05
1	48 ± 6	32 ± 2	77 ± 5	14 ± 2
2	55 ± 8	51 ± 15	132 ± 17	7.6 ± 3.7
3	42 ± 14	10 ± 7	138 ± 12	3.2 ± 0.9
4	47 ± 9	27 ± 5	117 ± 7	2.8 ± 0.7
17	107 ± 25	22.6 ± 2.5	102 ± 24	5.3 ± 2.1
18	97 ± 21	10.9 ± 2.7	122 ± 26	4.5 ± 1.3
19	102	35	103 ± 31	9.0 ± 3.5
20	92 ± 2	23.5 ± 7.7	92 ± 10	10 ± 6
21	107 ± 3	26.0 ± 5.6	114 ± 22	8.7 ± 1.5
22	96 ± 7	14.8 ± 10	106 ± 10	6.3 ± 3.1
23	103	63	66 ± 7	16 ± 5
24	85	37	93 ± 38	14 ± 8
28	83 ± 3	25.3 ± 7.3	155 ± 29	8.7 ± 5.5
29	93 ± 13	18.3 ± 6.6	133 ± 38	17 ± 6

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations; values without standard deviations represent a single experiment. [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.

dihydroquinoline series **1**,[1] it is evident that the substituents on the 5-aryl have less impact on the agonist activity in the new series than in the 1,2-dihydroquinoline series. For example, compounds **18** (5-*p*-chlorophenyl) and **20** (5-phenyl) have similar agonist activity, while compound **1** (5-*p*-chlorophenyl) is 10-fold more potent than its parent 5-phenyl analogue (see ref 1 for the bioassay data).

In a previous effort to understand how our nonsteroidal compounds mimic steroids, we suggested that the quinoline ring of compound **1** might overlap with the steroid D-ring based on a CoMFA study.[1] The charge distribution, dipole moment, and direction of the new 3-quinolinone analogues are dramatically different from the compound **1** series, and they do not fit the previous model. To evaluate the possible biological consequence caused by the differences of the new compounds, we employed the T47D cell line as secondary assay to further characterize their in vitro activity.

T47D human breast cancer cells express high levels of hPR, and they are one of the major models to

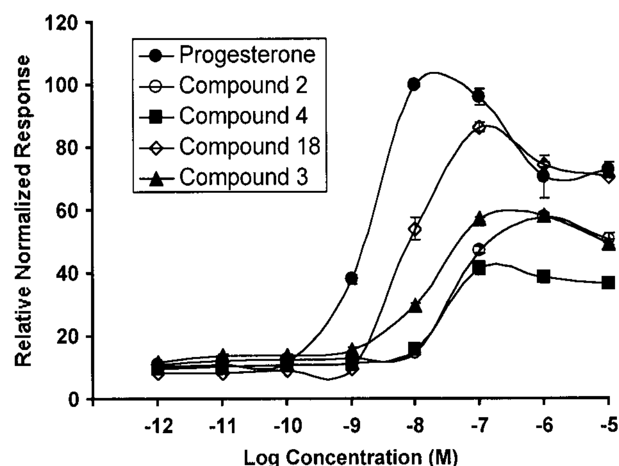


Figure 2. Concentration−response curves for progesterone and the representative compounds from each different nonsteroidal hPR agonist series in the T47D alkaline phosphatase assay.

characterize synthetic progestins or antiprogestins.[10] The new 3-quinolinones and a number of reference analogues from other related series as well as steroidal progestins were tested in this assay. Table 3 lists the EC_{50} values from the T47D cells and the CV-1 cells for comparison. Progesterone and MPA demonstrated similar agonist activity in both cell lines, while compounds **1**−**4**, which represent three different 1,2-dihydroquinoline series, showed much weaker agonist activity in the T47D cell line although they are full agonists in the CV-1 cell line. Interestingly, all the new 3-quinolinone analogues gave full agonist activities in both assays. Figure 2 illustrated the differences among these nonsteroidal series and progesterone in the T47D alkaline phosphatase assay. It seems that the 3-keto compounds are closer to steroids in terms of the agonist activity. The in vivo relevance of the difference in T47D cells is to be determined.

Conclusion

A novel 3-quinolinone hPR agonist series was developed and examined in the cotransfection and competitive binding assays. The new compounds demonstrated improved activity over their parent quinoline analogues in the 5-aryl series. The 3-keto group is the key to regaining the hPR agonist activity that was lost upon

removal of the 3,4-olefin in the 1,2-dihydroquinoline series. The assay results from the T47D human breast cancer cell line revealed that the new series behaved similarly to steroidal progestins but differently than other related nonsteroidal 1,2-dihydroquinoline series. Due to the lengthy synthesis and two stereogenic centers of the 3-quinolinones, these new structures pose obvious chemical disadvantages over other related series.

Experimental Section

General experimental methods have been previously described,[1] and reported yields are not optimized. All the chiral compounds were tested as racemic. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC400 spectrometer at 400 and 100 MHz, respectively, and are reported in δ (ppm) units; J values are given in hertz (Hz).

(*R,S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylene-5*H*-chromeno[3,4-*f*]quinoline (7). This compound was prepared from 4-bromochlorobenzene (1.4 g, 7 mmol) and lactone **6** (0.50 g, 1.7 mmol) by a previously described procedure[1] as a byproduct (53 mg, 8%) as a white solid: ^{1}H NMR ($CDCl_3$) 7.53 (d, J = 7.7, 1 H), 7.51 (d, J = 8.3, 1 H), 7.18 (d, J = 8.7, 2 H), 7.15 (d, J = 8.7, 2 H), 6.99 (t, J = 7.7, 1 H), 6.90 (t, J = 7.7, 1 H), 6.79 (d, J = 7.7, 1 H), 6.59 (s, 1 H), 6.58 (d, J = 8.3, 1 H), 4.93 (s, 1 H), 4.59 (s, 1 H), 4.09 (br s, 1 H), 2.43 (d, J = 12.3, 1 H), 2.18 (d, J = 12.3, 1 H), 1.34 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) 151.2, 144.3, 138.7, 137.7, 133.9, 130.4, 130.3, 128.7, 127.6, 124.9, 124.6, 122.2, 121.9, 119.4, 118.0, 117.3, 114.9, 114.4, 74.6, 50.9, 46.0, 30.9, 28.8, 27.7; IR (KBr) 3393, 2955, 1595, 1487, 1442, 1332, 1207, 756. Anal. ($C_{25}H_{22}ClNO\cdot 1/4H_2O$) C, H, N.

(*R,S*)-(*4l,5l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (8) and (*R,S*)-(*4l,5u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (9). To a solution of compound **1** (0.10 g, 0.25 mmol) in EtOAc (10 mL) was added 10% Pd/C (20 mg, 0.019 mmol), and the mixture was exposed to a hydrogen balloon overnight. Filtration from the catalyst and removal of solvent afforded compound **8** (80 mg, 80%) as a white solid: mp 158−159 °C; ^{1}H NMR (acetone-d_6) 7.63 (d, J = 7.8, 1 H), 7.53 (d, J = 8.5, 1 H), 7.24 (s, 4 H), 6.94 (t, J = 7.8, 1 H), 6.87 (t, J = 7.8, 1 H), 6.76 (d, J = 8.5, 1 H), 6.68 (d, J = 7.8, 1 H), 6.51 (s, H), 5.10 (br s, 1 H), 3.25 (m, 1 H), 1.89 (dd, J = 13.5, 6.4, 1 H), 1.76 (dd, J = 13.5, 4.4, 1 H), 1.30 (s, 3 H), 1.21 (s, 3 H), 0.83 (d, J = 7.3, 3 H); ^{13}C NMR ($CDCl_3$) 150.6, 144.5, 138.6, 134.0, 130.9, 130.5, 128.4, 127.6, 124.9, 123.2, 122.2, 121.9, 120.2, 118.0, 115.8, 74.5, 50.0, 44.3, 31.6, 31.3, 27.5, 22.8. Anal. ($C_{25}H_{24}ClNO$) C, H, N.

Compound **9** was also isolated as a white solid (15 mg, 15%): ^{1}H NMR ($CDCl_3$) 7.54 (d, J = 7.6, 1 H), 7.47 (d, J = 8.4, 1 H), 7.15 (d, J = 6.5, 2 H), 7.10 (d, J = 6.5, 2 H), 7.01 (t, J = 7.6, 1 H), 6.89 (t, J = 7.6, 1 H), 6.83 (d, J = 7.6, 1 H), 6.59 (d, J = 8.4, 1 H), 6.47 (s, 1 H), 3.73 (br s, 1 H), 2.82 (m, 1 H), 1.76 (dd, J = 13.5, 7.0, 1 H), 1.73 (dd, J = 13.5, 4.5, 1 H), 1.46 (d, J = 7.1, 3 H), 1.36 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$) 150.5, 143.9, 138.4, 134.0, 130.3, 129.4, 128.6, 127.6, 124.2, 122.6, 122.1, 119.6, 118.0, 115.4, 74.4, 50.1, 42.9, 32.2, 31.8, 27.3, 22.3. Anal. ($C_{25}H_{24}ClNO$) C, H, N.

(*R,S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinolin-4-one (10). To a solution of compound **7** (0.10 g, 0.26 mmol) in THF (6 mL) at −78 °C were added *n*-BuLi (0.25 mL, 1.6 M in hexane, 0.40 mmol) and a solution of *t*-Boc_2O (0.10 g, 0.44 mmol) in THF (3 mL). The reaction mixture was warmed slowly to room temperature and quenched with water. Extraction with EtOAc and removal of solvent followed by chromatography afforded N-*t*-Boc-protected compound **7** as an oil (75 mg, 59%).

A solution of the N-*t*-Boc-protected compound **7** in methanol (20 mL) at − 78 °C was subjected to O_3 for 3 min, and SMe_2 (0.5 mL) was added. The reaction mixture was warmed to room temperature and concentrated. Chromatography provided the product as a colorless oil, which was treated with TFA (0.5 mL) in CH_2Cl_2. Standard workup followed by chromatography afforded compound **10** as a yellow oil (35 mg, 47%): ^{1}H NMR (acetone-d_6) 7.86 (d, J = 8.8, 1 H), 7.60 (dd, J = 7.8, 1.5, 1 H), 7.40 (s, 1 H), 7.20 (s, 4 H), 7.06 (td, J = 7.8, 1.5, 1 H), 6.98 (d, J = 8.8, 1 H), 6.90 (td, J = 7.8, 1.5, 1 H), 6.83 (dd, J = 7.8, 1.5, 1 H), 6.38 (s, 1 H), 2.64 (d, J = 15.2, 1 H), 2.43 (d, J = 15.2, 1 H), 1.37 (s, 3 H), 1.27 (s, 3 H). Anal. ($C_{24}H_{20}ClNO_2$) C, H, N.

(*R,S*)-5-(4-Chlorophenyl)-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (11). To a solution of compound **10** (20 mg, 0.050 mmol) in toluene (2 mL) at −78 °C was added DIBAL-H (0.2 mL, 0.5 M in toluene, 0.10 mmol), and the resulting mixture was warmed to room temperature. The reaction was quenched with water, extracted with EtOAc, and concentrated, and chromatography afforded the 4-hydroxy intermediate as a colorless oil. The intermediate was treated with a catalytic amount of TsOH in CH_2Cl_2 (2 mL) at room temperature for 3 h and quenched with Na_2CO_3. Extraction with EtOAc and removal of solvent followed by chromatography afforded compound **11** as a colorless oil (10 mg, 54%): ^{1}H NMR (acetone-d_6) 7.60 (d, J = 7.9, 1 H), 7.52 (d, J = 8.5, 1 H), 7.27 (d, J = 8.6, 2 H), 7.24 (d, J = 8.6, 2 H), 7.01 (t, J = 7.9, 1 H), 6.88 (t, J = 7.9, 1 H), 6.81 (d, J = 7.9, 1 H), 6.69 (d, J = 8.5, 1 H), 6.57 (s, 1 H), 6.36 (d, J = 7.5, 1 H), 5.59 (d, J = 7.5, 1 H), 5.55 (s, 1 H), 1.32 (s, 3 H), 1.30 (s, 3 H). Anal. ($C_{24}H_{20}ClNO$) C, H, N.

(*R,S*)-(*4l,5u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinolin-3-one (17) and (*R,S*)-(*4l,5l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinolin-3-one (18). The title compounds were prepared by a four-step procedure from compound **1**, which includes the protection of the free NH with *t*-Boc group, hydroboration followed by oxidation with H_2O_2 and PCC, and hydrolysis of the *t*-Boc protection.

To a yellow solution of compound **1** (120 mg, 0.31 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (0.30 mL, 1.6 M in hexane, 0.48 mmol), the resulting solution was stirred for 15 min, and then a solution of di-*tert*-butyl dicarbonate (0.15 g, 0.69 mmol) in THF (2 mL) was introduced. The reaction mixture was allowed to warm to room temperature and was stirred for 5 h. The reaction was quenched with water and extracted with EtOAc (2 × 20 mL). Removal of solvent followed by chromatography (EtOAc−hexane, 10−30% gradient) afforded the *t*-Boc-protected compound **1** (0.10 g, 68%).

The *t*-Boc-protected intermediate (0.10 g, 0.21 mmol) in THF (4 mL) was treated with BH_3−THF (0.30 mL, 1.0 M in THF, 0.30 mmol) at room temperature for 3 h and was quenched with KOH (0.20 mL, 3 M aqueous). To the above solution was added H_2O_2 (0.20 mL, 30% in water), and the mixture was stirred for 30 min. The mixture was diluted with water and extracted, washed with brine, and concentrated. Chromatography of the crude mixture (EtOAc−hexane, 10−30% gradient) afforded compound **15a** (51 mg, 50%) and compound **16a** (26 mg, 25%) as colorless oils.

Compound **15a** (40 mg, 0.079 mmol) was oxidized with PCC (0.10 g, 0.46 mmol) in CH_2Cl_2 (5 mL) at room temperature for 60 min to yield the ketone as a colorless oil after chromatography. The colorless oil was then treated with TFA (0.4 mL) in CH_2Cl_2 (1 mL) for 30 min and was quenched with KOH (5 mL, 2% aqueous). The reaction mixture was extracted with EtOAc, washed with brine, and concentrated. Chromatography of the crude residue (EtOAc−hexane, 10−30% gradient) afforded compound **17** (25 mg, 78%) as a white solid: ^{1}H NMR ($CDCl_3$) 7.64 (d, J = 8.2, 2 H), 7.18 (d, J = 8.6, 2 H), 7.13 (d, J = 8.6, 2 H), 7.05 (t, J = 7.9, 1 H), 6.96 (t, J = 7.8, 1 H), 6.84 (d, J = 8.3, 1 H), 6.76 (d, J = 7.9, 1 H), 6.37 (s, 1 H), 3.73 (s, 1 H), 3.56 (q, J = 7.4, 1 H), 1.44 (s, 3 H), 1.26 (s, 3 H), 0.87 (d, J = 7.4, 3 H); ^{13}C NMR ($CDCl_3$) 214.1, 150.7, 143.2, 137.8, 134.7, 130.5, 130.3, 128.9, 128.6, 123.4, 122.7, 122.4, 122.2, 118.3, 116.8, 74.4, 60.2, 43.8, 28.1, 27.3, 16.6; IR (neat) 3400, 2950, 1740, 1490, 1330, 1230. Anal. ($C_{25}H_{22}ClNO_2$) C, H, N.

Compound **16a** (20 mg, 0.040 mmol) was oxidized with PCC for 6 h and then deprotected by a similar method as described above to yield compound **18** (13 mg, 84%) as a white solid: ^{1}H NMR ($CDCl_3$) 7.59 (d, J = 8.4, 1 H), 7.57 (d, J = 8.0, 1 H),

7.15 (d, J = 8.5, 2 H), 7.06 (d, J = 8.5, 2 H), 7.04 (m, 1 H), 6.94 (t, J = 7.8, 1 H), 6.85 (d, J = 7.6, 1 H), 6.83 (d, J = 8.3, 1 H), 3.73 (s, 1 H), 3.35 (d, J = 7.5, 1 H), 1.50 (d, J = 7.5, 3 H), 1.46 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR ($CDCl_3$) 213.1, 150.8, 142.7, 137.5, 134.4, 130.3, 130.0, 129.3, 128.9, 128.8, 128.6, 123.6, 122.8, 122.5, 122.4, 118.3, 116.8, 74.2, 60.1, 43.0, 31.2, 27.3, 26.6, 18.3. Anal. ($C_{25}H_{22}ClNO_2$) C, H, N.

***(R,S)*-(*3l,4u,5l*)-4-(Chlorophenyl)-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (15b).** Compound **15a** (10 mg, 0.020 mmol) was treated with TFA (0.2 mL) in CH_2Cl_2 (0.5 mL) for 1 h, and standard workup procedure provided the title compound as a colorless oil (8.0 mg, 97%): ^{1}H NMR ($CDCl_3$) 7.55 (d, J = 7.8, 1 H), 7.50 (d, J = 8.3, 1 H), 7.15 (d, J = 8.8, 2 H), 7.12(d, J = 8.8, 2 H), 6.99 (t, J = 7.8, 1 H), 6.91 (t, J = 7.8, 1 H), 6.75 (d, J = 7.9, 1 H), 6.70 (d, J = 8.3, 1 H), 6.32 (s, H), 3.74 (s, 1 H), 3.48 (m, 1 H), 2.99 (m, 1 H), 1.91 (d, J = 6.5, 1 H), 1.28 (s, 3 H), 1.18 (s, 3 H), 0.92 (d, J = 7.3, 3 H). Anal. ($C_{25}H_{24}ClNO_2$) C, H, N.

***(R,S)*-(*3l,4u,5u*)-4-(Chlorophenyl)-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (16b).** Compound **16a** (18 mg, 0.012 mmol) was converted to compound **16b** as a colorless oil (12 mg, 84%) in a similar fashion: ^{1}H NMR ($CDCl_3$) 7.55 (d, J = 7.8, 1 H), 7.51 (d, J = 8.4, 1 H), 7.13 (d, J = 8.6, 2 H), 7.05 (d, J = 8.6, 2 H), 7.03 (m, 1 H), 6.90 (t, J = 7.6, 1 H), 6.85 (d, J = 8.0, 1 H), 6.65 (d, J = 8.3, 1 H), 6.51 (s, 1 H), 3.74 (s, 1 H), 3.53 (dd, J = 7.3, 4.6, 1 H), 2.65 (qd, J = 7.8, 4.5, 1 H), 1.70 (d, J = 7.3, 1 H), 1.56 (d, J = 7.8, 3 H), 1.32 (s, 3 H), 1.13 (s, 3 H). Anal. ($C_{25}H_{24}ClNO_2$) C, H, N.

***(R,S)*-(*4l,5u*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno[3,4-*f*]quinolin-3-one (19) and *(R,S)*-(*4l,5l*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno-[3,4-*f*]quinolin-3-one (20).** The title compounds were prepared from compound **12** (0.10 g, 0.28 mmol) by the same method as described in the synthesis of **17** and **18**. Compound **19** was obtained in an 18% four-step yield (19 mg) as a white powder: mp 108−110 °C; ^{1}H NMR ($CDCl_3$) 7.66 (d, J = 7.7, 1 H), 7.64 (d, J = 8.2, 1 H), 7.20 (s, 5 H), 7.06 (t, J = 7.7, 1 H), 6.95 (t, J = 7.7, 1 H), 6.83 (d, J = 8.2, 1 H), 6.77 (d, J = 7.7, 1 H), 6.39 (s, 1 H), 3.72 (bs, 1 H), 3.58 (q, J = 7.4, 1 H), 1.44 (s, 3 H), 1.23 (s, 3 H), 0.80 (d, J = 7.4, 3 H); ^{13}C NMR ($CDCl_3$) 214.4, 151.0, 143.2, 139.3, 131.1, 128.9, 128.8, 128.6, 128.5, 123.4, 122.7, 122.2, 122.1, 122.0, 118.3, 116.6, 75.4, 60.2, 43.9, 28.1, 27.3, 16.3. Anal. ($C_{25}H_{23}NO_2$·3/4H_2O) C, H, N.

Compound **20** was obtained in a 10% four-step yield as a white powder (10 mg): ^{1}H NMR ($CDCl_3$) 7.59 (d, J = 8.3, 1 H), 7.57 (d, J = 7.6, 1 H), 7.21−7.12 (m, 5 H), 7.05 (t, J = 7.6, 1 H), 6.92 (t, J = 7.6, 1 H), 6.86 (d, J = 7.6, 1 H), 6.83 (d, J = 8.3, 1 H), 6.37 (s, 1 H), 3.72 (bs, 1 H), 3.41 (q, J = 7.5, 1 H), 1.50 (d, J = 7.5, 3 H), 1.45 (s, 3 H), 1.17 (s, 3 H). Anal. ($C_{25}H_{23}NO_2$) C, H, N

***(R,S)*-(*4l,5u*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-(3-fluorophenyl)-5*H*-chromeno[3,4-*f*]quinolin-3-one (21) and *(R,S)*-(*4l,5l*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-(3-fluorophenyl)-5*H*-chromeno[3,4-*f*]quinolin-3-one (22).** The title compounds were prepared from compound **13** (80 mg, 0.21 mmol) by the same method as described in the synthesis of **17** and **18**. Compound **21** was obtained in a 22% four-step yield (18 mg) as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.66 (d, J = 7.7, 1 H), 7.64 (d, J = 8.3, 1 H), 7.19 (td, J = 7.9, 5.8, 1 H), 7.09−6.86 (m, 5 H), 6.85 (d, J = 8.3, 1 H), 6.78 (d, J = 7.7, 1 H), 6.38 (s, 1 H), 3.72 (bs, 1 H), 3.58 (q, J = 7.4, 1 H), 1.44 (s, 3 H), 1.23 (s, 3 H), 0.87 (d, J = 7.4, 3 H); ^{13}C NMR ($CDCl_3$) 214.1, 162.9 (d, J = 246.2), 150.7, 143.3, 141.8 (d, J = 6.3), 130.4, 130.2, 130.1, 128.6, 124.6, 123.3, 122.7, 122.4, 122.3 (d, J = 22.1), 118.3, 116.9, 115.8 (d, J = 21.4), 74.5, 60.2, 43.9, 28.1, 27.3, 14.4. Anal. ($C_{25}H_{22}FNO_2$) C, H, N.

Compound **22** was obtained in a 16% four-step yield (13 mg) as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.60 (d, J = 8.3, 1 H), 7.58 (d, J = 7.7, 1 H), 7.15 (td, J = 7.9, 5.8, 1 H), 7.09 (t, J = 7.7, 1 H), 6.97−80 (m, 6 H), 6.34 (s, 1 H), 3.73 (s, 1 H), 3.38 (q, J = 7.3, 1 H), 1.50 (d, J = 7.3, 3 H), 1.46 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 213.2, 162.9 (d, J = 246.7), 150.8, 142.7, 141.6 (d, J = 6.4), 130.2, 130.1, 129.9, 128.5, 123.6, 122.8, 122.7, 122.4, 122.2, 118.3, 116.8, 115.5 (d, J = 21.6), 114.9 (d, J = 22.6), 74.2, 60.1, 43.0, 27.3, 26.6, 18.4. Anal. ($C_{25}H_{22}FNO_2$) C, H, N.

***(R,S)*-(*4l,5u*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-(3-trifluoromethylphenyl)-5*H*-chromeno[3,4-*f*]quinolin-3-one (23) and *(R,S)*-(*4l,5l*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-(3-trifluoromethylphenyl)-5*H*-chromeno[3,4-*f*]quinolin-3-one (24).** The title compounds were prepared from compound **14** (0.10 g, 0.24 mmol) by the same method as described in the synthesis of **17** and **18**. Compound **23** was obtained in a 19% four-step yield (20 mg) as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.67 (d, J = 8.3, 1 H), 7.65 (d, J = 7.7, 1 H), 7.52 (s, 1 H), 7.48 (m, 1 H), 7.35−7.30 (m, 2 H), 7.08 (t, J = 7.7, 1 H), 6.98 (t, J = 7.7, 1 H), 6.88 (d, J = 8.3, 1 H), 6.78 (d, J = 7.7, 1 H), 6.43 (s, 1 H), 3.75 (s, 1 H), 3.57 (q, J = 7.4, 1 H), 1.45 (s, 3 H), 1.24 (s, 3 H), 0.86 (d, J = 7.4, 3 H); ^{13}C NMR ($CDCl_3$) 214.0, 150.5, 143.3, 140.3, 132.1, 131.2 (q, J = 31.7), 130.0, 129.1, 128.7, 125.7, 123.3, 122.7, 122.6, 122.5, 122.2, 118.3, 117.1, 74.3, 60.2, 43.8, 28.2, 27.3, 16.5. Anal. ($C_{26}H_{22}F_3NO_2$·1/2H_2O) C, H, N.

Compound **24** was obtained in a 15% four-step yield (15 mg) as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.61 (d, J = 8.3, 1 H), 7.57 (d, J = 7.7, 1 H), 7.42 (t, J = 7.7, 1 H), 7.39 (s, 1 H), 7.38−7.30 (m, 2 H), 7.09 (t, J = 7.7, 1 H), 6.95 (d, J = 7.7, 1 H), 6.91 (d, J = 8.4, 1 H), 6.86 (d, J = 8.3, 1 H), 6.39 (s, 1 H), 3.77 (s, 1 H), 3.37 (q, J = 7.3, 1 H), 1.50 (d, J = 7.3, 3 H), 1.48 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) 213.1, 150.7, 142.8, 131.1, 129.4, 129.1, 128.6, 125.4, 124.6, 123.0, 122.7, 122.6, 122.5, 122.2, 118.3, 117.0, 74.0, 60.2, 43.1, 27.1, 26.5, 18.4. Anal. ($C_{26}H_{22}F_3NO_2$·1/4H_2O) C, H, N.

***(R,S)*-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4,4-tetramethyl-5*H*-chromeno[3,4-*f*]quinolin-3-one (25).** To a solution of 1-*tert*-butoxycarbonyl compound **17** (25 mg, 0.050 mmol) in THF (3 mL) were added NaH (10 mg, 60% in mineral oil, 0.25 mmol) and MeI (0.10 mL, 1.6 mmol); the resulting slurry was stirred at room temperature for 2 h and was quenched with water (5 mL). The mixture was extracted with EtOAc and concentrated to give the crude product, which was treated with TFA (0.5 mL) in CH_2Cl_2 (1 mL) at room temperature for 1 h. The mixture was quenched with NaOH (3 mL, 2 M aqueous), extracted, and concentrated, and chromatography provided compound **25** (10 mg, 48%) as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.59 (d, J = 8.2, 1 H), 7.56 (d, J = 7.8, 1 H), 7.13 (d, J = 8.7, 2 H), 7.09 (d, J = 8.7, 2 H), 7.01 (t, J = 7.9, 1 H), 6.91 (t, J = 7.9, 1 H), 6.85 (s, 1 H), 6.83−6.78 (m, 2 H), 3.83 (s, 1 H), 1.63 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H). Anal. ($C_{26}H_{24}ClNO_2$) C, H, N.

(*Z*)-5-(3-Fluorobenzylidene)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (26). A solution of lactone **6** (20 mg, 0.07 mmol) in EtOAc (10 mL) was hydrogenated with a hydrogen balloon in the presence of 10% Pd/C (5 mg) at room temperature overnight until the reaction went to completion by TLC. The reaction mixture was filtered and concentrated in vacuo to afford 1,2,3,4-tetrahydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (14 mg, 70%) as a yellow solid.

Addition of freshly prepared 3-fluorobenzylmagnesium bromide (0.10 mL, 1.0 M in ether, 0.10 mmol) to the above tetrahydroquinoline (14 mg, 0.05 mmol) and then treatment with an acid according to the previously described General Procedure for Preparing 5-Benezylidene Compounds[2] afforded compound **26** as a yellow solid (8.6 mg, 46%): R_f = 0.38 (silica gel, 25% EtOAc:Hex); ^{1}H NMR (acetone-d_6) 7.82 (d, J = 8.5, 1 H), 6.69 (m, 1 H), 7.62 (d, J = 8.5, 1 H), 7.58 (d, J = 8.5, 1 H), 7.40 (m, 1 H), 7.22 (m, 2 H), 7.08 (m, 1 H), 6.97 (m, 1 H), 6.74 (d, J = 8.5, 1 H), 6.24 (s, 1 H), 5.30 (brs, 1 H), 3.76 (m, 1 H). 1.97 (m, 1 H), 1.55 (m, 1 H), 1.40 (d, J = 6.6, 3 H), 1.30 (s, 3 H), 1.26 (s, 3 H). Anal. ($C_{26}H_{24}FNO$) C, H, N.

***(R,S)*-(*Z*)-5-(3-Fluorobenzylidene)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinolin-3-one (28).** To a yellow solution of compound **6** (0.22 g, 0.76 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (0.5 mL, 1.6 M in hexane, 0.80 mmol) to give a dark red solution. A solution of *t*-Boc_2O (0.25 g, 1.1 mmol) in THF (5 mL) was cannulated to the

reaction mixture, and the reaction was warmed slowly to room temperature and quenched with water. Extraction with EtOAc and removal of solvent followed by chromatography afforded 1-*tert*-butoxycarbonyl lactone **6** as a yellow oil (0.22 g, 74%): ^{1}H NMR ($CDCl_3$) 7.97 (dd, J = 8.0, 1.0, 1 H), 7.91 (d, J = 9.0, 1 H), 7.73 (d, J = 9.0, 1 H), 7.44 (td, J = 8.1, 1.2, 1 H), 7.32 (d, J = 8.0, 1 H), 7.30 (t, J = 8.1, 1 H), 5.77 (d, J = 1.1, 1 H), 2.13 (d, J = 1.1, 3 H), 1.55 (s, 9 H), 1.49 (s, 6 H).

The N-*t*-Boc-protected lactone **6** (0.22 g, 0.56 mmol) was converted to compound **27** by a hydroboration−oxidation procedure described in the synthesis of **17** and **18** in 22% yield (50 mg) as a yellow oil: ^{1}H NMR ($CDCl_3$) 8.03 (d, J = 8.9, 1 H), 8.00 (d, J = 8.1, 1 H), 7.67 (d, J = 8.9, 1 H), 7.48 (t, J = 8.1, 1 H), 7.35 (d, J = 8.1, 1 H), 7.33 (t, J = 8.1, 1 H), 5.25 (q, J = 7.3, 1 H), 1.87 (s, 3 H), 1.66 (d, J = 7.3, 3 H), 1.52 (s, 9 H), 1.36 (s, 3 H).

To a solution of compound **27** (15 mg, 0.037 mmol) in THF (1 mL) at −78 °C was added the freshly prepared 3-fluorobenzylmagnesium bromide (0.10 mL, 1.0 M in ether, 0.10 mmol), and the reaction was slowly warmed to room temperature and was quenched with water (1 mL). The mixture was extracted with EtOAc (2 × 5 mL) and was concentrated to provide the crude intermediate, which was treated with excess TFA (0.2 mL) in CH_2Cl_2 (1 mL) for 30 min and then quenched with 5% NaOH (5 mL). The mixture was extracted with EtOAc and concentrated, and chromatography afforded compound **28** in a 60% two-step yield as a yellowish oil (8.8 mg): ^{1}H NMR ($CDCl_3$) 7.73 (d, J = 7.8, 1 H), 7.70 (d, J = 11.1, 1 H), 7.60 (d, J = 8.3, 1 H), 7.42 (d, J = 7.8, 1 H), 7.31 (td, J = 8.0, 6.2, 1 H), 7.22 (d, J = 8.1, 1 H), 7.18 (d, J = 7.0, 1 H), 7.08 (t, J = 7.1, 1 H), 6.94 (td, J = 8.4, 2.4, 1 H), 6.85 (d, J = 8.3, 1 H), 5.87 (s, 1 H), 4.33 (q, J = 7.3, 1 H), 3.78 (s, 1 H), 1.56 (d, J = 7.3, 3 H), 1.51 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) 214.0, 162.4 (d, J = 244.0), 152.3, 147.0, 144.2, 137.2 (d, J = 8.1), 129.8 (d, J = 8.8 Hz), 128.7, 128.0, 125.4, 124.2, 123.0, 122.6, 122.4, 121.9, 121.8, 118.1, 116.5, 115.8 (d, J = 23.1), 114.1, 113.8 (d, J = 21.1), 60.1, 44.9, 27.7, 27.2, 17.4. Anal. ($C_{26}H_{22}FNO_2$) C, H, N.

(*R,S*)-(*Z*)-5-Benzylidene-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinolin-3-one (29). This compound was prepared from compound **27** (20 mg, 0.049 mmol) and benzylmagnesium bromide ether solution (0.10 mL, 1.0 M, 0.10 mmol) by the same procedure as described in the synthesis of compound **28** in a 40% two-step yield as a colorless oil (7.5 mg): ^{1}H NMR ($CDCl_3$) 7.81 (d, J = 7.3, 2 H), 7.72 (d, J = 7.7, 1 H), 7.59 (d, J = 8.4, 1 H), 7.39 (t, J = 7.3, 2 H), 7.24−7.18 (m, 2 H), 7.17 (d, J = 7.7, 1 H), 7.08 (t, J = 7.7, 1 H), 6.83 (d, J = 8.4, 1 H), 5.91 (s, 1 H), 4.37 (q, J = 7.3, 1 H), 3.76 (s, 1 H), 1.57 (d, J = 7.3, 3 H), 1.51 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) 214.1, 152.7, 146.0, 144.2, 135.1, 129.5, 128.6, 128.5, 127.1, 124.2, 122.8, 122.4, 122.2, 121.8, 121.7, 117.8, 116.5, 115.4, 60.1, 44.9, 27.7, 27.2, 17.4. Anal. ($C_{26}H_{23}NO_2$) 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. 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,[11] and the radioligands used in the competitive binding assays are progesterone for hPR-A, dihydrotestosterone for hAR, and dexamethasone for hGR.

T47D Alkaline Phosphatase Assay. The T47D alkaline phosphatase assays were performed as described previously.[10] Incubation of the T47D cells in the presence of test compound stimulates expression of alkaline phosphatase, and the absorbency was measured. All the experiments were carried out in 96-well plates by automation (Beckman Biomomek automated workstation).

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