5-Aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines as Potent, Orally Active, Nonsteroidal Progesterone Receptor Agonists: The Effect of D-Ring Substituents

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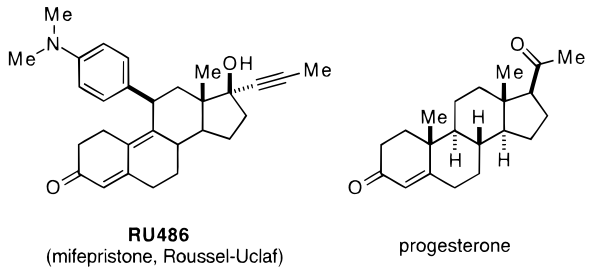
Received August 28, 1997

Several 5-(4-chlorophenyl)-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines were prepared to determine the effects of substitution at C(8) and C(9) on the progestational activity of this pharmacophore. In combination with a halogen (F or Cl) at C(9), replacement of the C(5) aryl group with variously substituted aryl groups resulted in optimization of the progestational activity, affording compounds with in vitro activity greater than that of progesterone as measured by a cotransfection assay using human progesterone receptor subtype-B (hPR-B). Binding affinities (K_i) to hPR-A were subnanomolar in many cases. These in vitro effects were verified in vivo using a rodent model. Compound **10** (LG120794, 9-chloro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline) was more potent than medroxyprogesterone acetate at counterpoising the effects of estradiol benzoate in the uterine wet weight assay using immature rats.

Introduction

Control of gene expression by intracellular receptors (IRs) is regulated by small molecule naturally occurring hormones.[1] The ability of certain small molecules to mimic (agonism) or to inhibit (antagonism) effects of natural hormones provides an opportunity to influence cell growth, cell differentiation, and other cellular processes. IRs, including sex steroid receptors, are therefore attractive targets for drug discovery.[2] The human progesterone receptor (hPR) is a member of a subgroup within the IR superfamily that includes the human androgen (hAR), estrogen (hER), glucocorticoid (hGR), and mineralocorticoid (hMR) receptors. Like the other members of this superfamily, after binding its cognate ligand, progesterone (Figure 1), hPR binds to specific hormone response elements (HREs) in target genes and modulates gene transcription.[1,3,4]

Drugs that modulate the transcriptional activity of hPR play important roles in medicine, and hPR agonists have been used therapeutically for decades.[5] For example, medroxyprogesterone acetate (MPA), norgestrel, and norethindrone are used in birth control formulations, generally in combination with estrogen receptor agonists;[5,6] moreover, hPR agonists are also useful for hormone replacement therapy (HRT)[7] and the treatment of certain carcinomas.[8] All hPR modulators (including hPR antagonists such as RU486, Figure 1) either currently marketed or undergoing clinical trials are steroids. Accordingly, these drugs display differing, but substantial, levels of cross-reactivity with other sex steroid receptors, particularly with hAR and hGR,[6,9] which can lead to undesirable side effects. The opportunity therefore exists for the discovery of more selective and efficacious hPR agonists and antagonists.



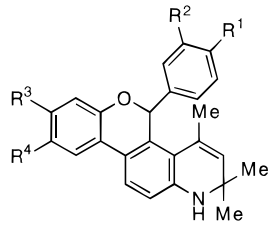


Figure 1. RU486, progesterone, and 5-aryl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline general structure **1**.

Utilizing the cotransfection assay[1,2a,10] as a guide to determining structure−activity relationships (SAR), we have been pursuing the discovery of nonsteroidal hPR modulators.[11,12] A previous report from these laboratories demonstrated that certain 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines (**1**, $R^3 = R^4 = H$, Figure 1) act as potent hPR agonists and reported optimization of the structure of the 5-aryl substituent.[13] This report discloses a series of hPR agonists based on the 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinoline pharmacophore (**1**, Figure 1) that was designed to determine the effects of D-ring substituents (R^3−R^4) upon hPR agonist activity. This series of nonsteroidal hPR agonists has yielded potent compounds with greatly improved activ-

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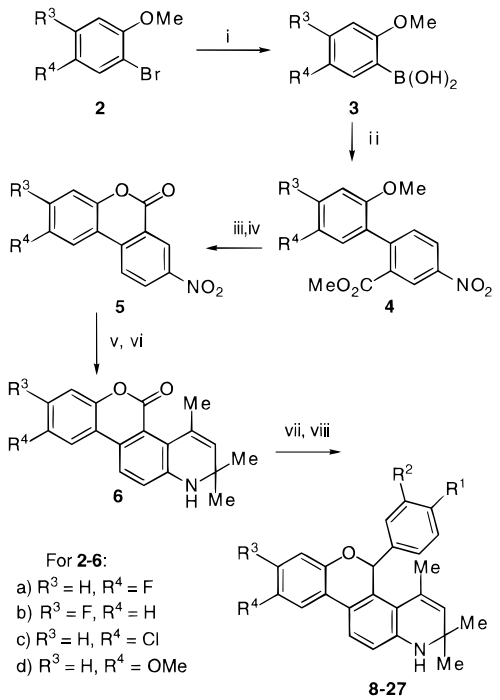
S0022-2623(97)00577-3 CCC: $15.00
Published on Web 01/14/1998

Scheme 1[a]



[a] (i) *n*-BuLi, THF, −78 °C, then $(MeO)_3B$, rt; (ii) methyl 2-bromo-5-nitrobenzoate, 5% $(Ph_3P)_4Pd$, DME, 2.0 M aq Na_2CO_3, 80 °C; (iii) 20% KOH, EtOH, THF, rt; (iv) $SOCl_2$, DCE, 80 °C; then $AlCl_3$, rt; (v) 10% Pd/C, H_2, EtOAc/EtOH, rt; (vi) acetone, I_2, 120−130 °C; (vii) ArLi, THF, −78 °C; (viii) BF_3−OEt_2, Et_3SiH, CH_2Cl_2, rt.

ity over the parent series **1** ($R^3 = R^4 = H$). In addition, the PR agonist effects have been demonstrated in vivo by oral administration to rodents.

Chemistry

The synthetic route to compounds of structure **1** (R^3 or $R^4 \neq H$) is shown in Scheme 1. The key intermediates, benzocoumarins **5**, were prepared by a modification of Snieckus' route to this type of structure.[14] Thus, lithium−halogen exchange of a bromoanisole **2** followed by transmetalation afforded the 2-methoxybenzene boronic acids **3** in 75−95% yields. Palladium-catalyzed[15] cross-coupling with commercial methyl 2-bromo-5-nitrobenzoate afforded the biphenyl esters **4** in 55−90% yields. This conversion is notable in that it affords an *o*,*o*′-disubstituted biphenyl, which is often problematic in palladium-catalyzed cross-couplings. Conversion of biphenyl esters **4** to benzocoumarins **5** followed a three-step, two-pot protocol. Hydrolysis of the methyl esters with ethanolic KOH afforded the biphenyl carboxylic acids in 95−99% yields. Treatment of a suspension of an acid in dichloroethane with $SOCl_2$ at reflux afforded the corresponding acid chloride; the reaction mixture was then cooled to room temperature and treated with $AlCl_3$, which effected an intramolecular acylation with concomitant O-demethylation to afford the nitrobenzocoumarins **5** in 95−99% yields.[16] Hydrogenolysis over palladium on carbon afforded the anilines, which were converted to the 1,2-dihydro-2,2,4-trimethylquinolines **6** in moderate yields utilizing a Skraup cyclization.[17] Treatment of **6** with an aryllithium reagent followed by reduction of the intermediate hemiketals with BF_3−OEt_2/Et_3SiH[18] afforded the 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines **8**−**27** in 30−75% yields. Compounds **8**−**27** are racemic, and all biological data were obtained using racemates.[19]

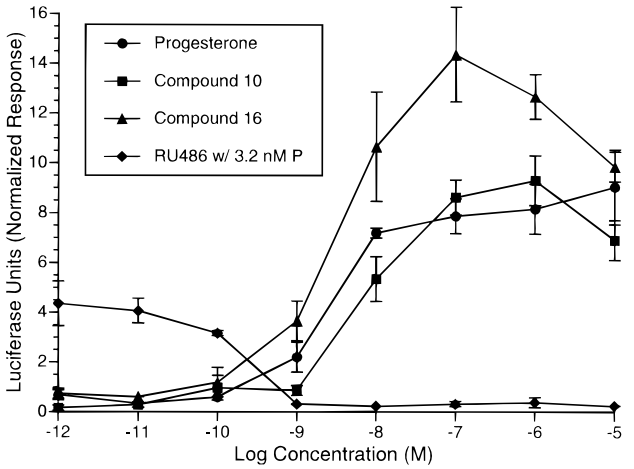


Figure 2. Concentration−response curves for progesterone, **10**, **16**, and RU486. RU486 was run in the antagonist mode; P = progesterone. See the Experimental Section for details.

In Vitro Biological Studies

The ability of quinolines **8**−**27** to modulate hPR activity in a cellular context was measured using a cotransfection assay, and ligand binding affinity was measured using a competitive binding assay using baculovirus-expressed hPR-A in Sf21 cells as described previously.[11a,b] The cotransfection assay is a tool for the functional characterization of interactions of small-molecule agonists or antagonists with IRs. Two plasmids, a receptor plasmid and a reporter plasmid, are transiently introduced into mammalian cells that do not normally express the IR of interest. In the experiments described below, the receptor plasmid contained hPR-B under constitutive control of the SV-40 promoter.[20] The reporter plasmid, MMTV-LUC, contained the cDNA for firefly luciferase (LUC) under control of the mouse mammary tumor virus (MMTV) long terminal repeat, a conditional promoter containing a progesterone response element (PRE).[10] Progesterone and other steroidal hPR agonists cause concentration-dependent increases in luciferase activity in the hPR-B cotransfection assay, which can be reversed by known steroidal hPR antagonists such as RU486 or ZK98299 (Figure 2). Cross-reactivity with other sex steroid IRs was assessed using similar hGR, hAR, hER, and hMR cotransfection assays. Because the assays are cell-based, a measurable response provides verification that the test compound crosses the cell membrane.

The hPR agonist data for 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines **8**−**27** are collected in Table 1. The data for three steroidal hPR agonists, progesterone, medroxyprogesterone acetate (MPA), and norethindrone (entries 1−3), are shown for comparison. Sample cotransfection experiment curves are depicted in Figure 2. One of the most active D-ring-unsubstituted 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines tested when this study was initiated[13] bore a 4-chlorophenyl group at C(5) (LG120546, structure **1**, R^1 = Cl, R^{2-4} = H, compound **7**), and the data for this compound is also shown (entry 4). Using this compound as a starting point, it was immediately evident that compounds which bore a halogen atom at C(9) (entries 5 and 7) were more potent and efficacious hPR agonists

Table 1. hPR-B Agonist Activity in Cotransfected CV-1 Cells and Binding Affinities to Baculovirus-Expressed HPR-A[a]

entry	ligand	R^1	R^2	R^3	R^4	EC_{50}[b,c]	efficacy[d]	K_i[b]
1			progesterone			2.89 ± 0.88	100 ± 0	3.5 ± 0.2
2			medroxyprogesterone acetate			0.15 ± 0.08	80 ± 4	0.34 ± 0.04
3			norethindrone			2.2 ± 1.3	125 ± 6	1.87 ± 0.13
4	**7**	Cl	H	H	H	15 ± 1.1	77 ± 5	0.70 ± 0.12
5	**8**	Cl	H	H	F	8.1 ± 3.2	108 ± 15	0.32 ± 0.07
6	**9**	Cl	H	F	H	10 ± 9.1	47 ± 7	2.7 ± 0.6
7	**10**	Cl	H	H	Cl	9.0 ± 1.2	110 ± 9	0.59 ± 0.16
8	**11**	Cl	H	H	OMe	3.1 ± 0.9	49 ± 3	2.4 ± 0.5
9	**12**	H	H	H	F	7.4 ± 3.1	82 ± 12	2.2 ± 0.1
10	**13**	H	Cl	H	F	2.8 ± 0.7	117 ± 7	0.32 ± 0.11
11	**14**	Cl	Me	H	F	2.7 ± 0.2	97 ± 6	0.49 ± 0.16
12	**15**	OMe	H	H	F	270 ± 70	77 ± 11	2.7 ± 0.5
13	**16**	H	Me	H	F	5.0 ± 2.0	149 ± 15	0.37 ± 0.10
14	**17**	H	CF_3	H	F	10 ± 2.9	132 ± 27	0.78 ± 0.33
15	**18**	F	Me	H	F	15 ± 7.2	102 ± 22	1.3 ± 0.2
16	**19**	H	H	H	Cl	6.9 ± 1.8	97 ± 8	0.74 ± 0.08
17	**20**	Br	H	H	Cl	5.2 ± 1.0	83 ± 11	0.59 ± 0.13
18	**21**	OMe	H	H	Cl	13 ± 5.4	94 ± 4	0.93 ± 0.27
19	**22**	H	Cl	H	Cl	3.6 ± 0.7	95 ± 12	0.48 ± 0.18
20	**23**	H	Me	H	Cl	7.1 ± 1.3	90 ± 12	0.55
21	**24**	H	CF_3	H	Cl	7.4 ± 3.0	140 ± 16	1.1
22	**25**	H	F	H	Cl	3.7 ± 0.5	125 ± 14	0.34
23	**26**	Cl	Me	H	Cl	9.4 ± 2.6	73 ± 10	0.50
24	**27**	F	Me	H	Cl	9.5 ± 2.8	112 ± 3	1.3 ± 0.4

[a] Cotransfection experiment values represent at least triplicate determinations. [b] Values are in nM, mean ± SEM, $n \geq 2$. If no SEM is noted, value is from a single determination. [c] EC_{50} values represent the concentration required to give half-maximal activation for that ligand. [d] Efficacy expressed as percent relative to progesterone = 100%.

relative to **7**. Compound **8** (LG120748, entry 5), for example, displayed 2-fold better binding to hPR-A than did the parent compound **7** and better agonist efficacy and potency in the cotransfection assay. The binding affinity of **8** for hPR-A (K_i = 0.32 nM) was more than 1 order of magnitude greater than that of progesterone (K_i = 3.5 nM). Compound **10** (LG120794) was similarly more active than **7**. In contrast, a C(8) fluoro (entry 6) or C(9) methoxy (entry 8) group afforded potent compounds with reduced efficacy. The SAR of the C(5) aryl group for compounds bearing either a fluorine or chlorine atom at C(9) was then investigated.

In the C(9) fluoro series (R^3 = H, R^4 = F), an unsubstituted phenyl group at C(5) provided a compound (**12**, entry 9) with comparable activity in the functional assay (EC_{50} = 7.4 nM) relative to **8**, albeit with reduced efficacy. Moving the chlorine atom of **8** over one position afforded compound **13** (LG120746, entry 10), with greatly improved potency (EC_{50} = 2.8 nM) compared to **8**. The addition of an *o*-methyl group to **8** also afforded a very potent hPR agonist (compound **14**, entry 11); both **13** and **14** are equipotent to progesterone (entry 1). A 4-methoxyphenyl group at C(5) afforded a compound with diminished binding affinity and less potent and efficacious functional activity (entry 12): this result was consistent with the parent series (R^1 = R^2 = H). Meta substituents on the C(5) aryl were well-tolerated: methyl and trifluoromethyl also provided highly potent compounds (entries 13 and 14). Notably, compound **16** (entry 13) was very active (EC_{50} = 5.0 nM, 149% efficacy), whereas the compound bearing a 3-methylphenyl substituent in the C(9)-unsubstituted series was much less active (EC_{50} = 145 nM, 95% efficacy). The efficacies of several compounds in this series were greater than that of progesterone (see, for example, Figure 2).

In the C(9) chloro series (R^3 = H, R^4 = Cl), an unsubstituted phenyl group at C(5) provided a very potent compound (entry 16), as did a 4-bromophenyl group (entry 17). Surprisingly, a 4-methoxyphenyl group at C(5) provided a compound with an EC_{50} of 13 nM (entry 18), 1 order of magnitude improvement over the C(9) fluoro compound **15** (entry 12). Meta substituents on the C(5) aryl were again well-tolerated (entries 19−22), providing compounds with potencies approaching that of progesterone. Compound **24**, bearing a 3-(trifluoromethyl)phenyl substituent at C(5), and compound **25**, bearing a 3-fluorophenyl substituent at C(5), were the most active of the four (entries 21 and 22). The combination of a *p*-halogen and a *m*-methyl group also provided very potent compounds (entries 23 and 24).

Table 2. Inhibition of Estradiol-Induced Uterine Wet Weight Gain in Immature Rats

compd	% efficacy[a]
MPA	100
20	60
10	108
8	116

[a] 100% = response to MPA at 1 mg/mouse.

The cross-reactivity with other IRs was also assessed. Although several compounds (**16**, **17**, **19**, and **27**) displayed moderate hAR antagonist activity (200−500 nM), most were only weakly active at this receptor (IC_{50} > 3 μM). Interestingly, several of the C(9) chloro derivatives also had moderate hGR agonist activity (e.g., **22** and **23**, EC_{50} ~ 350−500 nM, 60−70% efficacy). Activity on the hER and hMR was minimal (2−10 μM).

In Vivo Biological Activity

Several of the nonsteroidal agonists of structure **1** were tested at a dose of 1.0 mg/animal for the ability to counterpoise estradiol-induced uterine wet weight gain in immature female Sprague−Dawley rats, and the results from three of these experiments are shown in Table 2. A 1.0 mg/animal dose affords maximal inhibition using MPA, which for comparison defined a 100% response. As shown by the data, two compounds, **8**

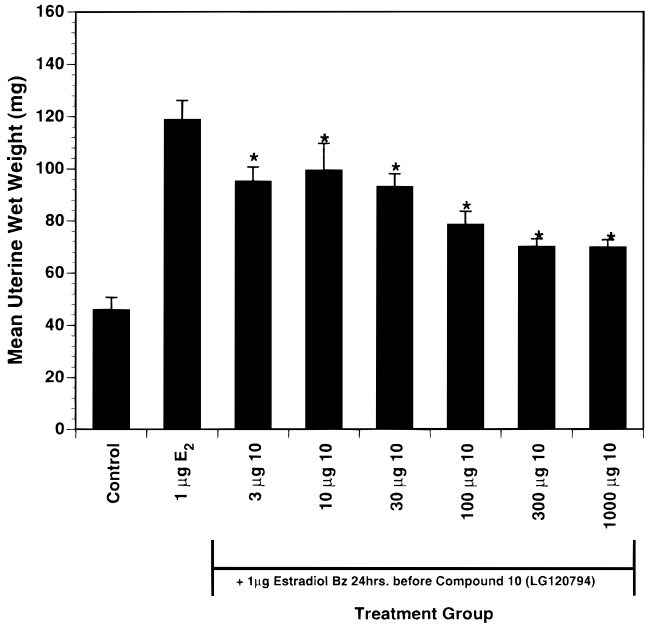


Figure 3. Effects of LG120794 (compound **10**) on uterine wet weights in estradiol benzoate (E-Bz)-primed 21-day-old immature rats (control and E-Bz, $n = 6$; all other groups, $n = 4$; $*p < 0.05$ vs E-Bz). Values represent mean ± SEM.

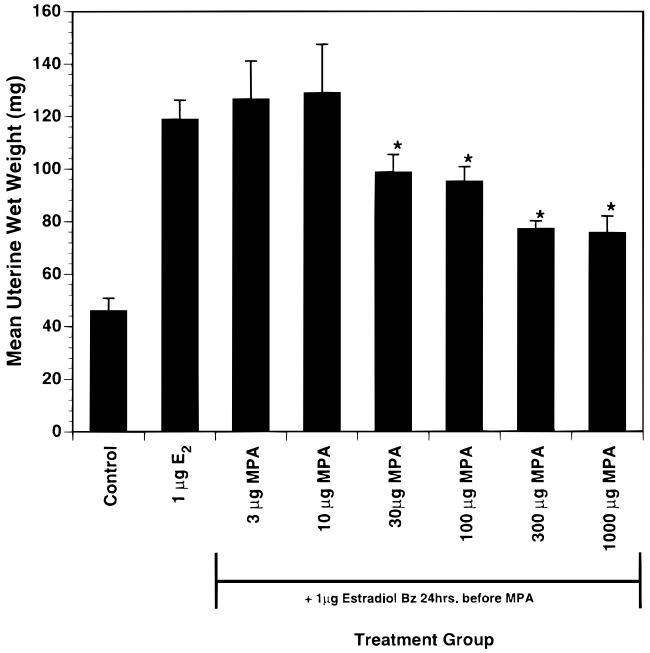


Figure 4. Effects of medroxyprogesterone acetate (MPA) on uterine wet weights in estradiol benzoate (E-Bz)-primed 21-day old immature rats (control and E-Bz, $n = 6$; all other groups $n = 4$; $*p < 0.05$ vs E-Bz). Values represent mean ± SEM.

(LG120748) and **10** (LG120794), were at least as efficacious as MPA (108−116% response) in this single-dose assay, whereas compound **20** was less efficacious (60% response).

A range of doses of compound **10** was examined to determine a dose−response curve for this agonist (Figure 3), using estradiol benzoate-primed animals. Compound **10** had a significant blunting effect on uterine wet weight gain at doses as low as 0.003 mg/animal, compared to a minimally effective dose for MPA of 0.03 mg/animal (Figure 4). In addition, maximal inhibition of estrogen-induced uterine wet weight gain using **10** was observed at 0.3 mg/animal, compared to 1.0 mg/animal for MPA. These studies demonstrate that the in vitro activity of the nonsteroidal hPR agonists translates to the in vivo situation and that LG120794 is more effective than MPA in this animal model for progestational action.

Discussion

Earlier studies had demonstrated that electron-withdrawing groups at the meta and para positions of the C(5) aryl substituent of 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines (**1**, $R^3 = R^4 = H$) afforded the most potent hPR agonists. Other substituents on the C(5) aryl group, such as methyl or methoxy, afforded compounds with lower binding affinities (higher K_i's) and reduced hPR agonist activity. The most active compounds in this earlier study displayed binding affinities (K_i) of 0.4−1 nM and agonist potencies (EC_{50}) in the hPR-B cotransfection assay of 15−20 nM. Specifically, a chlorine atom at the para-position of the C(5) aryl moiety (**7**, $R^1 = Cl$, $R^{2-4} = H$, entry 4, Table 1) afforded a compound which displayed subnanomolar binding to hPR-A ($K_i = 0.70$ nM) and was a 15 nM partial agonist in the hPR-B cotransfection assay.

The biological data for the compounds described in this report demonstrate that the addition of a C(9) fluorine or chlorine atom (**8**−**27**, $R^4 = F$ or Cl) to the tetracyclic core of structure **1** afforded more active hPR agonists (see Table 1). In addition, the influence of this substituent outweighed the influence of the C(5) aryl group, as demonstrated by the potent activity of **12**, **15**, **16**, and **21**, which bear C(5) substituents that afforded compounds of moderate potency in the unsubstituted series. Several of these compounds are as potent as and more efficacious than progesterone in the hPR cotransfection assay and bind to hPR-A at subnanomolar levels. In addition, cross-reactivity with other IRs is minimal. When administered orally to rodents, compound **10** (LG120794) is more potent and efficacious than MPA at inhibiting estrogen-induced uterine wet weight gain. These results and the results described in the preceding paper[13] demonstrate for the first time that nonsteroidal ligands can act as potent and efficient agonists of the human progesterone receptor in vitro and that the activity observed in the cellular assays translates to that observed in a rodent model in vivo. Although modeling studies presented in the previous paper suggest that the dihydroquinoline ring of **1** overlaps with the D-ring of steroidal progestins, experimental evidence supporting this hypothesis is lacking. In addition, there is currently no evidence suggesting that the steroidal and nonsteroidal progestins bind to the exact same binding site of hPR. The potent activity and excellent selectivity of these molecules bode well for the discovery of more selective and efficacious nonsteroidal hPR modulators with improved cross-reactivity profiles relative to steroidal progestins.

Experimental Section[21]

General Method 1. Preparation of Boronic Acids 3. 5-Fluoro-2-methoxyphenylboronic Acid (3a). In a 200-mL flask, a solution of 2-bromo-4-fluoroanisole (4.00 mL, 30.8 mmol) in THF (50 mL) was cooled to −78 °C. To this solution

a 2.5 M solution of *n*-BuLi in hexanes (12.4 mL, 31 mmol, 1.0 equiv) was added dropwise over a 30-min period. The reaction mixture was stirred at −78 °C for 60 min and treated with trimethyl borate (10.5 mL, 92.4 mmol, 3.0 equiv). The reaction mixture was allowed to slowly warm to room temperature (rt), stirred overnight (12 h), and cooled to 0 °C. The solution was treated with 5% HCl until the pH = 6. The reaction mixture was poured into saturated NH_4Cl (80 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were washed with saturated NH_4Cl (1 × 80 mL), combined, dried ($MgSO_4$), filtered through a pad of Celite, and concentrated to afford 4.90 g (94%) of **3a** as a white semisolid, which was used without further purification: ^{1}H NMR (acetone-d_6) 7.47 (dd, J = 8.8, 3.3, 1H), 7.17 (m, 1H), 7.05 (dd, J = 9.0, 3.9, 1H), 3.93 (s, 3H).

General Method 2. Preparation of Biphenylcarboxylates 4. Methyl 5′-Fluoro-2′-methoxy-4-nitro-2-biphenylcarboxylate (4a). In a 250-mL flask, a solution of methyl 2-bromo-5-nitrobenzoate (5.00 g, 19.2 mmol) in DME (60 mL) was treated with $(Ph_3P)_4Pd$ (0.67 g, 0.58 mmol, 3.0 mol %). The reaction mixture was stirred at rt for 10 min. A solution of **3a** (4.90 g, 29 mmol, 1.5 equiv) in EtOH (8 mL) was added followed by 2.0 M Na_2CO_3 (29 mL, 58 mmol, 3 equiv). The reaction mixture was heated to 80 °C for 6 h, cooled to rt, poured into 2.0 M Na_2CO_3 (100 mL), and extracted with EtOAc (3 × 100 mL). The extracts were washed with brine (1 × 100 mL), combined, dried ($MgSO_4$), filtered, and concentrated to an orange oil. Purification by silica gel chromatography (hexane−EtOAc, 10:1) afforded 4.25 g (72%) of **4a** as a yellow-orange solid: ^{1}H NMR ($CDCl_3$) 8.73 (d, J = 2.4, 1H), 8.39 (dd, J = 8.3, 2.4, 1H), 7.49 (d, J = 8.3, 1H); 7.09 (dt, J = 3.1, 8.5, 1 H); 7.00 (dd, J = 8.5, 3.1, 1 H); 6.85 (dd, J = 8.9, 3.2, 1 H); 3.76 (s, 3 H); 3.70 (s, 3 H).

General Method 3. Preparation of Dibenzo[*b,d*]pyran-6-ones 5. 2-Fluoro-8-nitro-6*H*-dibenzo[*b,d*]pyran-6-one (5a). In a 200-mL flask, a solution of **4a** (4.24 g, 13.9 mmol) in THF (50 mL) was cooled to 0 °C and treated with EtOH (10 mL) and 20% KOH (10 mL). The reaction mixture was allowed to warm to rt, stirred overnight, acidified to pH = 10 with 10% HCl, and extracted with EtOAc (3 × 75 mL). The extracts were washed with brine (1 × 80 mL), combined, dried ($MgSO_4$), filtered, and concentrated to afford 3.68 g (91%) of 5′-fluoro-2′-methoxy-4-nitro-2-biphenylcarboxylic acid as a yellow solid. The crude acid was suspended in DCE (30 mL), treated with $SOCl_2$ (0.92 mL, 12.6 mmol, 1.0 equiv), and heated to a gentle reflux for 90 min. The reaction vessel was cooled to 0 °C, and $AlCl_3$ (0.91 g, 6.8 mmol, 0.55 equiv) was added portionwise. The reaction mixture was allowed to slowly warm to rt, stirred for 5 h, and quenched with 5% HCl (100 mL). The crude product was extracted with EtOAc (4 × 150 mL). The extracts were washed with saturated NH_4Cl (1 × 100 mL), combined, dried ($MgSO_4$), filtered, and concentrated to afford 3.19 g (99%) of **5a** as a yellow solid: ^{1}H NMR (DMSO-d_6) 8.84 (d, J = 2.3, 1H), 8.67 (m, 2H), 8.40 (d, J = 9.2, 1H), 7.55 (m, 2H).

General Method 4. Preparation of Quinolines 6. 9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]-quinoline (6a). In a 500-mL flask, a suspension of 2-fluoro-8-nitro-6*H*-dibenzo[*b,d*]pyran-6-one (3.18 g, 12.2 mmol) in EtOAc (300 mL) was treated with 10% Pd/C (2.0 g) and AcOH (0.2 mL) and stirred under an atmosphere of H_2 for 1 h. The reaction mixture was filtered and the solids were rinsed with acetone (200 mL). Concentration of the filtrate afforded 2.19 g (78%) of 8-amino-2-fluoro-6*H*-dibenzo[*b,d*]pyran-6-one as a yellow solid. In a 200-mL resealable pressure tube, a suspension of 8-amino-2-fluoro-6*H*-dibenzo[*b,d*]pyran-6-one (1.10 g) in acetone (100 mL) was treated with iodine (0.50 g) and heated to 110 °C for 32 h. The reaction mixture was cooled to rt, concentrated to remove the bulk of the acetone, and dissolved in CH_2Cl_2 (200 mL). The organic layer was washed with 0.5 N $Na_2S_2O_3$ (2 × 200 mL) and saturated $NaHCO_3$ (1 × 100 mL). The aqueous layers were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated to afforded an orange solid. Purification by silica gel chromatography (hexane−EtOAc, 5:1) afforded 0.51 g (34%) of **6a** as a bright yellow solid: ^{1}H NMR (acetone-d_6) 7.95 (d, J = 8.7, 1H), 7.83 (dd, J = 10.1, 2.9, 1H), 7.29 (dd, J = 9.0, 4.9, 1H), 7.22 (d, J = 8.7, 1H), 7.17 (m, 1H), 6.25 (br s, 1H), 5.54 (t, J = 1.2, 1H), 2.06 (s, 3H), 1.30 (s, 6H), ^{13}C NMR (acetone-d_6) 160.2 (d, J_{C-F} = 239), 159.9, 148.2, 147.3, 132.9, 131.7, 125.3, 123.0, 121.9, 121.8, 119.1, 118.9 (d, J_{C-F} = 9.0), 115.6 (d, J_{C-F} = 25), 108.9 (d, J_{C-F} = 26), 51.0, 28.5, 21.6. Anal. ($C_{19}H_{16}FNO_2$) C, H, N, F.

4-Fluoro-2-methoxyphenylboronic Acid (3b). Following general method 1, from 2-bromo-5-fluoroanisole (5.50 g, 26.8 mmol, 1.0 equiv), 2.5 M *n*-BuLi in hexanes (10.7 mL, 27 mmol, 1.0 equiv), and trimethyl borate (9.1 mL, 80 mmol, 3.0 equiv) was obtained 4.22 g (93%) of **3b** as a white solid, which was used without further purification.

3-Fluoro-8-nitro-6*H*-dibenzo[*b,d*]pyran-6-one (5b). In a 200-mL round bottom flask, a solution of 2-bromo-5-nitrobenzoic acid (4.10 g, 16.7 mmol, 1.0 equiv) in DME (65 mL) was treated with $(Ph_3P)_4Pd$ (0.58 g, 0.50 mmol, 3.0 mol %). The reaction mixture was stirred at rt for 10 min. A solution of **3b** (4.20 g, 25 mmol, 1.5 equiv) in EtOH (10 mL) was added followed by 2.0 M Na_2CO_3 (30 mL). The reaction mixture was heated to 80 °C for 6 h, cooled to rt, poured into 5% HCl (100 mL), and extracted with EtOAc (3 × 100 mL). The extracts were washed with saturated NH_4Cl (1 × 100 mL) and brine (1 × 100 mL), combined, dried ($MgSO_4$), filtered, and concentrated to an orange solid. The crude material was suspended in DCE (80 mL), treated with $SOCl_2$ (1.2 mL), and heated at reflux for 90 min. The reaction mixture was cooled to rt, treated with $AlCl_3$ (0.4 g), and allowed to react overnight (11 h). The reaction mixture was poured into 20% KOH (80 mL) and extracted with methylene chloride (3 × 80 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated to an orange oil. The crude material was dissolved in methylene chloride (50 mL), adsorbed onto Celite (1 g), and concentrated to a fluffy orange powder. This powder was applied to a pad of silica gel in a 250-mL Buchner funnel (50 × 50 mm). The pad was rinsed with 100 mL of 2:1 hexane:EtOAc, which was discarded, and then 400 mL of 1:1 hexane−EtOAc. The filtrate was concentrated to afford 2.08 g (48%) of **5b** as an orange solid: ^{1}H NMR (acetone-d_6) 9.02 (d, J = 2.4, 1H), 8.71 (dd, J = 8.8, 2.4, 1H), 8.65 (d, J = 8.8, 1H), 8.53 (dd, J = 9.6, 6.1, 1H), 7.34 (m, 2H).

8-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (6b). Following general method 4, from **5b** (2.04 g, 7.9 mmol) and 10% Pd/C (0.4 g) was obtained 1.61 g (89%) of 8-amino-3-fluoro-6*H*-dibenzo[*b,d*]pyran-6-one as a yellow solid. The aniline was converted to the quinoline following general method 4 to afford an orange solid. Purification by silica gel chromatography (hexane−EtOAc, 5:1) afforded 0.46 g (21%) of **6b** as a bright-yellow solid: ^{1}H NMR (acetone-d_6) 8.12 (dd, J = 9.6, 5.9, 1H), 7.92 (d, J = 9.6, 1H), 7.22 (d, J = 8.6, 1H), 7.11 (m, 2H), 6.1 (br s, 1H), 5.53 (d, J = 1.2, 1H), 2.06 (s, 3H), 1.29 (s, 6H).

5-Chloro-2-methoxyphenylboronic Acid (3c). Following general method 1, from **2c** (2.00 g, 9.0 mmol, 1.0 equiv), 2.5 M *n*-BuLi in hexanes (3.62 mL, 9.0 mmol, 1.0 equiv), and trimethyl borate (3.0 mL, 26 mmol, 2.9 equiv) was obtained 1.30 g of a white semisolid. This compound was used directly with no further purification.

Methyl 5′-Chloro-2′-methoxy-4-nitro-2-biphenylcarboxylate (4c). Following general method 2, from methyl 2-bromo-5-nitrobenzoate (1.25 g, 4.8 mmol, 1.0 equiv), $(Ph_3P)_4$-Pd (0.16 g, 0.14 mmol, 2.9 mol %), and **3c** (1.30 g, 6.9 mmol, 1.5 equiv) was obtained 0.85 g (55%) of **4c** as a yellow-orange solid: ^{1}H NMR ($CDCl_3$) 8.73 (d, J = 2.4, 1H), 8.38 (dd, J = 8.5, 2.5, 1H), 7.49 (d, J = 8.5, 1H), 7.36 (dd, J = 8.7, 2.5, 1H), 7.23 (d, J = 2.5, 1H), 6.85 (d, J = 8.7, 1H), 3.76 (s, 3H), 3.70 (s, 3H).

2-Chloro-8-nitro-6*H*-dibenzo[*b,d*]pyran-6-one (5c). Following general method 3, from **4c** (0.83 g, 2.6 mmol) was obtained 0.75 g (95%) of the free acid, which was converted to **5c** with $SOCl_2$ (0.17 mL, 2.3 mmol) and $AlCl_3$ (0.30 g, 2.5 mmol) to afford 0.64 g (99%) of **5c**: ^{1}H NMR (acetone-d_6) 9.04 (d, J =

2.3, 1H), 8.73 (m, 2H), 8.51 (d, J = 2.4, 1H), 7.72 (dd, J = 8.6, 2.4, 1H), 7.50 (d, J = 8.7, 1H).

9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (6c). Following general method 4, from **5c** (0.64 g, 2.3 mmol) and 10% Pd/C (0.2 g) was obtained 0.50 g (88%) of 8-amino-6-chloro-6*H*-dibenzo[*b*,*d*]pyran-6-one as a yellow solid. The aniline was converted to the quinoline following general method 4 to afford an orange solid. Purification by silica gel chromatography (hexane−EtOAc, 5:1) afforded 0.14 g (21%) of **6c** as a bright-yellow solid: ^{1}H NMR (acetone-d_6) 8.10 (d, J = 2.4, 1H), 8.00 (d, J = 8.7, 1H), 7.39 (dd, J = 8.7, 2.3, 1H), 7.26 (d, J = 8.8, 1H), 7.23 (d, J = 8.6, 1H), 5.55 (s, 1H), 2.06 (s, 3H), 1.30 (s, 6H).

2,5-Dimethoxyphenylboronic Acid (3d). Following general method 1, from 1-bromo-2,5-dimethoxybenzene (2.00 mL, 13.3 mmol), 2.5 M *n*-BuLi in hexanes (5.34 mL, 13 mmol), and trimethyl borate (4.5 mL, 40 mmol) was obtained 2.43 g (99%) of a white semisolid which was used without further purification.

Methyl 2′,5′-Dimethoxy-4-nitro-2-biphenylcarboxylate (4d). Following general method 2, from methyl 2-bromo-5-nitrobenzoate (2.46 g, 9.46 mmol), $(PPh_3)_4Pd$ (0.33 g, 0.28 mmol), and **3d** (2.42 g, 13 mmol) was obtained 2.08 g (69%) of **4d** as a white solid: ^{1}H NMR ($CDCl_3$) 8.70 (d, J = 2.4, 1H), 8.37 (dd, J = 8.4, 2.5, 1H), 7.52 (d, J = 8.5, 1H), 6.92 (dd, J = 8.8, 3.0, 1H), 6.84 (m, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H).

2-Methoxy-8-nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (5d). Following general method 3, from **4d** (2.07 g) was obtained 1.93 g (99%) of the free acid, which was converted to **5d** with $SOCl_2$ (0.47 mL, 6.4 mmol) and $AlCl_3$ (0.67 g, 5.0 mmol) to afford 1.71 g (99%) of **5d** as an orange powder: ^{1}H NMR (acetone-d_6) 9.04 (d, J = 2.4, 1H), 8.74 (d, J = 8.9, 1H), 8.69 (dd, J = 8.9, 2.4, 1H), 7.92 (d, J = 2.9, 1H), 7.41 (d, J = 9.0, 1H), 7.30 (dd, J = 9.0, 2.9, 1H), 3.97 (s, 3H).

1,2-Dihydro-9-methoxy-2,2,4-trimethyl-5-coumarino-[3,4-*f*]quinoline (6d). Following general method 4, from **5d** (1.71 g, 6.3 mmol) and 10% Pd/C (0.60 g) was obtained 1.27 g (80%) of 8-amino-2-methoxy-6*H*-dibenzo[*b*,*d*]pyran-6-one as a white solid. The aniline was converted to the quinoline following general method 4 to afford an orange solid. Purification by silica gel chromatography (hexane−EtOAc, 4:1) afforded 0.25 g (15%) of **6d** as a yellow solid: ^{1}H NMR ($CDCl_3$) 7.73 (d, J = 8.6, 1H), 7.35 (d, J = 2.8, 1H), 7.23 (d, J = 8.9, 1H), 7.00 (d, J = 8.6, 1H), 6.92 (dd, J = 8.9, 2.8, 1H), 5.57 (s, 1H), 4.29 (br s, 1H), 3.88 (s, 3H), 2.11 (d, J = 1.1, 3H), 1.33 (s, 6H).

General Method 5. Preparation of Dihydroquinolines 8−27. (*R*/*S*)-5-(4-Chlorophenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (8). In a 20-mL 2-neck flask, a solution of 4-bromochlorobenzene (230 mg, 1.20 mmol, 6.0 equiv) in THF (2 mL) was cooled to −78 °C and treated with a 2.5 M solution of *n*-BuLi in hexanes (0.48 mL, 1.2 mmol, 6.0 equiv). The reaction mixture was stirred at −78 °C for 1 h. A solution of **6a** (61 mg, 0.20 mmol) in THF (1 mL) was added via syringe; the reaction mixture was stirred at −78 °C for 3 h and quenched with 1:1 MeOH−H_2O (2 mL). The reaction mixture was allowed to warm to rt, poured into H_2O (8 mL), and extracted with EtOAc (3 × 12 mL). The extracts were washed with brine (1 × 10 mL), combined, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (hexane−EtOAc, 4:1) afforded the hemiketal adduct, which was not characterized. The adduct was dissolved in CH_2Cl_2 (1 mL) and treated with Et_3SiH (0.16 mL, 1.0 mmol, 5.0 equiv) and BF_3−OEt_2 (0.12 mL, 1.0 mmol, 5.0 equiv). After stirring for 3 h, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ (2 mL), poured into saturated $NaHCO_3$ (8 mL), and extracted with EtOAc (3 × 10 mL). The extracts were washed with brine (1 × 10 mL), combined, dried ($MgSO_4$), filtered, and concentrated to an orange oil. Purification by silica gel chromatography (hexane−EtOAc, 16:1) afforded 60 mg (75%) of **8** as a white solid: ^{1}H NMR (acetone-d_6) 7.55 (d, J = 8.4, 1H), 7.34 (dd, J = 10.0, 2.8, 1H), 7.25 (m, 4H), 6.91 (s, 1H), 6.84 (d, J = 8.5, 1H), 6.75 (m, 2H), 5.65 (br s, 1H), 5.48 (d, J = 1.4, 1H), 1.98 (d, J = 1.4, 3H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (benzene-d_6) 159.2 (d, J_{C-F} = 238), 147.4, 146.3, 139.0, 134.5, 133.9, 130.5, 129.0, 128.7, 126.7 (d, J_{C-F} = 8.6), 124.8, 120.9, 119.9, 119.3 (d, J_{C-F} = 8.4), 115.6, 114.5 (d, J_{C-F} = 23), 109.2 (d, J_{C-F} = 24), 75.9, 50.9, 30.1, 29.2, 24.2. Anal. ($C_{25}H_{21}ClFNO$) C, H, N.

(*R*/*S*)-5-(4-Chlorophenyl)-8-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (9). Following general method 5, from **6b** (61 mg, 0.20 mmol) was obtained an orange oil, which was purified by silica gel chromatography (hexane−EtOAc, 16:1) to afford 33 mg (41%) of **9** as a clear oil: ^{1}H NMR (benzene-d_6) 7.25 (d, J = 8.2, 1H), 7.22 (dd, J = 8.6, 6.2, 1H), 7.00 (d, J = 8.4, 2H), 6.86 (d, J = 8.4, 2H), 6.84 (s, 1H), 6.71 (dd, J = 9.4, 3.5, 1H), 6.49 (td, J = 8.5, 2.7, 1H), 6.30 (d, J = 8.3, 1H), 5.13 (d, J = 0.7, 1H), 3.37 (br s, 1H), 1.70 (d, J = 0.7, 3H), 1.00 (s, 6H); ^{13}C NMR (benzene-d_6) 163.2 (d, J_{C-F} = 245), 152.7 (d, J_{C-F} = 10), 145.7, 138.9, 134.5, 134.0, 130.4, 129.4, 129.1, 129.0, 124.2, 124.0 (d, J_{C-F} = 10.0), 121.8, 121.1, 120.0, 115.8, 109.7 (d, J_{C-F} = 22), 105.8 (d, J_{C-F} = 23), 76.2, 50.9, 30.0, 29.1, 24.1. Anal. ($C_{25}H_{21}ClFNO$) C, H, N.

(*R*/*S*)-9-Chloro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (10). This compound was prepared via general method 5 from compound **6c** (0.27 g, 0.83 mmol) to afford 165 mg (47%) of compound **10** as a white solid: ^{1}H NMR (acetone-d_6) 7.60 (d, J = 2.5, 1H), 7.58 (d, J = 8.4, 1H), 7.27 (d, J = 8.6, 2H), 7.22 (d, J = 8.6, 2H), 6.96 (dd, J = 8.5, 2.5, 1H), 6.94 (s, 1H), 6.84 (d, J = 8.4, 1H), 6.81 (d, J = 8.5, 1H), 5.7 (br s, 1H), 5.49 (d, J = 1.1, 1H), 1.99 (d, J = 1.1, 3H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (acetone-d_6) 150.5, 148.3, 140.8, 135.1, 134.7, 131.5, 130.4, 129.6, 129.3, 128.1, 128.0, 127.9, 125.3, 122.9, 120.3, 119.9, 116.6, 116.5, 76.3, 51.6, 30.5, 29.7, 24.5. Anal. ($C_{25}H_{21}Cl_2NO$) C, H, N, Cl.

(*R*/*S*)-5-(4-Chlorophenyl)-1,2-dihydro-9-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (11). This compound was prepared via general method 5 from compound **6d** (61 mg, 0.19 mmol) to afford 28 mg (35%) of compound **11** as a white solid: ^{1}H NMR (benzene-d_6) 7.40 (d, J = 8.4, 1H), 7.24 (d, J = 2.8, 1H), 7.12 (d, J = 8.4, 2H), 6.89 (d, J = 8.4, 2H), 6.88 (s, 1H), 6.87 (d, J = 8.6, 1H), 6.50 (dd, J = 8.6, 2.9, 1H), 5.12 (d, J = 1.0, 1H), 3.38 (br s, 1H), 3.30 (s, 3H), 1.75 (d, J = 1.0, 3H), 0.99 (s, 6H); ^{13}C NMR (benzene-d_6) 155.8, 146.0, 145.6, 139.6, 134.3, 133.8, 130.8, 130.6, 129.4, 128.9, 128.3, 126.2, 124.7, 122.0, 120.1, 118.9, 115.6, 113.6, 75.8, 55.4, 50.9, 30.1, 29.1, 24.3. Anal. ($C_{26}H_{24}ClNO_2$) C, H, N.

(*R*/*S*)-9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno[3,4-*f*]quinoline (12). This compound was prepared via general method 5 from compound **6a** (60 mg, 0.19 mmol) to afford 44 mg (70%) of compound **12** as a white solid**:** ^{1}H NMR (benzene-d_6) 7.30 (d, J = 7.6, 1H), 7.23 (dd, J = 9.6, 3.0, 1H), 7.17 (d, J = 8.3, 1H), 6.99 (s, 1H), 6.95 (t, J = 7.6, 2H), 6.86 (t, J = 7.6, 1H), 6.73 (dd, J = 8.6, 4.9, 1H), 6.50 (td, J = 8.6, 3.0, 1H), 6.24 (d, J = 8.3, 1H), 5.10 (s, 1 H), 3.40 (br s, 1H), 1.77 (d, J = 1.2, 3H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (benzene-d_6) 159.1 (d, J_{C-F} = 237), 147.8, 146.3, 140.5, 133.7, 130.9, 129.4, 129.1, 128.7, 128.5, 126.9 (d, J_{C-F} = 8.0), 124.7, 121.2, 120.0, 119.3 (d, J_{C-F} = 8.6), 115.5, 114.4 (d, J_{C-F} = 23), 109.1 (d, J_{C-F} = 25), 76.6, 50.9, 39.2, 24.2. (Anal. ($C_{25}H_{22}$-FNO) C, H, N.

(*R*/*S*)-5-(3-Chlorophenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (13). This compound was prepared via general method 5 from compound **6a** (50 mg, 0.16 mmol) to afford 46 mg (70%) of compound **13** as a colorless solid: ^{1}H NMR (acetone-d_6) 7.55 (d, J = 8.4, 1H); 7.35 (dd, J = 9.9, 2.9, 1H), 7.20 (m, 4H), 6.93 (s, 1H), 6.84 (d, J = 8.4, 1H), 6.81 (dd, J = 8.5, 5.0, 1H), 6.73 (td, J = 8.5, 2.9, 1H), 5.67 (br s, 1H), 5.49 (s, 1H), 1.99 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3 H); ^{13}C NMR (acetone-d_6) 159.2 (d, J_{C-F} = 236), 147.8, 143.5, 134.8, 134.6, 130.7, 129.9, 129.1, 128.9, 127.8, 127.1 (d, J_{C-F} = 7.9), 125.0, 119.7, 119.6, 119.4 (d, J_{C-F} = 9.0), 116.1, 114.2 (d, J_{C-F} = 24), 109.1 (d, J_{C-F} = 25), 75.7, 51.2, 29.7, 29.4, 24.1. Anal. ($C_{25}H_{21}ClFNO$) C, H, N.

(*R*/*S*)-5-(4-Chloro-3-methylphenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (14). This compound was prepared via general method 5 from compound

6a (50 mg, 0.16 mmol) to afford 42 mg (62%) of Compound **14** as a colorless solid: ^{1}H NMR (benzene-d_6) 7.28 (dd J = 9.6, 2.9, 1H), 7.19 (m, 3H), 6.99 (m, 2H), 6.93 (s, 1H), 6.76 (dd, J = 8.7, 4.9, 1H), 6.57 (td, J = 8.4, 2.9, 1H), 6.27 (d, J = 8.4, 1H), 5.15 (s, 1H), 3.43 (br s, 1H), 1.96 (s, 3H), 1.80 (d, J = 1.0, 3H), 1.01 (s, 6H); ^{13}C NMR (benzene-d_6) 159.2 (d, J_{C-F} = 237), 147.5, 146.3, 139.3, 136.5, 134.7, 133.9, 131.6, 130.5, 129.5, 129.2, 128.0, 126.7 (d, J_{C-F} = 8.3), 124.8, 121.0, 119.9, 119.3 (d, J_{C-F} = 8.6), 115.6, 114.6 (d, J_{C-F} = 23), 109.2 (d, J_{C-F} = 24), 75.9, 50.9, 30.0, 29.2, 24.2, 20.3. Anal. ($C_{26}H_{23}ClFNO$) C, H, N.

(*R/S*)-9-Fluoro-1,2-dihydro-5-(4-methoxyphenyl)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (15). This compound was prepared via general method 5 from compound **6a** (60 mg, 0.19 mmol) to afford 45 mg (58%) of compound **15** as a clear film: ^{1}H NMR (benzene-d_6) 7.39 (dd, J = 9.4, 2.8, 1H), 7.30 (d, J = 8.6, 2H), 7.07 (s, 1H), 6.86 (dd, J = 8.8, 4.0, 1H), 6.63 (d, J = 8.6, 2H), 6.62 (m, 1H), 6.35 (d, J = 8.2, 1H), 5.22 (s, 1H), 3.48 (br s, 1H), 3.19 (s, 3H), 1.93 (d, J = 1.2, 3H), 1.09 (s, 3H), 1.08 (s, 3H) (the C(10)H is obscured by the benzene singlet); ^{13}C NMR (benzene-d_6) 160.1, 159.1 (d, J_{C-F} = 237), 147.8, 146.3, 133.6, 132.4, 131.4, 130.5, 129.5, 127.1 (d, J_{C-F} = 8.5), 124.7, 121.3, 119.9, 119.4 (d, J_{C-F} = 8.5), 115.4, 114.4 (d, J_{C-F} = 25), 114.3, 109.1 (d, J_{C-F} = 23), 76.5, 54.8, 50.9, 30.2, 29.1, 24.2. Anal. ($C_{26}H_{24}FNO_2$) C, H, N.

(*R/S*)-9-Fluoro-1,2-dihydro-5-(3-methylphenyl)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (16). This compound was prepared via general method 5 from compound **6a** (31 mg, 0.10 mmol) to afford 18 mg (46%) of compound **16** as a clear film: ^{1}H NMR (benzene-d_6) 7.25 (dd, J = 9.6, 2.9, 1H), 7.20 (d, J = 10.0, 2H), 7.02 (s, 1H), 6.91 (t, J = 7.6, 1H), 6.77 (m, 1H), 6.71 (d, J = 7.6, 2H), 6.51 (td, J = 8.4, 2.9, 1H), 6.25 (d, J = 8.3, 1H), 5.11 (s, 1H), 3.39 (br s, 1H), 1.92 (s, 3H), 1.82 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (benzene-d_6) 159.1 (d, J_{C-F} = 237), 147.9, 146.3, 140.6, 138.2, 133.7, 131.1, 129.8, 129.4, 128.7, 128.3, 126.9 (d, J_{C-F} = 8.8), 126.4, 124.7, 121.3, 120.0, 119.3 (d, J_{C-F} = 8.6), 115.5, 114.4 (d, J_{C-F} = 24), 109.2 (d, J_{C-F} = 24), 76.7, 50.9, 30.0, 29.1, 24.2, 21.6. Anal. ($C_{26}H_{24}$-FNO) C, H, N.

(*R/S*)-9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-[3-(trifluoromethyl)phenyl]-5*H*-chromeno[3,4-*f*]quinoline (17). This compound was prepared via general method 5 from compound **6a** (60 mg, 0.19 mmol) to afford 43 mg (51%) of compound **17** as a clear film: ^{1}H NMR (acetone-d_6) 7.58 (d, J = 8.5, 1H), 7.54 (s, 1H), 7.51 (m, 3H), 7.36 (dd, J = 10.0, 2.9, 1H), 7.04 (s, 1H), 6.86 (d, J = 8.5, 1H), 6.83 (dd, J = 8.7, 5.0, 1H), 6.74 (td, J = 8.6, 2.9, 1H), 5.70 (br s, 1H), 5.51 (s, 1H), 2.01 (d, J = 1.2, 3H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$): 158.5 (d, J_{C-F} = 238), 146.4, 145.8, 141.0, 134.4, 131.7, 130.7 (q, J_{C-F} = 32), 129.2, 128.7, 128.5, 125.8 (d, J_{C-F} = 8.6), 125.2 (q, J_{C-F} = 4.0), 125.0 (q, J_{C-F} = 3.6), 124.2, 124.2 (q, J_{C-F} = 273), 120.5, 119.9, 118.7 (d, J_{C-F} = 8.6), 115.7, 114.2 (d, J_{C-F} = 23), 108.7 (d, J_{C-F} = 25), 75.2, 50.9, 29.6, 29.2, 24.0. Anal. ($C_{26}H_{21}F_4NO$) C, H, N.

(*R/S*)-9-Fluoro-5-(4-fluoro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (18). This compound was prepared via general method 5 from compound **6a** (38 mg, 0.12 mmol) to afford 25 mg (51%) of compound **18** as a white foam: ^{1}H NMR (benzene-d_6) 7.25 (dd, J = 8.6, 2.8, 1H), 7.17 (d, J = 8.2, 1H), 7.10 (dd, J = 7.4, 1.8, 1H), 6.96 (m, 1H), 6.92 (s, 1H), 6.74 (dd, J = 8.9, 4.9, 1H), 6.58 (t, J = 8.9, 1H), 6.54 (td, J = 8.5, 2.9, 1H), 6.24 (d, J = 8.2, 1H), 5.13 (s, 1H), 3.40 (br s, 1H), 1.82 (d, J = 1.6, 3H), 1.79 (d, J = 1.1, 3H), 0.99 (s, 6H); ^{13}C NMR (benzene-d_6) 161.6 (d, J_{C-F} = 256), 159.2 (d, J_{C-F} = 237), 147.6, 146.3, 136.1, 133.8, 132.2 (d, J_{C-F} = 5.4), 130.8, 129.3, 128.4 (d, J_{C-F} = 8.2), 126.8 (d, J_{C-F} = 8.7), 125.2 (d, J_{C-F} = 18), 124.8, 121.1, 119.9, 119.3 (d, J_{C-F} = 8.5), 115.6, 115.3 (d, J_{C-F} = 22), 114.5 (d, J_{C-F} = 23), 109.2 (d, J_{C-F} = 25), 76.0, 50.9, 30.0, 29.2, 24.2, 14.7 (d, J_{C-F} = 3.0). Anal. ($C_{26}H_{23}F_2NO$) C, H, N.

(*R/S*)-9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno[3,4-*f*]quinoline (19). This compound was prepared via general method 5 from compound **6c** (75 mg, 0.23 mmol) to afford 61 mg (68%) of compound **19** as a white solid: ^{1}H NMR (acetone-d_6) 7.58 (d, J = 2.3, 1H), 7.56 (s, 1H), 7.27 (d, J = 8.6, 2H), 7.22 (m, 4H), 7.19 (m, 1H), 6.94 (dd, J = 8.5, 2.5, 1H), 6.94 (s, 1H), 6.83 (d, J = 8.5, 1H), 6.76 (d, J = 8.5, 1H), 5.63 (br s, 1H), 5.46 (d, J = 1.1, 1H), 1.98 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (benzene-d_6) 150.4, 140.4, 133.7, 130.7, 129.3, 129.1, 128.9, 128.6, 128.3, 127.9, 127.6, 127.2, 124.6, 122.7, 120.7, 119.9, 119.7, 115.5, 76.7, 50.9, 30.1, 29.2, 24.2. Anal. ($C_{25}H_{22}ClNO$) C, H, N.

(*R/S*)-5-(4-Bromophenyl)-9-chloro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (20). This compound was prepared via general method 5 from compound **6c** (50 mg, 0.15 mmol) to afford 23 mg (32%) of compound **20** as a white solid: ^{1}H NMR (acetone-d_6) 7.59 (d, J = 2.4, 1H), 7.58 (d, J = 8.3, 1H), 7.42 (d, J = 8.5, 2H), 7.16 (d, J = 8.5, 2H), 6.94 (dd, J = 8.2, 2.4, 1H), 6.92 (s, 1H), 6.84 (d, J = 8.4, 1H), 6.77 (d, J = 8.4, 1H), 5.68 (br s, 1H), 5.48 (s, 1H), 1.98 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (benzene-d_6) 150.0, 146.3, 139.4, 133.9, 132.0, 130.7, 130.0, 129.0, 128.0, 127.9, 127.0, 124.7, 122.9, 122.7, 120.4, 119.8, 119.6, 115.7, 75.9, 50.9, 30.0, 29.2, 24.1. Anal. ($C_{25}H_{21}BrClNO$) C, H, N.

(*R/S*)-9-Chloro-1,2-dihydro-5-(4-methoxyphenyl)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (21). This compound was prepared via general method 5 from compound **6c** (40 mg, 0.12 mmol) to afford 21 mg (41%) of compound **21** as a white solid: ^{1}H NMR (acetone-d_6) 7.59 (d, J = 2.5, 1H), 7.56 (d, J = 8.5, 1H), 7.11 (d, J = 8.7, 2H), 6.94 (d, J = 8.7, 2H), 6.94 (dd, J = 8.5, 2.4, 1H), 6.89 (s, 1H), 6.82 (d, J = 8.5, 1H), 6.75 (m, 1H), 5.61 (br s, 1H), 5.45 (s, 1H), 3.69 (s, 3H), 1.99 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (benzene-d_6) 160.1, 150.5, 146.3, 133.6, 132.3, 131.1, 130.5, 129.4, 128.3, 127.9, 127.6, 127.4, 124.6, 122.6, 120.8, 119.8, 115.5, 114.3, 76.6, 54.8, 50.9, 30.2, 29.2, 24.2. Anal. ($C_{26}H_{24}ClNO_2$) C, H, N.

(*R/S*)-9-Chloro-5-(3-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (22). This compound was prepared via general method 5 from compound **6c** (40 mg, 0.12 mmol) to afford 19 mg (37%) of compound **22** as a white solid: ^{1}H NMR (acetone-d_6) 7.61 (d, J = 2.3, 1H), 7.59 (d, J = 9.0, 1H), 7.25 (m, 4H), 6.95 (m, 2H), 6.85 (d, J = 8.3, 1H), 6.83 (d, J = 7.3, 1H), 5.72 (br s, 1H), 5.50 (s, 1H), 2.00 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (benzene-d_6) 150.0, 146.3, 142.8, 135.1, 134.0, 130.1, 129.8, 128.8, 128.1, 127.9, 127.0, 126.9, 124.7, 122.7, 120.4, 119.9, 119.7, 115.8, 75.8, 50.9, 29.9, 29.3, 24.0. Anal. ($C_{25}H_{21}Cl_2NO$) C, H, N.

(*R/S*)-9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-(3-methylphenyl)-5*H*-chromeno[3,4-*f*]quinoline (23). This compound was prepared via general method 5 from compound **6c** (20 mg, 0.06 mmol) to afford 10 mg (41%) of compound **23** as a white solid: ^{1}H NMR (acetone-d_6) 7.59 (d, J = 2.4, 1H), 7.58 (d, J = 9.1, 1H), 7.19 (m, 2H), 6.95 (m, 3H), 6.92 (s, 1H), 6.83 (d, J = 8.5, 1H), 6.78 (d, J = 8.5, 1H), 5.64 (br s, 1H), 5.51 (s, 1H), 2.20 (s, 3H), 2.05 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (benzene-d_6) 150.5, 146.3, 140.5, 138.3, 133.7, 130.8, 129.7, 129.5, 129.4, 128.8, 127.9, 127.6, 127.2, 126.4, 124.6, 122.7, 120.8, 120.0, 119.7, 115.6, 76.8, 50.9, 30.0, 29.3, 24.2, 21.6. Anal. ($C_{26}H_{24}ClNO$) C, H, N.

(*R/S*)-9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-[3-(trifluoromethyl)phenyl]-5*H*-chromeno[3,4-*f*]quinoline (24). This compound was prepared via general method 5 from compound **6c** (40 mg, 0.83 mmol) to afford 21 mg (38%) of compound **24** as a white solid: ^{1}H NMR (acetone-d_6) 7.61 (d, J = 2.3, 1H), 7.52 (m, 4H), 7.07 (s, 1H), 6.99 (m, 2H), 6.87 (d, J = 8.3, 1H), 6.84 (d, J = 8.3, 1H), 5.73 (br s, 1H), 5.51 (s, 1H), 2.01 (s, 3H), 1.27 (s, 6H); ^{13}C NMR (benzene-d_6) 149.9, 146.4, 141.8, 134.2, 131.9, 131.2 (q, J_{C-F} = 33), 129.7, 129.3, 128.9, 126.8, 126.5, 125.5 (q, J_{C-F} = 8), 125.4 (q, J_{C-F} = 4), 124.7, 124.2 (q, J_{C-F} = 273), 119.9, 119.6, 115.8, 75.6, 50.9, 29.6, 29.4, 24.0. Anal. ($C_{26}H_{21}ClF_3NO$) C, H, N.

(*R/S*)-9-Chloro-5-(3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (25). This compound was prepared via general method 5 from compound **6c** (40 mg, 0.12 mmol) to afford 25 mg (50%) of compound **25** as a white solid: ^{1}H NMR (acetone-d_6) 7.61 (d, J = 2.4, 1H), 7.59 (d, J = 8.4, 1H), 7.29 (m, 1H), 7.04 (d, J = 7.9, 1H), 6.97 (m, 4H), 6.85 (d, J = 8.5, 1H), 6.80 (d, J = 8.5, 1H), 5.69 (br s, 1H), 5.50 (s, 1H), 2.01 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (benzene-d_6) 163.6 (d, J_{C-F} = 246), 150.1, 146.3, 143.3 (d, J_{C-F} = 6.5),

134.0, 130.3 (d, $J_{C-F} = 8.3$), 130.0, 129.0, 128.3, 128.0, 127.9, 126.9, 124.6 (d, $J_{C-F} = 6.5$), 122.7, 120.4, 119.9, 119.7, 115.9 (d, $J_{C-F} = 22$), 115.7, 115.6 (d, $J_{C-F} = 22$), 75.9, 50.9, 39.9, 29.3, 24.0. Anal. ($C_{25}H_{21}ClFNO$) C, H, N.

(*R/S*)-9-Chloro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (26). This compound was prepared via general method 5 from compound **6c** (100 mg, 0.31 mmol) to afford 75 mg (56%) of compound **26** as a white solid: ^{1}H NMR (acetone-d_6) 7.60 (d, $J = 2.4$, 1H), 7.57 (d, $J = 8.5$, 1H), 7.23 (m, 2H), 7.00 (m, 2H), 6.91 (s, 1H), 6.84 (d, $J = 8.2$, 1H), 6.79 (d, $J = 8.5$, 1H), 5.68 (br s, 1H), 5.48 (s, 1H), 2.23 (s, 3H), 1.99 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (acetone-d_6) 150.2, 147.8, 139.8, 136.4, 134.7, 134.4, 132.0, 130.1, 129.5, 128.9, 128.4, 127.6, 127.5, 124.7, 127.4, 124.8, 122.5, 119.9, 119.3, 116.1, 75.9, 51.2, 29.8, 29.3, 24.1, 20.2. Anal. ($C_{26}H_{23}Cl_2NO$) C, H, N.

(*R/S*)-9-Chloro-5-(4-fluoro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (27). This compound was prepared via general method 5 from compound **6c** (40 mg, 0.12 mmol) to afford 22 mg (43%) of Compound **27** as a white solid: ^{1}H NMR (acetone-d_6) 7.59 (d, $J = 2.6$, 1H), 7.57 (d, $J = 8.6$, 1H), 7.12 (d, $J = 8.1$, 1H), 6.99 (m, 1H), 6.96 (dd, $J = 8.2$, 2.4, 1H), 6.90 (s, 1H), 6.84 (d, $J = 8.4$, 1H), 6.77 (d, $J = 8.5$, 1H), 5.68 (br s, 1H), 5.48 (s, 1H), 2.14 (s, 3H), 1.99 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (benzene-d_6) 161.6 (d, $J_{C-F} = 256$), 150.2, 146.3, 135.9 (d, $J_{C-F} = 3.7$), 133.8, 132.2 (d, $J_{C-F} = 5.4$), 130.6, 129.2, 128.3 (d, $J_{C-F} = 8$), 127.9, 127.8, 127.2, 125.3 (d, $J_{C-F} = 18$), 124.7, 122.7, 120.6, 119.8, 119.7, 115.6, 115.3 (d, $J_{C-F} = 22$), 76.1, 50.9, 30.0, 29.2, 24.2, 14.7 (d, $J_{C-F} = 3.6$). Anal. ($C_{26}H_{23}ClFNO$) C, H, N.

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JM9705770