Discovery and Preliminary SAR Studies of a Novel, Nonsteroidal Progesterone Receptor Antagonist Pharmacophore

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A series of 6-aryl-1,2-dihydro-2,2,4-trimethylquinolines was synthesized and tested for functional activity on the human progesterone receptor isoform B (hPR-B) in mammalian (CV-1) cells. The lead compound LG001447 (1,2-dihydro-2,2,4-trimethyl-6-phenylquinoline) was discovered via directed high throughput screening of a defined chemical library utilizing an hPR-B cotransfection assay. Electron-withdrawing substituents at the meta position of the C(6) aryl group afforded substantial improvements in hPR modulatory activity. Several analogues were able to potently block the effects of progesterone in vitro. Two compounds, **10** (LG120753) and **11** (LG120830) with potencies comparable or equal to the steroidal hPR antagonist onapristone (ZK98,299), were demonstrated to act as antiprogestins in vivo after oral administration to rodents. This is the first disclosure of orally active nonsteroidal antiprogestins.

Introduction

We have been engaged in the discovery of nonsteroidal progesterone receptor modulators.[1] To date there have been few classes of nonsteroidal progesterone receptor modulators reported, and none have reached the clinic,[2] although steroidal hPR antagonists, typified by mifepristone[3] (**1**, RU486) and onapristone[4] (**2**, ZK98,-299), have been studied clinically. The potential uses for antiprogestins include therapies for various gynecological diseases,[5] and nonsteroidal antiprogestins might be expected to display novel pharmacology.[6] Using a high throughput hPR-B screen,[7,8] a nonsteroidal antiprogestin lead from Ligand's defined chemicals collection was discovered[9] (**3**, Figure 1). This article discloses preliminary structure−activity relationship studies of a series of nonsteroidal hPR-B antagonists based on the 1,2-dihydro-2,2,4-trimethyl-6-phenylquinoline pharmacophore, **3**. Whereas previous studies of nonsteroidal progesterone receptor antagonists have failed to demonstrate oral activity in vivo,[1,2] two of the novel antiprogestins presented here have definitive antiprogestational effects when dosed orally to rodents.

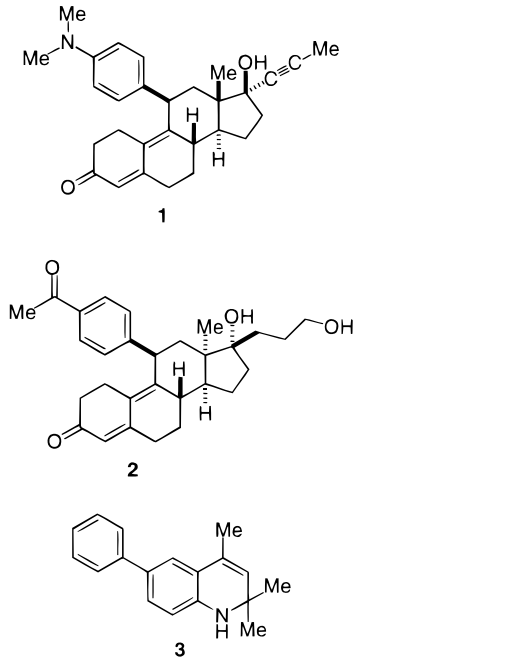

Figure 1. Mifepristone (**1**), onapristone (**2**), and LG001447 (**3**).

Chemistry

The initial lead, LG001447 (**3**), was screened for activity on various intracellular receptors.[10] It was found to exhibit modest (IC_{50} = 783 nM) antagonist activity on hPR-B, and was selected for preliminary SAR investigations. To efficiently examine the effect of C(6)-aryl substitution on the biological activity of this novel pharmacophore, we chose the boronic acid **6** as an advanced intermediate. The synthesis of **6** and **8**−**13** is depicted in Scheme 1. Thus, treatment of 4-bromoaniline (**4**) with acetone and iodine, a process recognized as the Skraup reaction,[11] afforded the dihydroquinoline **5** in modest yield. Protection of N-1 as a *tert*-butylcarbamate followed by lithium−halogen exchange and treatment with trimethylborate afforded the key intermediate, boronic acid **6**. A palladium-catalyzed (Suzuki[12]) cross-coupling of **6** with various aryl bromides **7**, followed by removal of the *t*-butoxycarbonyl group with trifluoroacetic acid afforded the dihydroquinolines **8**−**13** in acceptable overall yields (Scheme 1).

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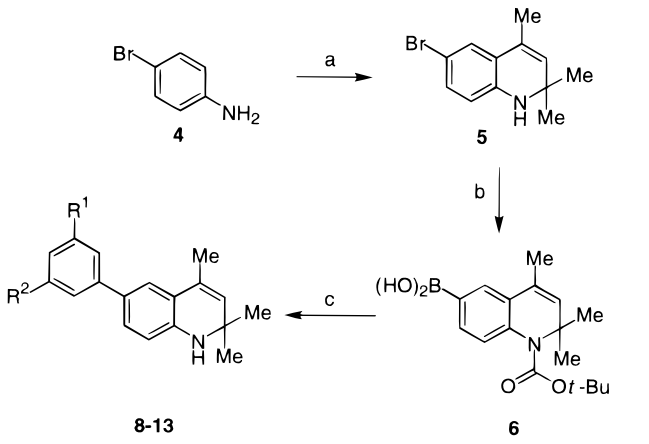
Scheme 1[a]



8: $R^1 = F$, $R^2 = H$ **10**: $R^1 = CN$, $R^2 = H$ **12**: $R^1 = NO_2$, $R^2 = H$
9: $R^1 = R^2 = F$ **11**: $R^1 = CN$, $R^2 = F$ **13**: $R^1 = NO_2$, $R^2 = F$

[a](a) Acetone, iodine (4 mol %), reflux (30%). (b) (i) *n*-BuLi (1.1 equiv), THF, −78 °C, then di-*tert*-butyl dicarbonate (1.5 equiv) (67%); (ii) *t*-BuLi (2.5 equiv), THF, −78 °C, then $(MeO)_3B$ (40−50%). (c) (i) ArBr (**7**) (1 equiv), 50% EtOH/toluene, K_2CO_3 (2 equiv), $(Ph_3P)_4Pd$ (5−10 mol %), reflux; (ii) excess trifluoroacetic acid (30−70% for 2 steps).

Biological Activities

The in vitro biological activities on hPR of **3** and **8**−**13** are depicted in Table 1 along with data for the steroidal hPR antagonists **1** and **2** for comparison. The parent compound **3** was a 783 nM antagonist on hPR-B in the cotransfection assay and displayed moderate (K_i = 133 nM) affinity for hPR-A (entry 3). Although the addition of a C(3′)-fluoro substituent to the C(6)-aryl moiety of **3** did not affect the hPR activity (**8**, entry 4), C(3′)−C(5′)-difluoro substitution resulted in an order of magnitude improvement of activity in both the functional and binding assays (**9**, entry 5). The monosubstituted C(3′)-cyano compound **10** (entry 6) was a potent antagonist on hPR-B; the addition of a C(5′)-fluoro substituent to **10** had only a small effect on in vitro activity (**11**, entry 7). A C(3′)-nitro group also imparted potent hPR-B antagonist activity (**12**), while the C(5′)-fluoro-C(3′)-nitro compound **13** had comparable in vitro activity. Notably, the binding affinity of **13** for baculovirus-expressed hPR-A (K_i = 5 nM) was comparable to that of the natural hormone, progesterone (K_i = 3 nM).

A limitation to the use of the steroidal PR antagonists mifepristone and onapristone is their significant cross-reactivities on hAR and hGR. These novel nonsteroidal PR antagonists displayed limited cross-reactivity with hGR and hAR; LG120753 (**10**) and LG120830 (**11**) were 5- to 7-fold less potent on hAR and greater than 20-fold less potent on hGR, hER, and hMR. These results indicate favorable cross-reactivity profiles for this pharmacophore compared with those of the known steroids (Table 2).

The in vitro antiprogestational effects of several of these nonsteroidal hPR antagonists were then verified using animal models. A definitive in vivo assay for progestational effects is the implantation assay. Implantation is the process by which the blastocyst becomes attached to the endometrium of the uterus, and this process is regulated by progestins.[13] In this model, oral dosing of antiprogestins such as mifepristone or onapristone blocks implantation and, hence, the establishment of pregnancy.[14] The effects of oral administration of onapristone (**2**) to mated females is depicted in Figure 2. Although doses of 0.5 or 1.0 mg/mouse of **2** had little effect, a dose of 2.5 mg/mouse completely blocked implantation in these animals.

Compounds **10** (LG120753) and **11** (LG120830) were also tested in this assay and the results are depicted in Figures 3 and 4, respectively. Oral administration of **10** blocked implantation in a dose-dependent manner (Figure 3). The 100% efficacious dose of 5.0 mg/mouse indicates that **10** is 2-fold less potent than **2** in vivo. Compound **11** (Figure 4) was 100% efficacious at 2.5 mg/mouse, which is equivalent in potency and efficacy to onapristone (**2**). Although **10** and **11** are 10-fold less potent than **2** in vitro (Table 1), the comparable activity in vivo may be due to favorable pharmacokinetic or pharmacodynamic characteristics. This is the first definitive demonstration of in vivo antiprogestational activity by a nonsteroidal hPR ligand following oral administration. Additionally, this is the first report of a nonsteroidal compound that has been shown to have activity equipotent to a known leading steroidal antiprogestin. Although no overt signs of toxicity were observed, hepatomegaly was noted in the test animals, especially in the high-dose groups.[15]

To verify that the antifertility effects of **11** were due to its antiprogestational activity, an infertility reversal experiment was performed (Figure 5). Co-administration of **11** (2.5 mg/mouse orally) and the known steroidal progestin R5020[16] (1.0 mg/animal subcutaneously) resulted in a 100% pregnancy rate, demonstrating that, like mifepristone (**1**), the antifertility effects of **11** could be reversed by progestin supplementation. A similar experiment was performed testing compound **10** combined with R5020. The results (not shown) were comparable to that of compound **11**. These results verify that the antifertility effects of **10** and **11** are due to antiprogestational activity rather than toxicity.

Conclusion

These studies demonstrate for the first time that nonsteroidal compounds can act as antagonists of the human progesterone receptor with activities comparable to those of known steroidal hPR antagonists. Due to the novel structure class differing from the steroid core, it has been shown that these compounds are favorably less active on the other steroid receptors (hAR, hER, hMR, and hGR) thus making them more selective for the target hPR. Since one of the major problems with steroid therapies is cross-reactivity, we view this as an important feature of these compounds.

It has been demonstrated that the in vitro effects can be verified using a known rodent model. This is the first time a new, nonsteroidal pharmacophore has demonstrated oral activity in vivo as an antagonist on the progesterone receptor. Further, the pharmacological effects of one of these nonsteroidal hPR antagonists (**11**, LG120830) was shown to be equivalent to onapristone (**2**) in a mouse antifertility model using oral administration.[17]

The antifertility effects of **10** and **11** were completely reversed by co-administration of the steroidal progestin

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

				hPR-B activity		
entry	ligand	R^1	R^2	IC_{50}[b] (nM)	efficacy[c] (%)	hPR-A activity, K_i[b] (nM)
1	**1**	mifepristone		0.30 ± 0.04	99 ± 0	1.1 ± 0.32
2	**2**	onapristone		2.2 ± 0.4	95 ± 1	18 ± 33
3	**3**	H	H	783 ± 162	72 ± 4	133 ± 71
4	**8**	F	H	750	94	182
5	**9**	F	F	79 ± 43	85 ± 6	10 ± 2
6	**10**	CN	H	38 ± 6	81 ± 2	19 ± 3
7	**11**	CN	F	30 ± 4	82 ± 3	10 ± 1
8	**12**	NO_2	H	42 ± 6	83 ± 1	20 ± 2
9	**13**	NO_2	F	70 ± 18	78 ± 2	5 ± 2

[a] Cotransfection experimental values represent at least triplicate determinations. [b] Values are in nM, mean ± SEM, N ≥ 2. If no SEM is noted, the value is from a single determination. IC_{50} values represent the concentration required to give half maximal inhibition for that ligand. [c] Efficacy expressed as percent relative to maximal inhibition (e.g, no agonist) = 100%.

Table 2. Antagonist Cross-Reactivities of Nonsteroidal PR Antagonists and Steroidal Antagonist Standards on hAR, hER, hGR, and hMR[a]

	hAR		hER		hGR		hMR	
ligand	potency (nM)	efficacy (%)	potency (nM)	efficacy (%)	potency (nM)	efficacy (%)	potency (nM)	efficacy (%)
mifepristone (**1**)	5 ± 2	7 ± 2	>1000	40 ± 7	0.8 ± 0.1	98 ± 1	>1000	77 ± 5
onapristone (**2**)	269 ± 57	93 ± 4	>1000	27 ± 4	27 ± 4	100 ± 0	>1000	34 ± 9
LG120753 (**10**)	227 ± 63	86 ± 2	>1000	<20	>1000	7 ± 18	>1000	94 ± 1
LG120830 (**11**)	210[a]	88[a]	>1000	<20	>1000	<20	>1000	80 ± 2

[a] Antagonist efficacies were determined as a function (%) of maximal inhibition in the presence of an EC_{50} concentration of DHT, estradiol, dexamethasone, or aldosterone for hAR, hER, hGR, and hMR, respectively; potencies = IC_{50} values. Values represent the mean ± SEM of at least two independent experiments except where indicated (a = 1).

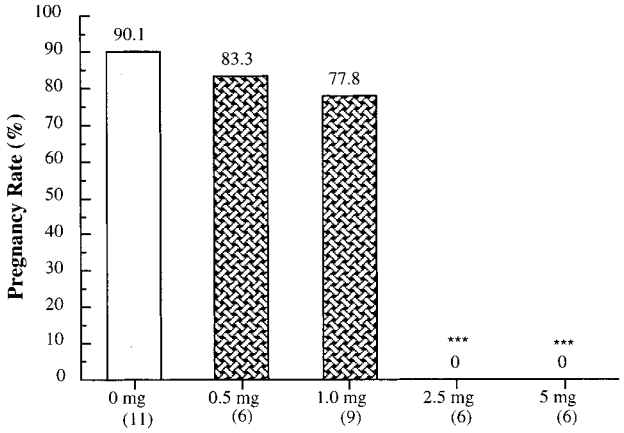


Figure 2. Effect of **2** (mg/mouse) on mouse implantation when given orally once daily for three days (day 2−4 of pregnancy). Virgin female mice were caged with fertile males overnight and examined the next morning for vaginal plugs (day 1 of pregnancy). Mice (n ≥ 6 per dose group) were treated orally with **2** at 32, 46, and 80 h post coitus. Control animals (n = 11) received an equivalent volume of sesame oil. Necropsies were performed on Day 8 post coitus, and the number of implantation sites was recorded. ***P < 0.001 compared to oil-treated group.

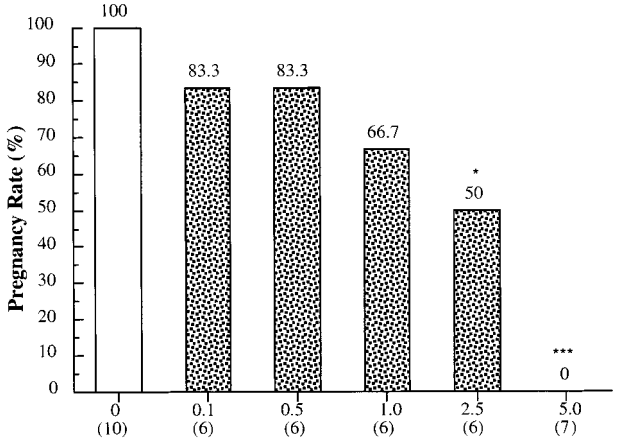


Figure 3. Effect of **10** (mg/mouse) on mouse implantation when given orally once daily for three days (day 2−4 of pregnancy). Virgin female mice were caged with fertile males overnight and examined the next morning for vaginal plugs (day 1 of pregnancy). Mice were treated orally with **10** (0.1, 0.5, 1.0, 2.5, or 5.0 mg/animal) between day 2 and day 4 of pregnancy. Control animals (n = 10) received an equivalent volume of sesame oil. Autopsies were carried out at day 8 of pregnancy, and the number of implantation sites was recorded. Number of animals per treatment group is given in parentheses. * = P < 0.05; *** = P < 0.001 vs control.

R5020, decisively demonstrating that the in vivo activities of **10** and **11** are specifically directed against progesterone-mediated reproductive processes. These studies provide the basis for the discovery of new nonsteroidal progesterone receptor modulators to address unmet clinical needs in the areas of female reproductive oncology.

Experimental Section[18]

6-Bromo-1,2-dihydro-2,2,4-trimethylquinoline (5). A 2-L round-bottom flask equipped with a magnetic stir bar and a reflux condenser attached to a Soxhlet apparatus was charged with 4-bromoaniline, **4**, (100 g, 581 mmol), catechol (6.0 g, 39 mmol), iodine (5.0 g, 20 mmol), and acetone (1.5 L). The Soxhlet apparatus contained oven-dried 4 Å sieves. The mixture was warmed to reflux for 48 h at which point it was cooled to room temperature. Celite (350 mL) was added, followed by evaporation of the solvent to afford a powder that was then applied to a silica gel column for purification. The eluting solvent was 3% ethyl acetate in hexanes. Material from the column was further purified by recrystallization in warm hexanes to afford the pure product, **5** (28.7 g, 20%): ^{1}H

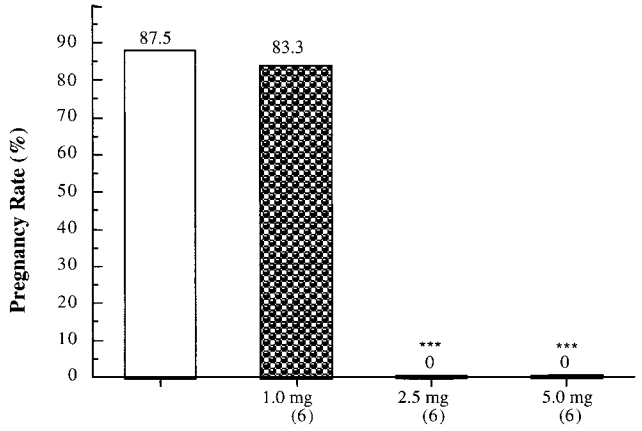


Figure 4. Effect of **11** (mg/mouse) on mouse implantation when given orally once daily for three days (day 2−4 of pregnancy). Virgin female mice were caged with fertile males overnight and examined the next morning for vaginal plugs (day 1 of pregnancy). Mice ($n \geq 6$ per dose group) were treated orally with **11** at 32, 46, and 80 h post coitus. Control animals ($n = 8$) received an equivalent volume of sesame oil. Necropsies were performed on day 8 post coitus, and the number of implantation sites was recorded. ***P < 0.001 compared to oil-treated group.

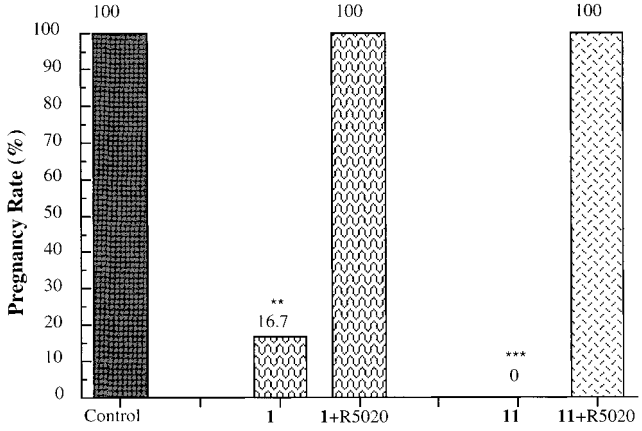


Figure 5. Reversal of mifepristone (**1**) or LG120830 (**11**) induced infertility by co-administration of R5020 for three days (day 2−4 of pregnancy). Virgin female mice were caged with fertile males overnight and examined the next morning for vaginal plugs (day 1 of pregnancy). Mice ($n = 6$ per dose group) were treated orally with **1** (0.5 mg/animal) or **11** (2.5 mg/animal) between day 2 and day 4 of pregnancy, accompanied by three daily subcutaneous injections of R5020 (1.0 mg/animal). Control animals ($n = 6$) received an equivalent volume of sesame oil. Necropsies were carried out on day 8 of pregnancy, and the number of implantation sites was recorded. ** = P < 0.01; ***P < 0.01 vs control.

NMR (400 MHz, acetone-d_6) 7.06 ppm (d, $J = 4.0$, 1H), 6.99 (dd, $J = 8.0$, 4.0, 1H), 6.42 (d, $J = 8.0$, 1H), 5.36 (s, 1H), 5.28 (br s, 1H) 1.92 (d, $J = 4.0$, 3H), 1.24 (s, 6H).

6-Bromo-1-*tert*-butyl-carboxycarbonyl-1,2-dihydro-2,2,4-trimethylquinoline. An oven-dried 250-mL round-bottom flask equipped with a magnetic stirrer and an airtight nitrogen inlet was charged with **5** (4.04 g, 16.0 mmol). The white crystals were dissolved in 40 mL THF (anhydrous). The clear solution was cooled to −78 °C with constant stirring. A thermocouple was used to monitor the internal reaction temperature. *n*-Butyllithium (11.2 mL, 17 mmol, 1.5 M) was added slowly by syringe over a period of 15 min (internal temperature was maintained between −70 °C and −65 °C) turning the reaction mixture bright yellow. The reaction was allowed to continue stirring at −75 °C for an additional 15 min. The reaction was warmed to 0 °C, and the di-*tert*-butyldicarbonate (3.85 g, 18 mmol) was added in one portion. Note: a significant exotherm was observed upon the addition of the dicarbonate (∼0−12 °C). The reaction was monitored by TLC (50% ethyl acetate/methylene chloride) as it warmed to room temperature until all of the intermediate (*tert*-butylcarboxycarbonyl-1,2-dihydro-2,2,4-trimethylquinoline) had been consumed (3−5 h). The reaction mixture was quenched with saturated ammonium chloride (100 mL) and partitioned between ethyl acetate (100 mL). The organic layer was rinsed two times with saturated ammonium chloride (50 mL each). The organic layer was rinsed once with brine (100 mL). The aqueous layers were combined and back-extracted with methylene chloride (75 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The crude mixture was purified by flash chromatography (400 mL silica, 2% ethyl acetate/hexane); 3.8 g oil, 67%: ^{1}H NMR (400 MHz, acetone-d_6) 7.30 ppm (s, 1H), 7.28 (d, $J = 8.0$, 1H), 7.11 (d, $J = 8.0$, 1H), 5.60 (s, 1H), 2.00 (s, 3H), 1.49 (s, 9H), 1.48 (s, 6H).

(1-*tert*-butoxycarbonyl-1,2-dihydro-2,2,4-trimethyl-6-quinolinyl)-boronic Acid (6). A 25-mL round-bottom flask, equipped with a magnetic stir bar, was charged with 6-bromo-1-*tert*-butylcarboxycarbonyl-1,2-dihydro-2,2,4-trimethylquinoline (3.77 g, 11 mmol) under nitrogen. The oil was dissolved in 11 mL THF (anhydrous) and cooled to −78 °C. *tert*-Butyllithium (12.6 mL, 21 mmol, 1.7 M) was added by syringe over a period of 10 min (maintaining the temperature below −70 °C) turning the reaction mixture from pale yellow to bright yellow. The reaction was allowed to continue at −75 °C until all of the starting material had been consumed as judged by TLC (15% ethyl acetate/hexane). At that point, trimethyl borate (30 mmol) was added by syringe over 5−10 min (temperature between −70 °C and −65 °C). After the reaction was monitored to completion, the product mixture was quenched with saturated ammonium chloride (200 mL). After the addition of ethyl acetate (200 mL), the mixture was partitioned into two phases. The organic phase was rinsed two times with saturated ammonium chloride (100 mL) and once with brine (100 mL). The combined aqueous layers were back-extracted with ethyl acetate (100 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The crude mixture was applied to a small column containing 200 mL silica and 10% ethyl acetate/hexane. The higher R_f impurities were eluted with 2 L of 10% ethyl acetate/hexane. The boronic acid, **3**, was eluted off the column with 500 mL of ethyl acetate followed by 750 mL of ethanol to provide 1.48 g (44%) of **6**: ^{1}H NMR (400 MHz, acetone-d_6) 7.73 ppm (d, $J = 1.2$, 1H), 7.66 (dd, $J = 8.0$, 1.2, 1H), 7.13 (d, $J = 8.0$, 1H), 5.49 (s, 1H), 2.01 (d, $J = 1.6$, 3H), 1.50 (s, 9H), 1.46 (s, 6H).

General Method. Biaryl Suzuki Coupling of an Aryl Bromide with the 6-Quinolinylboronic Acid (6). A 10-mL recovery flask equipped with a magnetic stir bar was charged with the aryl bromide (1.0 equiv) which was then diluted with toluene (0.1 M). Tetra*kis*(triphenylphosphine) palladium (1 mol percent), **6** (1.0 equiv in 0.1 M solution of ethanol), and 2.0 M potassium carbonate (2 mol percent) were added to the reaction flask sequentially under a nitrogen atmosphere. A reflux condenser was fitted to the flask. The cloudy, reddish solution was stirred rapidly and heated to reflux for about 4 h until the starting material had been completely consumed as judged by TLC (15% ethyl acetate/hexane). The product mixture was then cooled to room temperature and quenched with saturated ammonium chloride (4−5 mL). Ethyl acetate (5 mL) was used to partition the mixture. The organic layer was rinsed two times with saturated ammonium chloride (5 mL each). The aqueous layers were back-extracted with ethyl acetate (5 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The crude mixture was isolated and applied to a column (200 mL silica, 10% ethyl acetate/hexane).

The purified material was charged to a 10-mL recovery flask. Methylene chloride was added so that the residue was completely dissolved (0.1 mL to 0.3 mL). The mixture was cooled to 0 °C, and trifluoroacetic acid was added quickly by syringe (∼40 equiv), turning the solution from colorless to dark

green/black. The progress of the reaction was monitored by TLC (15% ethyl acetate/hexane) over 1 h until all the starting material had been consumed.

3-Bromo-5-fluorobenzonitrile. A 1-L round-bottom flask equipped with a magnetic stir bar was charged with 1,3-dibromo-5-fluorobenzene (44.0 g, 173 mmol), DMF (268 mL), pyridine (28 mL), and copper(I) cyanide (15.5 g, 173 mmol) under nitrogen. A reflux condenser was attached to the flask. The green, cloudy mixture was stirred at reflux for 3 h. Once lower R_f impurities were observed, the reaction was allowed to cool to room temperature. The reaction mixture was quenched with 200 mL of ether, and a precipitate formed in the dark solution. The precipitate was gravity-filtered through Celite. The filtrate was rinsed three times with ether (100 mL/50 g bromide). The isolated solution was added to a separatory funnel. The organic layer was washed with a 2:1 mixture of water and concentrated ammonium hydroxide (200 mL), followed by saturated ammonium chloride solution (2 × 200 mL) and saturated sodium bicarbonate (200 mL). The aqueous layers were back-rinsed with ether (3 × 100 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The product, 3-bromo-5-fluorobenzonitrile, was purified by flash column chromatography (30 mL of silica, hexane) followed by recrystallization from hexane: ^{1}H NMR (acetone-d_6) 7.81 (s, 1H), 7.73 (dd, J = 8.4, 1.9, 1H), 7.65 (dd, J = 8.5, 2.0, 1H).

1,2-Dihydro-6-phenyl-2,2,4-trimethylquinoline (3). In a 300-mL pressure tube, a solution of 4-aminobiphenyl (2.40 g, 14.2 mmol) in acetone (130 mL) was treated with iodine (0.3 g). The tube was sealed and heated to 90 °C for 16 h. The reaction mixture was allowed to cool to room temperature, concentrated, and purified by silica gel chromatography (hexane/EtOAc, 40:1) to afford 2.35 g (66%) **3** as a white solid, mp 103−104 °C: ^{1}H NMR (acetone-d_6) 7.56 (d, J = 1.8, 1H), 7.43 (m, 3H), 7.23 (m, 2H), 6.58 (d J = 8.1, 1H), 5.36 (s, 1H), 5.20 (br s, 1H), 2.04 (d, J = 1.3, 3H), 1.28 (s, 6H); ^{13}C NMR (acetone-d_6) 144.8, 142.6, 129.5, 129.0, 127.7, 126.7, 126.6, 122.7, 122.0, 113.9, 52.5, 31.4, 18.9; IR (salt plate) 3383.7, 2973.1. Anal. ($C_{18}H_{19}N$) C, H, N.

1,2-Dihydro-6-(3-fluorophenyl)-2,2,4-trimethylquinoline (8). This compound was prepared according to the general method. From **6** (68.0 mg, 0.21 mmol) and commercially available 3-fluorobromobenzene (40.1 mg, 0.18 mmol, Lancaster) was isolated **8** (20.0 mg, 29%) which was purified by reverse phase HPLC (ODS column, 97% methanol/water, 3.0 mL/min, retention time = 9.14 min): ^{1}H NMR (acetone-d_6) 7.32 (m, 5H), 6.95 (m, 1H), 6.58 (d, J = 8.1, 1H), 5.37 (s, 1H), 5.31 (br s, 1H), 2.04 (d, J = 1.1, 3H), 1.27 (s, 6H); ^{13}C NMR (acetone-d_6) 164.2 (d, J_{C-F} = 242.8), 145.3, 145.2 (d, J_{C-F} = 7.8), 131.2, 131.1, 129.6, 128.9, 127.9, 127.9, 127.8, 122.8, 122.4, 122.4, 122.0, 113.9, 113.1, 113.0, 112.9, 112.8, 52.5, 31.5, 18.9. Anal. ($C_{18}H_{18}FN$) C, H, N.

6-(3,5-Difluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (9). This compound was prepared according to the general method. From **6** (59.7 mg, 0.19 mmol) and commercially available 3,5-difluorobromobenzene (36.2 mg, 0.19 mmol, Lancaster) was isolated **9** (7.0 mg, 10%) which was purified by reverse phase HPLC (ODS column, 97% methanol/water, 3.0 mL/min): ^{1}H NMR (acetone-d_6) 7.35 (d, J = 2.2, 1H), 7.28 (dd, J = 8.2, 2.1, 1H), 7.20 (ddd, J = 13.0, 4.3, 2.1, 2H), 6.80 (tt, J = 9.1, 2.1, 1H), 6.57 (d, J = 8.3, 1H), 5.43 (s, 1H), 5.37 (br s, 1H), 2.04 (d, J = 1.1, 3H), 1.28 (s, 6H); ^{13}C NMR (acetone-d_6) 164.5 (dd, J_{C-F} = 245.5, 14.5), 146.4 (t, J_{C-F} = 9.3), 145.9, 129.7, 128.9, 127.9, 126.6, 122.8, 121.9, 113.8, 109.1, 109.0 (d, J_{C-F} = 25.7), 108.9, 101.2 (t, J_{C-F} = 25.0), 52.6, 31.6, 18.8. Anal. ($C_{18}H_{17}F_2N$) C, H, N.

6-(3-Cyanophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (10). This compound was prepared according to the general method. From **6** (900 mg, 3 mmol) and commercially available 3-bromobenzonitrile (515 mg, 3 mmol, Lancaster) was isolated **10** (268 mg, 34%) which was purified by recrystallization from hexanes, mp 88−92 °C: ^{1}H NMR (acetone-d_6) 7.93 (d, J = 1.6, 1H), 7.86 (ddd, J = 7.2, 2.1, 1.8, 1H), 7.55 (m, 2H), 7.38 (d, J = 2.1, 1H), 7.29 (dd, J = 8.4, 2.3, 1H), 6.59 (d, J = 8.4, 1H), 5.37 (s, 2H), 2.04 (s, 3H), 1.28 (s, 6H); ^{13}C NMR (acetone-d_6) 145.5, 130.8, 130.5, 129.8, 129.7, 129.6, 128.8, 127.8, 126.7, 122.7, 121.9, 119.6, 113.9, 113.5, 52.5, 31.5, 18.8; IR (salt plate): 3371.8, 2965.3, 2917.8, 2226.9. Anal. ($C_{19}H_{18}N_2$) C, H, N.

6-(3-Cyano-5-fluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (11). This compound was prepared according to the general method from **6** (3.9 g, 12 mmol) and 3-bromo-5-fluorobenzonitrile (2.5 g, 12 mmol). The product was purified by recrystallization from hexane to afford the product (2.2 g, 53%), mp 127−129 °C: ^{1}H NMR (acetone-d_6) 7.83 (t, J = 1.1, 1H), 7.67 (dt, J = 10.2, 2.2, 1H), 7.42 (d, J = 2.2, 1H), 7.38 (m, 1H), 7.35 (dd, J = 9.0, 2.9, 1H), 6.58 (d, J = 8.3, 1H), 5.52 (br s, 1H), 5.38 (s, 1H), 2.04 (d, J = 1.2, 3H), 1.28 (s, 6H); ^{13}C NMR (acetone-d_6) 163.7 (d, J_{C-F} = 247.0), 146.3, (d, J_{C-F} = 26.6), 129.7, 128.8, 128.1, 126.2 (d, J_{C-F} = 3.0), 125.4 (d, J_{C-F} = 2.7), 123.0, 121.9, 118.6, 117.7 (d, J_{C-F} = 22.0), 116.2, (d, J_{C-F} = 25.0), 114.8, (d, J_{C-F} = 10.5), 113.9, 113.9, 52.7, 31.6, 31.6, 18.9; IR (salt plate) 3377.3, 2965.0, 2919.1, 2858.2, 2230.6. Anal. ($C_{19}H_{17}FN_2$) C, H, N.

1,2-Dihydro-6-(3-nitrophenyl)-2,2,4-trimethylquinoline (12). This compound was prepared according to the general method from compound **6** (19.4 mg, 0.06 mmol) and commercially available 3-nitrobromobenzene (12.3 mg, 0.06 mmol). The product (2.9 mg, 16%) was isolated and purified by flash column chromatography (75 mL silica, hexane to 5% ethyl acetate/hexane) followed by reverse phase flash column chromatography (50 mL ODS, 80% methanol/water): ^{1}H NMR (acetone-d_6) 8.34 (t, J = 1.8, 1H), 8.00 (ddd, J = 25.2, 8.3, 2.1, 1H), 7.60 (t, J = 8.0, 1H), 7.38 (d, J = 2.1, 1H), 7.32 (dd, J = 8.4, 2.2, 1H), 6.60 (d, J = 8.3, 1H), 5.42 (br s, 1H), 5.38 (s, 1H), 2.04 (s, 3H), 1.29 (s, 6H): ^{13}C NMR (acetone-d_6) 149.8, 145.8, 144.3, 132.6, 130.7, 129.7, 128.8, 128.0, 126.6, 122.8, 122.0, 120.9, 120.7, 114.0, 52.6, 31.6, 18.9. Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

1,2-Dihydro-6-(5-fluoro-3-nitrophenyl)-2,2,4-trimethylquinoline (13). This compound was prepared according to the general method from compound **6** (140 mg, 0.44 mmol) and 3-nitro-5-fluoroiodobenzene (117 mg, 0.44 mmol). The product (95.0 mg, 69%) was isolated and purified by flash column chromatography (150 mL silica, hexane to 20% acetone/hexane) followed by second flash column chromatography (100 mL silica, hexane to 20% ethyl acetate/hexane), mp 167−169 °C: ^{1}H NMR (acetone-d_6) 8.21 (t, J = 1.7, 1H), 7.78 (m, 2H), 7.43 (d, J = 2.1, 1H), 7.37 (dd, J = 8.4, 2.3, 1H), 6.60 (d, J = 8.3, 1H), 5.55 (br s, 1H), 5.40 (s, 1H), 2.04 (s, 3H), 1.29 (s, 6H); ^{13}C NMR (acetone-d_6) 163.7 (d, J_{C-F} = 246.8), 150.6 (d, J_{C-F} = 10.6), 146.3 (d, J_{C-F} = 8.9), 129.8, 128.8, 128.2, 125.3, 123.0, 122.0, 119.0 (d, J_{C-F} = 22.3), 116.8 (d, J_{C-F} = 2.6), 114.0, 108.2 (d, J_{C-F} = 26.5), 52.7, 52.6, 31.7, 31.6, 18.9; IR (salt plate) 3398.1, 2966.9. Anal. ($C_{18}H_{19}FN_2O_2$) C, H, N.

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(18) For general experimental conditions see ref 1c.

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