Synthesis and Biological Activity of a Novel Series of Nonsteroidal, Peripherally Selective Androgen Receptor Antagonists Derived from 1,2-Dihydropyridono[5,6-*g*]quinolines

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A new nonsteroidal antiandrogenic pharmacophore has been discovered using cell-based cotransfection assays with human androgen receptor (hAR). This series of AR antagonists is structurally characterized by a linear tricyclic 1,2-dihydropyridono[5,6-*g*]quinoline core. Analogues inhibit AR-mediated reporter gene expression and bind to AR as potently as or better than any known AR antagonists. Several analogues also showed excellent in vivo activity in classic rodent models of AR antagonism, inhibiting growth of rat ventral prostate and seminal vesicles, without accompanying increases in serum gonadotropin and testosterone levels, as is seen with other AR antagonists. Investigations of structure−activity relationships surrounding this pharmacophore resulted in molecules with complete specificity for AR, antagonist activity on an AR mutant commonly observed in prostate cancer patients, and improved in vivo efficacy. Molecules based on this series of compounds have the potential to provide unique and effective clinical opportunities for treatment of prostate cancer and other androgen-dependent diseases.

Introduction

Prostate cancer is currently the most commonly diagnosed nondermatologic cancer among United States males, with an estimated incidence of 984 000 cases in the U.S. alone and 200 000 new cases diagnosed each year.[1] Approximately one in five males will be diagnosed with this life-threatening disease by the age of 60. While historically both surgical and pharmaceutical methods have been utilized to address this disease, recent powerful advances in the area of early detection through monitoring of prostate-specific antigen (PSA)[2] levels have created a shift in strategy for treatment of prostate cancer toward drug therapy and away from surgical measures.

The male sexual accessory organs, such as the prostate and seminal vesicles, play important roles in reproductive function.[3] These glands are stimulated to grow and are maintained in size and secretory function by the continued actions of testosterone (T) and dihydrotestosterone (DHT). Testosterone is the androgen produced by the Leydig cells (testis) in the greatest proportion (95%) under the control of pituitary-luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and is converted to the more active DHT within the prostate by 5α-reductase. These endogenous hormones exert their effects at the level of the androgen receptor (AR) which, as a member of the intracellular receptor (IR) superfamily, acts as a ligand-dependent transcription factor.[4] Small molecules with the ability to block this transcriptional activation represent attractive clinical targets.[5]

Prostatic tumor cells also require T for their continued growth. Although 20% of the total prostatic DHT in the rat and about 40% in 65-year-old men is of adrenal origin, adrenal DHT is not sufficient to maintain normal prostate and seminal vesicle growth and function, and castration without concomitant adrenalectomy leads to almost complete involution of these glands.[6] In castrated prostate cancer patients, however, there is emerging evidence that the adrenal glands produce steroid precursors that are converted to T in the prostate, thereby exacerbating the disease.[7] For this reason, administration of AR antagonists either following castration or in combination with luteinizing hormone-releasing hormone (LHRH) agonists has become the standard in treatment of prostate cancer.

Over the past two decades, AR antagonists have been demonstrated clinically to constitute effective therapy for the treatment of prostate cancer, including cyproterone acetate (**1**),[8] flutamide (**2a**),[9] and bicalutamide (Casodex, **3**).[10] These and other agents have been the subject of extensive clinical investigations for use either alone as single-agent therapy[11] or in combination with a LHRH agonist.[12] Additionally, there exists significant clinical opportunity to address other androgen-dependent conditions, such as benign prostatic hypertrophy (BPH),[13] hirsutism in women,[14] alopecia (male pattern baldness),[15] and acne[16] through receptor-mediated inhibition of androgen-regulated gene transcription.

Of the AR antagonists currently marketed or undergoing clinical trials, none achieves effective therapeutic results without suboptimal pharmacokinetic properties or substantial efficacy-limiting side effects. These side effects in part reflect central effects of increases in

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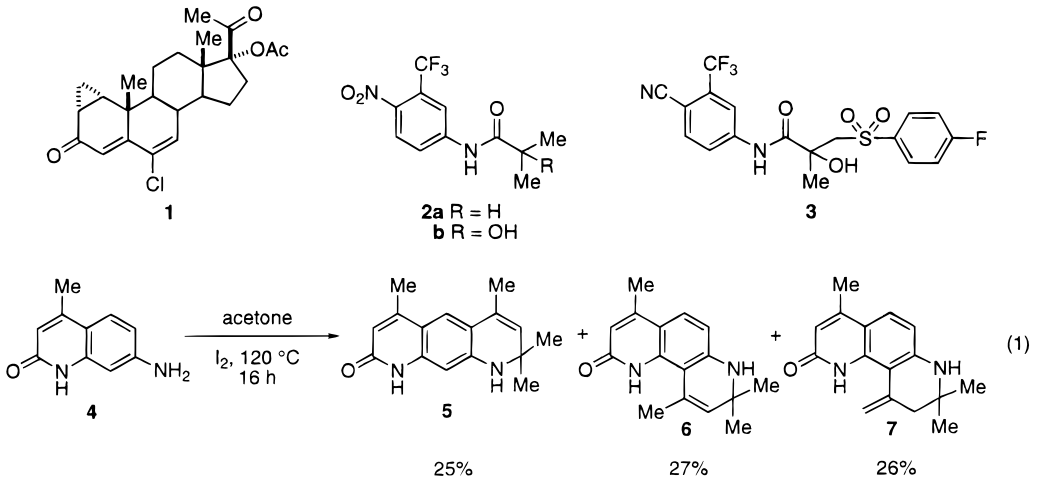


circulating concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and dihydrotestosterone (DHT) induced by these drugs. Additionally, severe gynecomastia, nausea, diarrhea, and liver toxicity[17] have been observed in many patients, and the predominance of prostate cancer patients undergoing antiandrogen therapy ultimately become resistant to antiandrogen therapy.[18] It is postulated that emergence of this resistance is linked to mutations in the AR, which subsequently recognize most antagonists as agonists.[19] The specific mechanisms by which these latter side effects are manifested are as yet unclear. Novel agents which selectively interact with the hAR to inhibit cell growth and differentiation processes downstream in male sexual accessory tissues may have the potential to provide the therapeutic benefit of AR antagonism without these liabilities.

In connection with our long-standing interest in the discovery of structurally novel modulators of sex-steroid receptor activation[20] using cotransfection assays,[21] intensive screening efforts resulted in the discovery of a novel antagonist pharmacophore for the hAR. A cross-reactivity screening campaign in support of another internal discovery program led to the observation of AR antagonist activity in the linear tricyclic pyridonodihydroquinoline compound **5**. Through further screening efforts, it was discovered that **5** inhibited dihydrotestosterone-stimulated reporter gene expression in an hAR cotransfection assay with excellent potency (IC_{50} = 43 nM) but showed poor selectivity for AR, exhibiting nearly equivalent antagonist activity when screened against hPR-B. Further investigation into analogues of **5**, possessing a linear tricyclic core resulted in substantially more potent effects on AR, much greater selectivity for AR over PR (many with 1000-fold or greater selectivity), and good oral activity in standard rodent models for AR antagonism. Compounds described herein are based on an entirely novel pharmacophore for modulation of AR-mediated gene transcription.

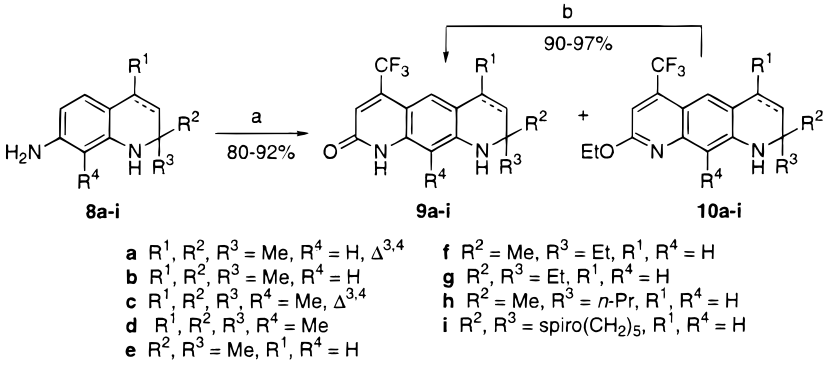
Chemistry

Quinolines and dihydroquinolines are well-studied bicyclic systems in the area of heterocyclic chemistry, with powerful synthetic tools for their construction.[22] Our initial synthetic efforts to access linear tricyclic pyridonoquinolines such as **5** were adapted from early synthetic work in this area and involved execution of the Skraup[23] reaction (acetone, I_2) on aromatic amines. The Skraup cyclizations carried out on these particular substrates, such as carbostyril 124 (**4**, eq 1), suffered from very low yields and extremely poor regioselectivities and usually required high temperatures and sealed tube conditions. It was generally observed that the undesired, biologically inactive angular tricyclic regioisomer such as **6** was produced in great excess to the desired linear regioisomer such as **5**, which was typically isolated in very low yield as a minor product.

A more practicable synthetic strategy was developed whereby each terminal ring was successively built up around a central aryl core fragment through sequential cyclization reactions. Installment of the 2-pyridone ring in the final step using the Knorr[24] reaction allowed for completely regioselective cyclization of diamine substrates **8** and a β-keto ester (Scheme 1), with the favorable electronic donation of the dihydroquinoline nitrogen facilitating the incipient C−C bond formation. Under the standard conditions employed for the Knorr cyclization (ethyl 4,4,4-trifluoroacetoacetate, $ZnCl_2$, EtOH, reflux), ethoxypyridine isomers **10** were also obtained, typically comprising 20−40% of the reaction mixture. These byproducts were easily transformed (essentially quantitatively) into the desired 2-pyridone products **9** by treatment with 57% HI.

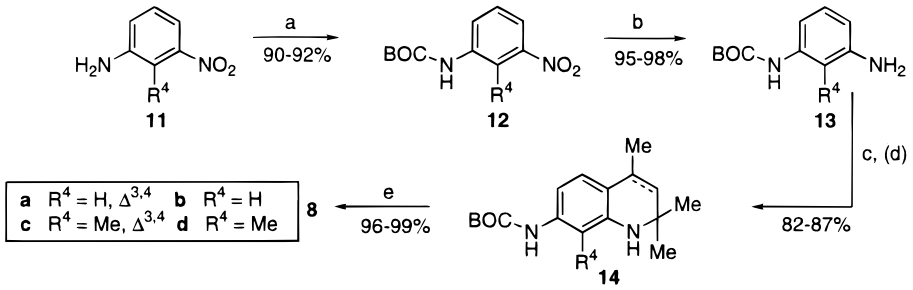
The syntheses of diamines **8a**−**d** and **8e**−**i** as precursors for the Knorr reaction are outlined in Schemes 2 and 3, respectively. The commercially available nitroanilines **11** (R = H or Me) were used as the starting materials to access analogues with 4-methyl substitution and 3,4-unsaturation (Scheme 2). Protection of the aniline nitrogen using di-*tert*-butyl dicarbonate and 4-(*N*,*N*-dimethylamino)pyridine (DMAP), followed by catalytic hydrogenation of the nitro group, affords the desired substrates for a completely regioselective Skraup cyclization reaction of the BOC-differentiated diamine **13**. After optional saturation of the 3,4-olefin by catalytic hydrogenation, deprotection of the N-BOC group is accomplished using trifluoroacetic acid (TFA) in CH_2Cl_2 to yield diamines **8a**−**d**. Diamines **8e**−**i** were synthesized in a conceptually similar fashion by copper chloride-catalyzed cyclization[25] of aniline with 1,1-disubstituted propargyl acetates **15** to yield dihydroquinolines **17** (Scheme 3). Catalytic hydrogenation of the 3,4-olefin, followed by nitration and subsequent

Scheme 1[a]



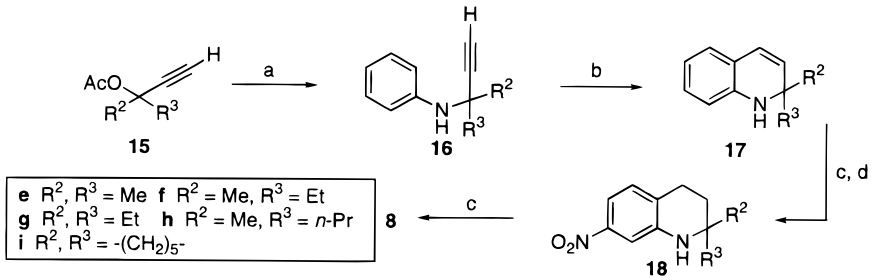
[a] (a) Ethyl 4,4,4-trifluoroacetoacetate, $ZnCl_2$, EtOH, reflux, 5 h; (b) 57% aqueous HI, 60 °C, 3 h.

Scheme 2[a]



[a] (a) BOC_2O, THF, DMAP, 0 °C to rt, 12 h; (b) H_2, 10% Pd/C, EtOH/EtOAc (1:1), 6 h; (c) I_2, acetone, $MgSO_4$, 4-*t*-Bu-catechol, reflux, 8 h; (d) H_2, 10% Pd/C, EtOH/EtOAc (1:1), 6 h; (e) CF_3CO_2H, CH_2Cl_2, 3 h.

Scheme 3[a]



[a] (a) Aniline, CuCl, NEt_3, THF, reflux; (b) CuCl, THF, reflux; (c) H_2, 10% Pd/C, EtOH/EtOAc (1:1), 6 h; (d) HNO_3, H_2SO_4, 0 °C.

reduction of the nitro group, afforded diamine Knorr precursors **8e**−**i**.

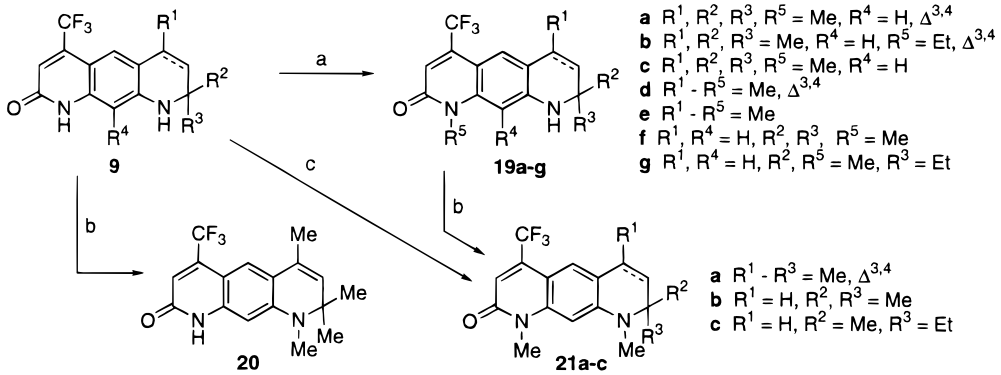
Selective alkylation of either nitrogen of AR antagonist analogues **9** was accomplished in a straightforward fashion by treatment with sodium hydride in THF, followed by iodoalkane (9 N) to give alkyl amides **19a**−**g**, or by reductive amine alkylation using paraformaldehyde/HOAc/sodium cyanoborohydride[26] (1 N) to give **20** (Scheme 4). Alternatively, tandem methylation of amide/amines **9** was accomplished using excess KOH with iodomethane in DMF to give **21a**−**c** directly.

The more synthetically complex 3- and/or 4-alkyl-substituted analogues **29a**−**f** were prepared from a common bicyclic intermediate (Scheme 5). Protection of dihydroquinoline **17** with a BOC group provided intermediate **22**, which then underwent regioselective hydroboration and subsequent benzylic oxidation with activated manganese dioxide to give BOC-protected 4-oxotetrahydroquinoline **23**. Nitroquinolines **28a**−**f** were obtained from standard nitration of intermediates **25**, **26**, and **27**. These intermediates were prepared from the common intermediate ketone **23** by one of two methods: alkyl-Grignard additions to the 4-ketone (superior results were obtained using the corresponding organocerium reagents),[27] followed by benzylic alcohol reduction employing TFA-catalyzed hydrogenation over 10% palladium on carbon afforded intermediates **25**; enolate alkylation of **23** gave 3-substituted ketones **24** prior to either alkyl-Grignard addition or reduction to quinoline intermediates **26** or **27**, respectively. Standard nitro reduction of **28** and Knorr reaction of the corresponding diamines afforded 3- and/or 4-substituted analogues **29a**−**f**.

Tetracyclic analogues **33** and **34** were obtained through the intermediacy of tricyclic amine **32**, prepared in three steps from aniline and chloro-substituted propargyl acetate **30** in a manner similar to that used for synthesis of **9e**−**i** (Scheme 6).

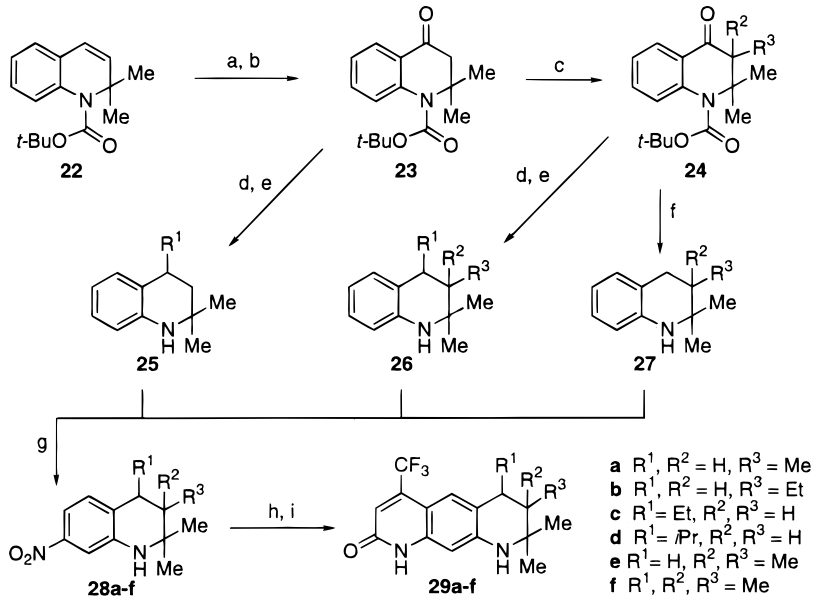
Limitations in the synthetic routes used for the preparation of analogues in this series included the inability to efficiently access 3,4-unsaturated analogues (such as **36**, eq 2) other than those bearing the 2,2,4-trimethyldihydroquinoline ring introduced through the Skraup protocol. This was in part due to the failure of attempts to nitrate dihydroquinoline **17** without prior reduction of the 3,4-olefin, as well as the failure of the

Scheme 4[a]



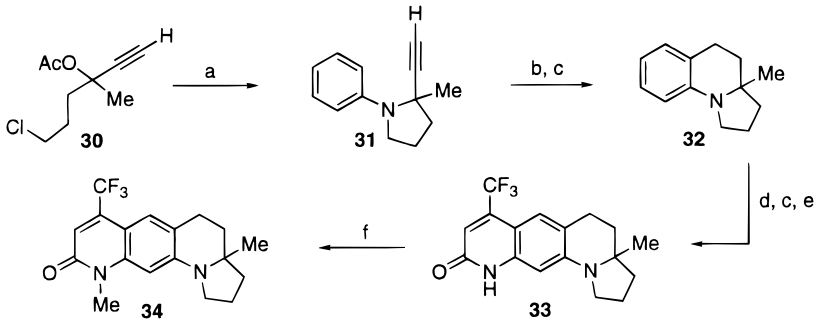
[a] (a) NaH, DMF, 0 °C, then R^5I, rt, 8 h; (b) $(CH_2O)_n$, $NaCNBH_3$, HOAc, rt, 6 h; (c) KOH, DMF, MeI, rt, 16 h.

Scheme 5[a]



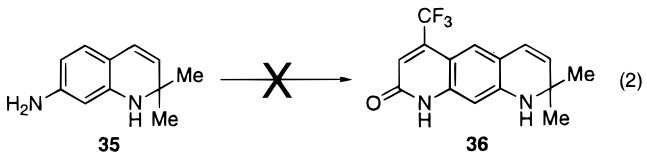
[a] (a) 9-BBN, THF, reflux; then H_2O_2, NaOH, rt; (b) MnO_2, CH_2Cl_2, reflux; (c) NaH, DMF, 0 °C; then R^2I, rt; (d) R^1MgX, $CeCl_3$, THF, 0 °C; (e) H_2, 10% Pd/C, EtOH, TFA; (f) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, 100 °C, sealed tube; (g) HNO_3, H_2SO_4, 0 °C; (h) H_2, 10% Pd/C, EtOAc/EtOH (1:1) rt; (i) ethyl 4,4,4-trifluoroacetoacetate, $ZnCl_2$, EtOH, reflux.

Scheme 6[a]



[a] (a) Aniline, CuCl, NEt_3, THF, reflux; (b) CuCl, THF, reflux; (c) H_2, 10% Pd/C, EtOH/EtOAc (1:1), 6 h; (d) HNO_3, H_2SO_4, 0 °C; (e) ethyl 4,4,4-trifluoroacetate, $ZnCl_2$, PhH, 4 Å molecular sieves, reflux, 8 h; (f) NaH, DMF, 0 °C, then MeI, rt, 12 h.

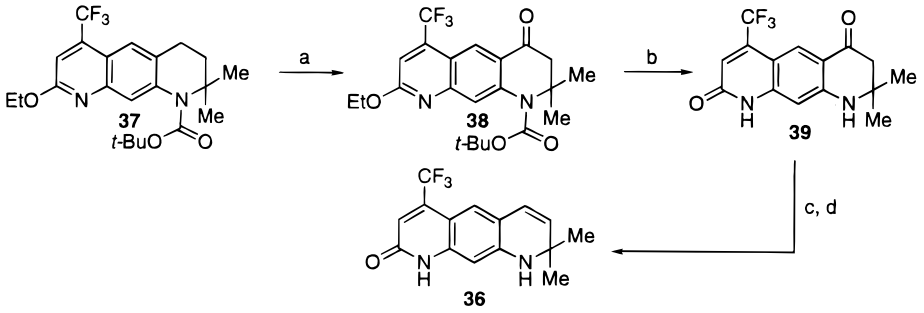
Knorr reaction with diamine **35** (eq 2), prepared through a very low-yielding route using a CuCl-mediated cyclization of monoprotected diamine **13**.



(2)

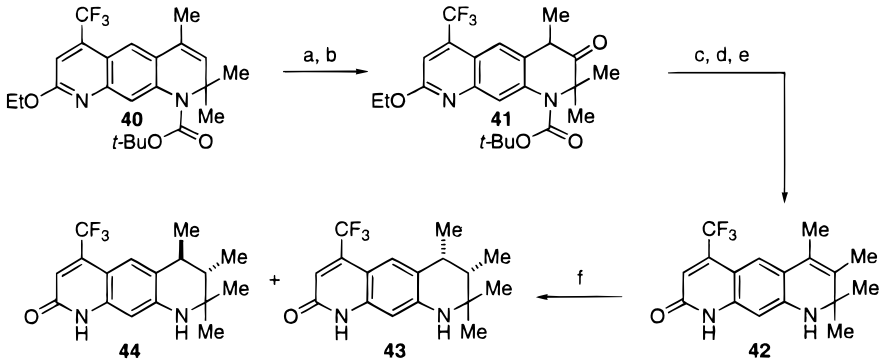
Access to these 3,4-unsaturated analogues was achieved by installation of unsaturation at the 3,4-positions after construction of the tricyclic core (Scheme 7). The 2-ethoxypyridine moiety present in **10e**, the major byproduct of Knorr cyclization reaction to prepare analogue **9e**, served as an excellent protective group for further chemistry to functionalize the benzylic 4-position. This 2-alkoxypyridine moiety could readily be

Scheme 7[a]



[a] (a) PCC, CH_2Cl_2, rt; (b) 57% aqueous HI, 60 °C, 3 h; (c) $NaBH_4$, MeOH, 0 °C; (d) *p*-TsOH, PhH, 65 °C.

Scheme 8[a]



[a] (a) BH_3·THF, THF, rt; then H_2O_2, NaOH; (b) PDC, CH_2Cl_2, rt; (c) MeMgBr, THF, 0 °C; (d) *p*-TsOH, PhH, rt; (e) 57% aqueous HI, 60 °C, 3 h; (f) Et_3SiH, TFA, 1,2-dichloroethane, reflux, 9 h.

installed by O-selective alkylation of pyridones **9** using CsF and the appropriate alkyl halide.[28] Protection of the amine portion of **10e** was accomplished using the procedure previously used for preparation of bicyclic intermediate **22**, yielding carbamate **37**. Benzylic oxidation to the 4-oxo compound **38** was achieved using PCC.[29] Both protective groups were simultaneously removed using 57% HI to afford ketoamide **39**. The 3,4-olefin was then introduced by a two-step procedure involving sodium borohydride reduction followed by *p*-TsOH-catalyzed dehydration to yield **36**.

Synthesis of a 3,4-dimethyl analogue with 3,4-unsaturation also required functionalization after preconstruction of the linear tricyclic core using intermediate **40**, derived from protection of **10a** (Scheme 8). Regioselective hydroboration of **40** and subsequent oxidative workup, followed by PCC oxidation of the resultant diastereomeric mixture of alcohols, afforded 3-ketone **41**. Methyl Grignard addition, followed by acid-catalyzed dehydration and hydrolysis of the ethoxypyridine moiety, gave 3,4-dimethyl analogue **42**, which was subjected to TFA-catalyzed triethylsilane reduction of the 3,4-olefin to give a diastereomeric mixture of **43** and **44**, separable only by preparative HPLC.

In Vitro and in Vivo Biological Activity

Cotransfection and Binding Assays. The AR modulatory activity of analogues in this series as well as that of known AR antagonists was studied experimentally in a cellular background both through ligand-dependent inhibition of DHT-stimulated reporter gene (luciferase) induction using the cotransfection assay and a whole-cell receptor binding assay. These results are summarized in Table 1. Cross-reactivity data obtained in antagonist cotransfection assays with human progesterone receptor (hPR-B) are also included. Compounds in this series were found to posses no intrinsic AR agonist activity. Activity on other IRs including human glucocorticoid receptor (hGR), human mineralocorticoid receptor (hMR), and human estrogen receptor (hER) were also determined, and there was found to be no agonist or antagonist response induced by the analogues in this series.[30]

Immature Castrated Rat Assay. The androgen-induced growth of the ventral prostate (VP) of immature male rats was measured as a quantitative end point for AR antagonist effects, as this male sexual accessory organ is among the tissues most sensitive to modulation by androgens, this sensitivity to changes in androgen concentrations being greatest before puberty. Weight gain and loss in VP reflects changes in cell number (DNA content) and cell mass (protein content) in response to serum androgen concentrations.[31] Therefore, measurement of organ wet weight reflects the bioactivity of AR antagonists. Daily injections of 1 mg/kg testosterone propionate (TP) to immature castrated rats achieved a steady serum T level within physiologic range, and caused dose-dependent increases in VP weight. Compounds from the present series of AR antagonists were tested for activity against exogenous TP and compared to the known AR antagonists **1**, **2a**, and **3**. Test compounds were administered daily simultaneously with 1 mg/kg of TP (the ED80) for 3 days. Each compound significantly inhibited the TP-mediated increases in VP weight (Figure 1); results for **1**, **2a**, and **3** are in agreement with published studies.

Mature Intact Rat Assay. Because there is no blunting of the effects of endogenous hormones, the

Table 1. hAR Antagonist and hPR-B Antagonist Activity in Cotransfected CV-1 Cells and Binding Affinities for hAR in Transiently-Transfected COS-1 Cells[a]

compound	hAR		hPR-B		hAR binding
	IC_{50}[b] (nM)	efficacy[c] (%)	IC_{50} (nM)	efficacy (%)	K_i[b] (nM)
1	26 ± 23	48 ± 6	>10000	12 ± 8	14 ± 5
2b[d]	15 ± 2	83 ± 1	2013 ± 194	90 ± 2	27 ± 8
3	157 ± 35	78 ± 3	1819 ± 245	88 ± 2	117 ± 35
RU-486	5 ± 2	75 ± 2	0.18 ± 0.02	96 ± 1	22 ± 1
5	36 ± 6	89 ± 2	109 ± 24	83 ± 3	62 ± 18
9a	28 ± 4	70 ± 3	49 ± 11	62 ± 5	115 ± 24
9b	26 ± 4	65 ± 5	231[e]	86	76 ± 1
9c	23 ± 3	82 ± 2	3346 ± 879	88 ± 1	82 ± 4
9d	22 ± 4	78 ± 2	3726 ± 371	74 ± 4	85 ± 32
9e	27 ± 5	74 ± 2	330e	80	26 ± 5
9f	23 ± 3	66 ± 3	543 ± 215	91 ± 2	29 ± 13
9g	27 ± 5	75 ± 2	2708[e]	81	102 ± 25
9h	42 ± 7	65 ± 3	1144[e]	86	69 ± 10
9i	35 ± 6	85 ± 2	1828[e]	94	9 ± 2
19a	34 ± 6	89 ± 2	233 ± 69	88 ± 3	81 ± 17
19b	692 ± 32	95 ± 2	1763[e]	55	670 ± 467
19c	73 ± 29	81 ± 5	585 ± 41	98 ± 1	46 ± 10
19d	2413 ± 786	74 ± 8	4395[e]	68	874 ± 178
19e	31 ± 10	70 ± 4	2931[e]	79	40 ± 12
19f	36 ± 5	87 ± 3	1239[e]	74	56 ± 14
19g	48 ± 4	85 ± 1	3277[e]	73	69 ± 28
20	156 ± 26	87 ± 2	1678[e]	55	695 ± 432
21a	46 ± 11	86 ± 1	136 ± 88	91 ± 2	39 ± 23
21b	19 ± 3	81 ± 3	2200[e]	85	17 ± 4
21c	24 ± 4	62 ± 6	1105[e]	92	10 ± 3
29a	30 ± 5	81 ± 2	348[e]	89	73 ± 11
29b	46 ± 12	83 ± 2	2334[e]	82	251 ± 45
29c	27 ± 7	49 ± 7	274 ± 122	74 ± 5	54 ± 11
29d	159 ± 83	66 ± 4	3162[e]	59	650 ± 264
29e	83 ± 19	88 ± 2	876 ± 68	98 ± 1	189 ± 89
29f	57 ± 6	74 ± 2	362[e]	93	358 ± 86
33	325 ± 68	86 ± 6	>10000[e]	11	169 ± 88
34	27 ± 5	85 ± 2	398[e]	84	78 ± 13
36	58 ± 22	71 ± 2	390 ± 138	81 ± 7	86 ± 51
42	68 ± 4	84 ± 3	393 ± 152	65 ± 9	268 ± 110
43	164 ± 62	83 ± 2	310[e]	95	456
44	7042	20	735[e]	92	151 ± 35

[a] Cotransfection assay experiment values represent at least triplicate determinations. [b] Values represent mean ± SEM. IC_{50} values represent the concentration of ligand required to give half-maximal inhibition in the presence of DHT at its EC_{50}. [c] Efficacies were determined as a function of maximal inhibition. [d] 2-Hydroxyflutamide (**2b**) was used for in vitro assays, as this is the active metabolite of **2a** in vivo. [e] Assayed once.

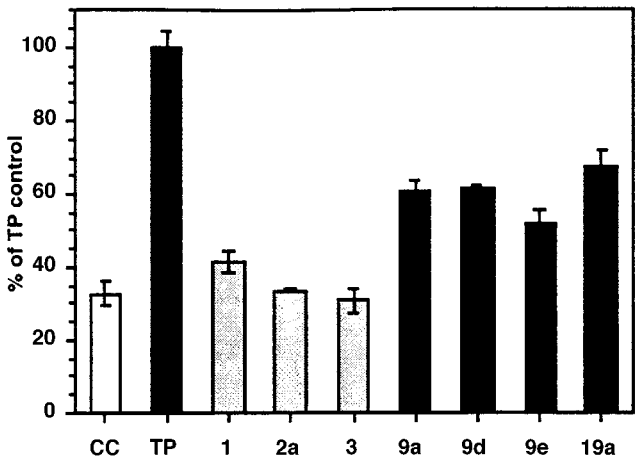


Figure 1. Effects of AR antagonists **1**, **2a**, **3**, **9a**,**d**,**e**, and **19a** (30 mg/kg po, once a day for 3 days) on ventral prostate wet weight in castrated immature rats. CC = castrated control; TP = testosterone propionate (1 mg/kg sc once a day for 3 days) treated control.

normal intact male rat model provides a more stringent test for AR antagonists compared to the immature castrated rat model. In the central nervous system, gonadal T acts to inhibit the pulsatile release of hypothalamic LHRH, which results in decreased production and secretion of pituitary LH and FSH, i.e., a negative feedback control for gonadal androgen production.[32] Therefore, the hypothalamus, pituitary gland, testis, and gonadal steroid-sensitive end organs form a closed homeostatic loop. Each component of this reproductive hormonal axis functions in a closely regulated manner to maintain the appropriate concentrations of circulating gonadal steroids required for normal male sexual development and behavior.

When AR antagonists are administered to intact rats, they act peripherally to modulate AR actions at the target organs, but can also interact with AR in the brain (hypothalamus and pituitary) to block the feedback control system, leading to overproduction of LH and FSH, which in turn stimulate Leydig cells to produce significantly higher amounts of T. Compounds **2a**, **3**, **9a**, and **9e** (20 or 40 mg/kg daily for 2 weeks) were studied for their capacity to antagonize endogenous androgens in this model, which allows the measurement of multiple end-points including increases in VP and seminal vesicle (SV) weights (Figure 2), and alterations in regulatory feedback mechanisms as reflected by changes in concentrations of LH and T (Figure 3).

Although **2a** completely blocked the accessory sex organ growth induced by exogenous T in castrated rats,

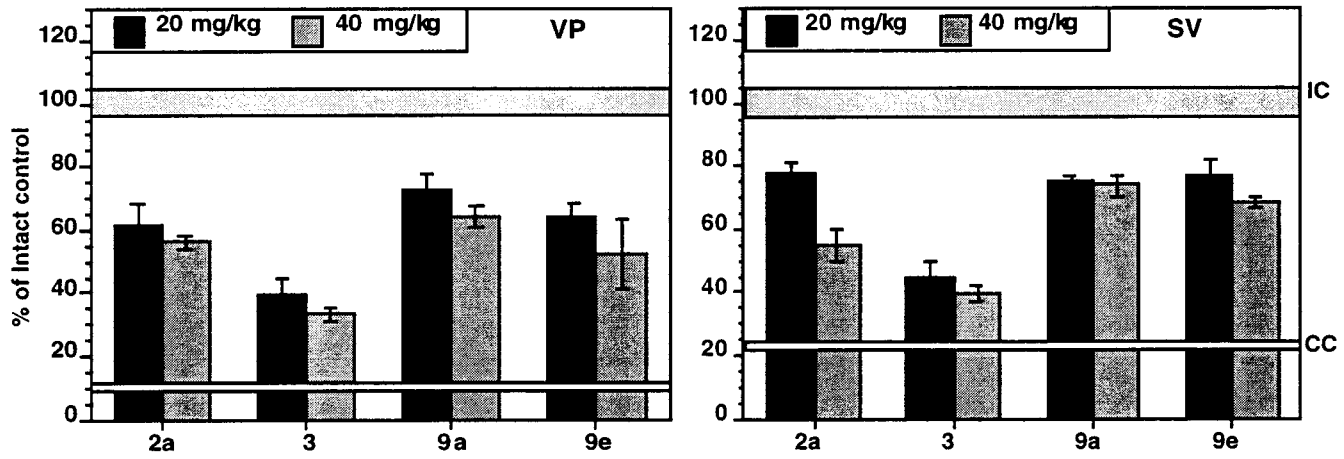


Figure 2. Effects of AR antagonists **2a**, **3**, and **9a**,**e** (20 mg/kg or 40 mg/kg po, once a day for 2 weeks) on ventral prostate (VP) and seminal vesicle (SV) wet weight in intact mature rats. IC = intact control values; CC = castrated control values. The width of the IC and CC lines represent the average standard errors for control animals.

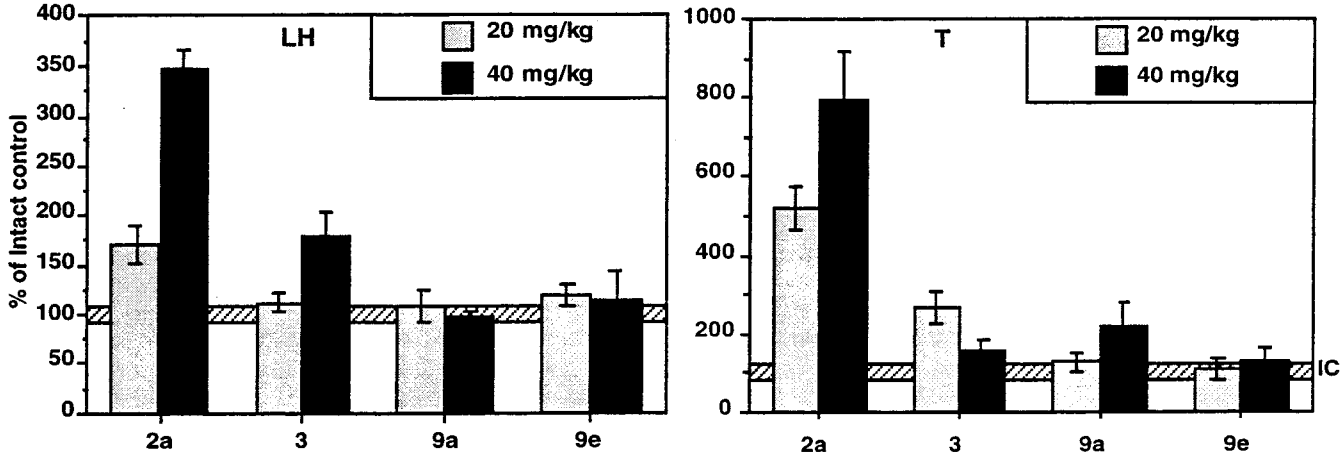


Figure 3. Effects of AR antagonists **2a**, **3**, and **9a**,**e** (20 mg/kg or 40 mg/kg po, once a day for 2 weeks) on serum luteinizing hormone (LH) and testosterone (T) levels in intact mature rats. IC = intact control values. The width of the IC line represents the average standard error for control animals.

it caused only a partial decrease in sex organ weights in intact rats. Bicalutamide (**3**) was more potent than **2a** in decreasing organ growth in intact animals, due at least in part to its peripheral selectivity, exhibiting only limited penetration of the blood−brain barrier, resulting in at most 2-fold increases in serum LH and T.[33]

Oral administration of **9a** or **9e** caused significant inhibition of VP and SV growth comparable to that following **2a** administration. Effects on organ weights occurred without alteration of serum concentrations of LH and T. **2a** induced approximately 2−3-fold increases in serum LH concentrations, accompanied by 5−8-fold increases in serum T concentrations. These results are consistent with data described for **2a** in preclinical and clinical studies.[34] By contrast with **2a** and **3**, neither **9a** nor **9e** caused any statistically relevant change in serum hormone concentrations.

Discussion of Structure−Activity Relationships

The initial lead molecule **5** suffered from extremely poor solubility properties and also failed to achieve blood levels in rodents sufficient to elicit a pharmacologic response. The use of ethyl 4,4,4-trifluoroacetoacetate as the β-keto ester component in the Knorr cyclization reaction allowed installation of a trifluoromethyl group at the 6-position in place of the methyl group in **5**, which greatly improved solubility and pharmacokinetic properties. Additionally, the increased electrophilicity imparted to the trifluoromethyl ketone carbonyl of this β-keto ester enhanced the Knorr reaction efficiency with this substrate, and analogues with a 6-trifluoromethyl substituent were generally pursued. Saturation of the 3,4-double bond in these analogues, while not significantly affecting in vitro activity, greatly improved in vivo efficacy. It was generally observed that alkylations in the "southern" region of these analogues (positions 1, 9, or 10) had a profound effect on biological activity. In most cases, methylation of the pyridone nitrogen (position 9, **19a**−**g**) had little effect on receptor binding or cotransfection assay activity with AR, although this change tended to confer greater selectivity for AR over PR. Analogues bearing a 10-methyl group (**9c**, **9d**) enhanced this selectivity, as well as conferring antagonist activity on several AR mutants, including that found in the LNCaP cell line.[35] However, these changes offered no significant enhancement of in vivo activity, and were typically characterized by reduced animal exposure levels.[36] Alkylation at the quinoline nitrogen (position 1) curiously had an inconsistent effect. Alone

(**20**, **33**), this change caused the loss of an order of magnitude in AR antagonist cotransfection assay activity, whereas in combination with 9-methylation (**21a**−**c**), in vitro activity was fully restored. These nitrogens and adjacent regions are likely to play a critical role in terms of receptor interactions, through participation in hydrogen bonding with residues in the hormone binding domain of the hAR. The receptor was quite tolerant of varying alkyl substitution at positions 2, 3, and 4, although geminal substitution at C-2 was essential for AR antagonist activity, and 4-position alkyls generally resulted in diminished in vivo exposure levels. None of the compounds in this series exhibited AR agonist activity in vitro or in vivo.

Conclusion

Through ongoing efforts characterizing the SAR within this lead series, we have identified a series of analogues which act as AR antagonists and represent attractive pharmaceutical opportunities. Most analogues are easily synthesized (five or fewer steps from inexpensive starting materials), novel non-steroids exhibiting antagonist potencies of 10−30 nM in the presence of 5 nM DHT in cell-based reporter assays with hAR, and comparable whole-cell binding K_i values. These analogues are also highly selective for AR and are up to 1000-fold more potent on AR than any other IR in cotransfection assays and binding studies. Additionally, some analogues (**9c**,**d**, **19a**,**b**, **20**) have the ability to inhibit transcriptional activation of a mutant AR commonly found in hormone-refractory prostate tumor cells (LNCaP),[36] which responds to some AR antagonists as if they were agonists. Many of the active members in this series (e.g., **9a**−**e**) are orally active as inhibitors of male accessory sex organ growth in both castrated and intact rats, some with oral in vivo efficacy equivalent to known agents. Furthermore, **9e** exhibited in vivo efficacy superior to flutamide (**2a**) as an inhibitor of intact male rat sexual accessory organ growth. This oral in vivo efficacy occurs with complete peripheral selectivity, causing no accompanying increase in serum concentrations of LH or T, as compared with the 8−10-fold increase seen with **2a** administration and the 2-fold increase reported to occur with bicalutamide (**3**) administration. This may reflect greater selectivity for peripheral as opposed to central ARs relative to known AR antagonists, providing pharmacological profiles distinct from those of existing agents. We believe this series of compounds demonstrates significant potential for the development of therapeutically useful AR antagonists. Guided by these initial findings, further studies are in progress, directed at the discovery of analogues that possess superior pharmacological efficacy and pharmacokinetic properties, while maintaining the desirable receptor and tissue selectivities observed with this novel pharmacophore.

Experimental Section

General Chemical Procedures. Proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with $CDCl_3$ as the solvent at 400 and 100 MHz, respectively (Brüker AC 400), except where otherwise noted. Chemical shifts are given in parts per million (ppm) downfield from internal reference tetramethylsilane in δ-units, and coupling constants (J values) are given in hertz (Hz). Selected data are reported in the following manner: chemical shift, multiplicity, coupling constants, and assignment. Infrared (IR) spectra were recorded on a Mattson Galaxy Series 3000 FT infrared spectrometer. Liquid samples were measured as neat films on NaCl plates; solid samples were measured as KBr pellets. The reported frequencies are given in reciprocal centimeters (cm^{-1}) with the following relative intensities: s (strong, 70−100%), m (medium, 40−70%), w (weak, 20−40%), br (br). Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY; Galbraith Laboratories, Inc., Knoxville, TN; or Quantitative Technologies, Inc., Whitehouse, NJ. Melting points were taken on an Electrothermal IA9100 digital apparatus and are uncorrected. Boiling points are reported uncorrected. Kügelrohr distillations were performed using a Büchi GKR-51 apparatus and reported boiling points correspond to uncorrected oven air bath temperatures. Flash column chromatography refers to the method of Still[37] using Merck 230-400 mesh silica gel. Gradient elution refers to applying the compound as a solution in hexanes to the hexanes-equilibrated column and then eluting with progressively more polar hexanes/EtOAc solutions. Analytical thin layer chromatography (TLC) was performed using Merck 60-F-254 0.25 mm precoated silica gel plates. Compounds were visualized using ultraviolet light, iodine vapor, or cerium molybdate/sulfuric acid/methanol. Preparative thin layer chromatography (PTLC) was performed using Merck 60-F-254 0.50 or 1.00 mm precoated silica gel plates. High-performance liquid chromatography (HPLC) was performed on a Beckman System Gold 126 chromatograph. Column: 4.6 × 250 mm Beckman Ultrasphere ODS. Preparative HPLC was performed on a Waters Delta Prep 4000. The detector wavelength was set to 254 nm. Ethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled directly prior to use from sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2), benzene, and toluene were dried and stored under nitrogen over 4 Å molecular sieves. Organic amines were distilled from CaH_2 and stored over solid KOH pellets under nitrogen. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of common inorganic salts used in workups are aqueous solutions. All moisture-sensitive reactions were carried out using oven-dried or flame-dried round-bottomed (rb) flasks and glassware under an atmosphere of dry nitrogen.

1,2-Dihydro-2,2,4,6-tetramethyl-8-pyridono[5,6-*f*]quinoline (5). A solution of carbostyril 124 (4, 500 mg, 2.8 mmol) and iodine (40 mg, 0.16 mmol, 6.0 mol %) in acetone (25 mL) was heated in a 70-mL sealed tube at 120 °C for 16 h. The mixture was then cooled to room temperature, and the solvent was removed under reduced pressure. The residue was then dissolved in 50 mL of EtOAc, and the organic solution was washed with 30 mL water, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) afforded 175 mg (25%) of the desired tricyclic lactam as a pale yellow solid (mp 282−284 °C), along with the isomers **6** and **7**, obtained in 27% and 26% yield, respectively. **Data for 1,2-dihydro-2,2,4,6-tetramethyl-8-pyridono[5,6-*g*]quinoline (5):** ^{1}H NMR 11.50 (br s, CON*H*), 7.24 (s, 1H, 5-H), 6.34 (s, 1H, 7-H), 6.23 (s, 1H, 10-H), 5.37 (s, 1H, 3-H), 2.41 (s, 3H, 6-CH_3), 2.04 (s, 3H, 4-CH_3), 1.29 [s, 6H, 2-C(CH_3)$_2$]; ^{13}C NMR 165.0, 149.8, 146.5, 140.3, 129.2, 127.6, 119.1, 118.5, 114.9, 112.5, 97.2, 52.4, 31.8, 19.3, 18.9; IR (KBr) 2966, 2918, 1658, 1641, 1425, 1257. Anal. ($C_{16}H_{18}N_2O$) C, H, N. **Data for 1,2-dihydro-2,2,4,8-tetramethyl-6-pyridono[6,5-*e*]quinoline (6):** ^{1}H NMR (acetone-d_6) 7.50 (d, 1H, J = 8.1, 10-H), 7.33 (s, 1H, 7-H), 6.52 (d, 1H, J = 8.1, 9-H), 6.10 (s, 1H, 3-H), 6.09 (s, 1H, 1-H), 2.79 (s, 3H, 8-CH_3), 2.46 (s, 3H, 4-CH_3) 1.37 [s, 6H, 2-C(CH_3)$_2$]. **Data for 1,2,3,4-tetrahydro-2,2,8-trimethyl-4-methylene-6-pyridono-[6,5-*e*]quinoline (7):** ^{1}H NMR (acetone-d_6) 7.35 (d, 1H, J = 8.9, 10-H), 6.47 (d, 1H, J = 8.9, 9-H), 6.03 (s, 1H, 7-H), 5.49 and 5.33 (2s, 2 × 1H, 4-CH_2), 2.36 and 2.34 (AB q, 2H, J_{AB} = 11.2, 3-H), 2.35 (s, 3H, 8-CH_3), 1.26 [s, 6H, 2-C(CH_3)$_2$].

1-(*tert*-Butyloxycarbamoyl)-3-nitrobenzene (12). To a

flame-dried 500-mL rb flask containing 3-nitroaniline **11a** (20.0 g, 145 mmol) in 150 mL of THF was added di-*tert*-butyl dicarbonate (31.6 g, 145 mmol, 1.00 equiv), and the mixture was cooled to 0 °C. 4-(*N*,*N*-Dimethylamino)pyridine (19.5 g, 159 mmol, 1.10 equiv) was added portionwise, and the mixture was allowed to warm to room temperature overnight. Ethyl acetate (400 mL) was added, and the mixture was washed with 1 M $NaHSO_4$ (2 × 200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) afforded 31.4 g (91%) of the desired carbamate as a white solid (mp 96−97 °C): ^{1}H NMR 8.31 (dd, 1H, J = 2.2, 2.2, 2-H), 7.88 (dd, 1H, J = 7.9, 1.5, 4-H), 7.69 (br d, 1H, J ≈ 7.8, 6-H), 7.44 (dd, 1H, J = 8.3, 8.1, 5-H), 6.74 (br s, 1H, NH), 1.54 [s, 9H, (CH_3)$_3$CO)].

3-(*tert*-Butyloxycarbamoyl)aniline (13). General Procedure for the Reduction of an Aromatic Nitro Group. To an oven-dried 1-L rb flask containing protected aniline **12a** (20.0 g, 83.9 mmol) in 500 mL of 1:1 EtOAc/ethanol at room temperature was added 10% Pd on C (90 mg, ca. 1 mol %), and the mixture was stirred under an atmosphere of H_2 gas for 6 h. The reaction mixture was then filtered and concentrated under reduced pressure to give 17.4 g (quantitative) of the desired aniline as a white solid: ^{1}H NMR 7.04 (dd, 1H, J = 8.0, 8.0, 5-H), 6.98 (br s, 1H, NH), 6.53 (dd, 1H, J = 7.9, 1.8, 4-H), 6.36 (m, 2H, 6,2-H), 3.66 (br s, 2H, NH_2), 1.51 [s, 9H, (CH_3)$_3$CO)].

7-(*tert*-Butyloxycarbamoyl)-1,2-dihydro-2,2,4-trimethylquinoline (14). To an oven-dried 1-L rb flask containing aniline **13a** (17.4 g, 83.5 mmol), $MgSO_4$ (50 g, 5 equiv), and 4-*tert*-butylcatechol (420 mg, 3.0 mol %) in 120 mL of acetone (ca. 0.75 M in the aniline) was added iodine (1.1 g, 5.0 mol %), and the mixture was heated to reflux for 8 h. The crude reaction mixture was then cooled to room temperature, filtered through a bed of Celite on a fritted-glass funnel, rinsing with EtOAc, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, gradient elution) afforded 19.9 g (82%) of the desired cyclization product as a white solid, which was further purified by recrystallization from CH_3CN to give white needles (mp 163−164 °C): ^{1}H NMR 6.93 (d, 1H, J = 8.3, 5-H), 6.81 (br s, 1H, *H*NBOC), 6.34 (m, 2H, 6,8-H), 5.21 (d, 1H, J = 0.9, 3-H), 3.71 (br s, 1H, N*H*), 1.94 (d, 3H, J = 1.0, 4-CH_3), 1.50 [s, 9H, (CH_3)$_3$CO)], 1.24 [s, 6H, 2-C(CH_3)$_2$]. Anal. ($C_{17}H_{24}N_2O_2$) C, 70.80; H, 8.39; N, 9.71. Found: C, 70.91; H, 8.14; N, 9.84.

7-Amino-1,2-dihydro-2,2,4-trimethylquinoline (8a). General Procedure for Removal of BOC Protective Group. To an oven-dried 25-mL rb flask containing dihydroquinoline **14a** (400 mg, 1.38 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added TFA (1.1 mL, 10 equiv), and the mixture was allowed to warm to room temperature. After 3 h at room temperature, the reaction mixture was diluted with 50 mL of CH_2Cl_2, transferring to a 125-mL Erlenmeyer flask, and cooled to 0 °C before adjusting to pH 8 with saturated $NaHCO_3$. The biphasic mixture was transferred to a separatory funnel, the layers were separated, and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford a light reddish oil. The crude material thus obtained was of greater than 98% purity by ^{1}H NMR and was carried on to the next step without further purification. While the 7-aminoquinolines **14** obtained began to decompose appreciably within a few hours upon standing at room temperature, ethanolic solutions could be stored at −20 °C for 2−3 days without substantial adverse effect on the subsequent reaction outcome. Typically, however, the material was stored in bulk as the crystalline BOC-protected amine and deprotected as needed: ^{1}H NMR 6.86 (d, 1H, J = 8.2, 5-H), 5.99 (dd, 1H, J = 8.0, 2.3, 6-H), 5.79 (d, 1H, J = 2.0, 8-H), 5.12 (d, 1H, J = 1.4, 3-H), 3.53 (br s, 3H, NH_2, NH), 1.93 (d, 3H, J = 1.2, 4-CH_3), 1.24 [s, 6H, 2-(CH_3)$_2$].

Knorr Reaction of 7-Amino-1,2-dihydro-2,2,4-trimethylquinoline (8a). General Procedure for the Knorr Cyclization of 7-Amino-1,2-dihydroquinolines 8a-i with 4,4,4-Trifluoroacetoacetate. To an oven-dried 10-mL rb flask containing 7-amino-1,2-dihydro-2,2,4-trimethylquinoline (100 mg, 0.53 mmol) and ethyl 4,4,4-trifluoroacetoacetate (85.4 μL, 0.58 mmol, 1.10 equiv) in 2.5 mL of absolute ethanol was added $ZnCl_2$ (110 mg, 0.81 mmol, 1.5 equiv), and the mixture was heated to reflux for 3 h. Upon being cooled to room temperature, the reaction mixture was diluted with 40 mL of EtOAc, and the organic solution was washed with saturated NH_4Cl, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, gradient elution) afforded 70 mg (40%) of the ethyl imino ether (**10a**, R_f 0.61, hexanes/EtOAc, 2:1) as a pale yellow crystalline solid and 72 mg (44%) of the 2-quinolone (**9a**, R_f 0.14, hexanes/EtOAc, 2:1) as a bright fluorescent-yellow solid, which was recrystallized from 95% EtOH (mp 286-288 °C). **Data for 1,2-dihydro-2,2,4-trimethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9a):** ^{1}H NMR 11.45 (br s, 1H, CON*H*), 7.38 (s, 1H, 5-H), 6.66 (s, 1H, 7-H), 6.27 (s, 1H, 10-H), 5.42 (s, 1H, 3-H), 4.35 [br s, 1H, (CH_3)$_2$CN*H*], 2.03 (s, 3H, 4-CH_3), 1.33 [s, 6H, 2-(CH_3)$_2$]; ^{13}C NMR (acetone-d_6) 162.1, 148.5, 142.9, 138.8 (q), 130.6, 127.5, 125.5 (q), 119.8, 119.0, 114.4, 105.4, 96.6, 53.2, 32.0, 18.6; IR (KBr) 3345 (m, br), 2973 (m, br), 1659 (s), 1628 (s), 1476 (m), 1443 (m). Anal. ($C_{16}H_{15}F_3N_2O$) C, H, N. **Data for 8-ethoxy-1,2-dihydro-2,2,4-trimethyl-6-(trifluoromethyl)-pyridino[5,6-*g*]quinoline (10a):** ^{1}H NMR 7.56 (d, 1H, J = 1.8, 5-H), 6.84 (s, 1H, 7-H), 6.74 (s, 1H, 10-H), 5.52 (s, 1H, 3-H), 4.47 (q, 2H, J = 7.0, CH_3CH_2O), 4.12 [br s, 1H, (CH_3)$_2$-CN*H*], 2.09 (d, 3H, J = 1.3, 4-CH_3), 1.42 (t, 3H, J = 7.0, CH_3-CH_2O), 1.34 [s, 6H, 2-(CH_3)$_2$]; IR (neat) 3393 (m, br), 2969 (m, br), 1611 (s), 1524 (m), 1495 (s). This product was readily converted to the 2-quinolone isomer **9a** virtually quantitatively by heating neat with excess 57% HI at 60 °C for 3 h, followed by neutralization with saturated $NaHCO_3$, extraction with EtOAc, and recrystallization.

1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9b). This compound was prepared from amine **14b** (98 mg, 0.51 mmol) in the manner previously described for **9a**, affording 66 mg (42%) of the desired 2-quinolone as a fluorescent-yellow solid (mp 299-300 °C dec): ^{1}H NMR 11.32 (br s, 1H, CON*H*), 7.50 (s, 1H, 5-H), 6.64 (s, 1H, 7-H), 6.41 (s, 1H, 10-H), 4.55 [br s, 1H, (CH_3)$_2$-CN*H*], 2.91 (ddq, 1H, J = 12.6, 12.4, 6.3, 4-H), 1.76 and 1.41 [d of AB q, 2H, J_{AB} = 12.8, J_A = 5.5 (3-H_{eq}), J_B = 12.4 (3-H_{ax})], 1.37 (d, 3H, J = 6.8, 4-CH_3), 1.22 and 1.18 [2s, 2 × 3H, 2-(CH_3)$_2$]; ^{13}C NMR 163.8, 147.7, 140.0, 139.2, 124.0, 122.6, 112.6, 105.9, 96.7, 49.7, 43.6, 31.1, 28.6, 27.3, 19.6. Anal. ($C_{16}H_{17}F_3N_2O$) C, H, N.

1,2-Dihydro-2,2,4,10-tetramethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9c). This compound was prepared from amine **14c** (100 mg, 0.49 mmol) in the manner previously described for **9a**, affording 75 mg (47%) of the desired 2-quinolone as a fluorescent-yellow solid (mp 245−246 °C): ^{1}H NMR 9.23 (br s, 1H, CON*H*), 7.37 (s, 1H, 5-H), 6.67 (s, 1H, 7-H), 5.45 (s, 1H, 3-H), 4.14 [br s, 1H, (CH_3)$_2$CN*H*], 2.12 (s, 3H, 10-CH_3), 2.04 (d, 3H, J = 1.1, 4-CH_3), 1.37 [s, 6H, 2-(CH_3)$_2$]; ^{13}C NMR 162.6, 144.3, 139.4, 138.7, 127.5, 124.3, 120.5, 118.2, 117.8, 113.8, 106.0, 101.4, 52.8, 32.2, 18.6, 9.4. Anal. ($C_{17}H_{17}F_3N_2O$) C, H, N.

1,2,3,4-Tetrahydro-2,2,4,10-tetramethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9d). This compound was prepared from amine **14d** (2.92 g, 14.3 mmol) in the manner previously described for **9a**, affording 2.04 g (44%) of the desired 2-quinolone as a pale fluorescent-yellow solid (mp 239−240 °C): ^{1}H NMR 9.70 (br s, 1H, CON*H*), 7.50 (s, 1H, 5-H), 6.68 (s, 1H, 7-H), 4.13 [br s, 1H, (CH_3)$_2$CN*H*], 3.00 (ddq, 1H, J = 12.9, 12.4, 6.3, 4-H), 2.15 (s, 3H, 10-CH_3), 1.83 and 1.46 [dd of AB q, 2H, J_{AB} = 13.0, J_A = 5.3, 1.6 (3-H_{eq}), J_B = 12.9, 0 (3-H_{ax})], 1.40 (d, 3H, J = 6.6, 4-CH_3), 1.36 and 1.25 [2s, 2 × 3H, 2-(CH_3)$_2$]; ^{13}C NMR 162.5, 144.9, 139.1, 137.1, 124.3, 122.7, 120.9, 113.8, 105.7, 101.6, 50.2, 43.5, 31.8, 28.9, 27.6, 20.1, 9.7. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

(2-Methyl-3-butyn-2-yl)phenylamine (16e). In a 500-mL rb flask, a solution of 2-methyl-3-butyn-2-ol (10.0 mL, 0.10 mol,

1.30 equiv) in CH_2Cl_2 (100 mL) was treated sequentially with Et_3N (15.0 mL, 0.11 mol, 1.40 equiv), acetic anhydride (11.6 mL, 0.12 mol, 1.50 equiv), and DMAP (0.6 g, 5.0 mmol, 5.0 mol %). The reaction mixture was stirred at room temperature for 2 h and poured into saturated NH_4Cl (60 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with 1 N HCl (2 × 100 mL), dried ($MgSO_4$), filtered through a pad of Celite, and concentrated under reduced pressure. The residue was dissolved in THF (100 mL), and aniline (7.00 mL, 770 mmol) was added slowly via syringe, followed by CuCl (0.76 g, 10 mol %). The reaction mixture was heated to reflux for 3 h. The resulting red solution was allowed to cool to room temperature, and concentrated under reduced pressure. The residue was then diluted with EtOAc (120 mL), and the solution was washed with saturated NH_4Cl (2 × 100 mL) and brine (1 × 100 mL). The aqueous layers were extracted with EtOAc (2 × 100 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 16:1) afforded 10.5 g (87%) of amine **16e** as a pale yellow liquid: ^{1}H NMR 7.20 (t, 2H, J = 7.7, 3,5-H), 6.95 (d, 2H, J = 7.7, 2,6-H), 6.80 (t, 1H, J = 7.7, 4-H), 3.65 [br s, 1H, $(CH_3)_2CNH$], 2.36 (s, 1H, C≡C*H*), 1.61 [s, 6H, 2-$(CH_3)_2$].

1,2,3,4-Tetrahydro-2,2-dimethylquinoline (17e). In a 1-L rb flask, a solution of **16e** (24.3 g, 152 mmol) in THF (200 mL) was treated with CuCl (1.7 g, 11 mol %) and heated at reflux for 14 h. The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was poured into saturated NH_4Cl (200 mL) and extracted with EtOAc (3 × 250 mL). The combined organics were washed with saturated NH_4Cl (1 × 200 mL) and brine (1 × 200 mL), dried ($MgSO_4$), filtered through a pad of Celite, and concentrated under reduced pressure to an orange oil. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 40:1) afforded 18.0 g (74%) of 1,2-dihydro-2,2-dimethylquinoline as a pale yellow oil: ^{1}H NMR 6.95 (t, 1H, J = 7.7, 7-H), 6.87 (d, 1H, J = 7.3, 5-H), 6.57 (t, 1H, J = 7.3, 6-H), 6.40 (d, 1H, J = 7.7, 8-H), 6.25 (d, 1H, J = 9.7, 4-H), 5.46 (d, 1H, J = 9.7, 3-H), 3.63 [br s, 1H, $(CH_3)_2CNH$], 1.31 [s, 6H, 2-$(CH_3)_2$]. To a 1-L rb flask containing a solution of the dihydroquinoline (16.2 g, 102 mmol) in 1:1 EtOH/EtOAc (300 mL) was added 10% Pd/C (1.05 g, 0.99 mol %), and the mixture was stirred under an atmosphere of H_2 for 4 h. The reaction mixture was purged with N_2 and filtered through a pad of Celite, rinsing with EtOAc (200 mL). Concentration of the filtrate afforded 16.2 g (99%) of the tetrahydroquinoline as a pale yellow oil: ^{1}H NMR 6.98 (m, 2H, 7,5-H), 6.60 (t, 1H, J = 7.3, 6-H), 6.44 (d, 1H, J = 8.0, 8-H), 2.77 (dd, 2H, J = 6.7, 6.7, 4-H), 1.70 (dd, 2H, J = 6.7, 6.7, 3-H), 1.21 [s, 6H, 2-$(CH_3)_2$].

1,2,3,4-Tetrahydro-2,2-dimethyl-7-nitroquinoline (18e). To a 250-mL rb flask containing **17e** (6.06 g, 37.6 mmol) in H_2SO_4 (40 mL) at −5 °C was added 90% HNO_3 (1.70 mL) dropwise over a 15 min period. The reaction mixture was stirred an additional 15 min and poured over ice (300 g), and K_2CO_3 (100 g) was added slowly with vigorous stirring. The mixture was extracted with CH_2Cl_2 (3 × 300 mL), and the combined extracts were washed with H_2O (200 mL) and saturated $NaHCO_3$ (100 mL), dried ($MgSO_4$), filtered through pad of Celite, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 40:1 to 20:1 gradient) afforded 4.40 g (57%) of the product as an orange solid: ^{1}H NMR 7.39 (dd, 1H, J = 7.9, 2.2, 6-H), 7.27 (d, 1H, J = 2.2, 8-H), 7.04 (d, 1H, J = 7.9, 5-H), 3.95 [br s, 1H, $(CH_3)_2CNH$], 2.81 (dd, 2H, J = 6.7, 6.7, 4-H), 1.72 (dd, 2H, J = 6.7, 6.7, 3-H), 1.21 [s, 6H, 2-$(CH_3)_2$].

7-Amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline (8e). This compound was prepared from **18e** (1.00 g, 4.84 mmol) in the manner previously described for aniline **13**, affording 0.85 g (99%) of the crude aniline as a reddish oil: ^{1}H NMR 6.77 (d, 1H, J = 7.9, 5-H), 6.00 (dd, 1H, J = 7.9, 2.2, 6-H), 5.81 (d, 1H, J = 2.2, 8-H), 3.47 [br s, 1H, $(CH_3)_2CNH$], 3.40 (br s, 2H, NH_2), 2.66 (dd, 2H, J = 6.7, 6.6, 4-H), 1.65 (dd, 2H, J = 6.7, 6.6, 3-H), 1.18 [s, 6H, 2-$(CH_3)_2$].

1,2,3,4-Tetrahydro-2,2-dimethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9e). This compound was prepared from amine **8e** (0.85 g, 5.08 mmol) in the manner previously described for **9a**, affording 0.74 g (52%) of quinolone **9e** as a yellow powder, which was further purified by recrystallization from 2-propanol to give yellow needles (mp 287−289 °C), along with 0.54 g (35%) of ethoxypyridine **10e** as a yellow solid. **Data for 9e:** ^{1}H NMR (DMSO-d_6) 11.70 (s, 1H, CON*H*), 7.18 (s, 1H, 5-H), 6.85 (s, 1H, 7-H), 6.35 (s, 1H, 10-H), 2.65 (dd, 2H, J = 6.6, 6.6, 4-H), 1.61 (dd, 2H, J = 6.6, 6.6, 3-H), 1.17 [s, 6H, 2-$(CH_3)_2$]; ^{13}C NMR 163.6, 147.6, 140.0, 138.9 (q), 124.8, 122.9 (q), 118.4, 112.9, 105.9, 97.0, 49.4, 33.8, 29.4, 24.1; IR (KBr) 3302 (m, br), 2971 (m, br), 1662 (s), 1630 (s), 1439 (m). Anal. ($C_{15}H_{15}F_3N_2O$) C, H, N. **Data for 8-ethoxy-1,2,3,4-tetrahydro-2,2-dimethyl-6-(trifluoromethyl)pyridino[5,6-*g*]quinoline (10e):** ^{1}H NMR 7.56 (d, 1H, J = 1.4, 5-H), 6.84 (s, 1H, 7-H), 6.78 (s, 1H, 10-H), 4.46 (q, 2H, J = 7.1, OCH_2CH_3), 4.16 (s, 1H, N*H*), 2.96 (t, 2H, J = 6.7, 4-H), 1.78 (t, 2H, J = 6.7, 3-H), 1.41 (t, 3H, J = 7.2, OCH_2CH_3), 1.27 [s, 6H, $NC(CH_3)_2$].

2-Ethyl-1,2,3,4-tetrahydro-2-methyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9f). This compound was prepared from amine **8f** (0.26 g, 1.36 mmol) in the manner previously described for **9a**, affording 282 mg (67%) of **9f** as a yellow solid (R_f 0.35, EtOAc/CH_2Cl_2, 3:2), a portion of which was recrystallized from methanol to give yellow needles (mp 268 °C): ^{1}H NMR 12.6 (br s, 1H, CON*H*), 7.34 (s, 1H, 5-H), 6.62 (s, 1H, 7-H), 6.49 (s, 1H, 10-H), 4.65 [br s, 1H, $(CH_3)_2CNH$], 2.78 (br t, 2H, J = 6.2, 4-H), 1.65−1.75 and 1.55−1.65 (2 m, 2 × 1H, 3-H), 1.46 (br q, 2H, J = 7.3, CH_2CH_3), 1.10 [s, 6H, 2-$(CH_3)_2$], 0.87 (t, 3H, J = 7.4, CH_2CH_3); ^{13}C NMR 163.7, 148.0, 140.0, 138.9 (q, J = 31), 124.7, 122.8 (q, J = 275), 118.7, 112.5, 105.8, 97.0, 51.7, 34.0, 31.2, 26.2, 23.7, 7.8. Anal. ($C_{16}H_{17}F_3N_2O$) C, H, N.

2,2-Diethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9g). This compound was prepared from **8g** (0.230 g, 1.13 mmol) in the manner previously described for **9a**, affording 0.103 g (28%) of **9g** as a yellow solid (R_f 0.34, EtOAc/CH_2Cl_2, 3:2). An analytically pure sample was obtained by recrystallization from methanol (mp 261−262 °C): ^{1}H NMR 12.5 (br s, 1H, CON*H*), 7.36 (s, 1H, 5-H), 6.66 (s, 1H, 7-H), 6.45 (s, 1H, 10-H), 4.52 [br s, 1H, $(CH_3)_2CNH$], 2.80 (t, 2H, J = 6.6, 4-H), 1.71 (t, 2H, J = 6.6, 3-H), 1.60−1.40 (m, 4H, CH_2CH_3), 0.87 (t, 6H, J = 7.5, CH_2CH_3); ^{13}C NMR 163.7, 147.9, 140.0, 138.9 (q, J = 31), 124.8, 122.8 (q, J = 276), 118.9, 112.9 (br), 105.9, 97.2, 54.2, 30.5, 29.0, 23.4, 7.5. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

1,2,3,4-Tetrahydro-2-methyl-2-propyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9h). This compound was prepared from **8h** (0.774 g, 3.79 mmol) in the manner previously described for **9a**, affording 690 mg (56%) of **9h**. Recrystallization from MeOH/CH_2Cl_2 afforded 383 mg (31%) of **9h** as a yellow solid (mp 254−256 °C): ^{1}H NMR 12.32 (br s, 1H, CON*H*), 7.36 (s, 1H, 5-H), 6.65 (s, 1H, 7-H), 6.41 (s, 1H, 10-H), 4.53 [br s, 1H, $(CH_3)_2CNH$], 2.81 (t, 2H, J = 6.4, 4-H), 1.72−1.82 (m, 1H, 3-H), 1.62−1.72 (m, 1H, 3-H), 1.25−1.50 (m, 4H, $CH_2CH_2CH_3$), 1.16 (s, 3H, 2-CH_3), 0.91 (t, 3H, J = 7.0, CH_2CH_3); ^{13}C NMR 163.8, 148.0, 140.1, 138.8 (q, J = 31), 124.7, 122.7 (q, J = 276), 118.6, 112.3 (br), 105.7, 96.9, 51.4, 43.9, 31.8, 26.8, 23.6, 16.7, 14.4. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

1,2,3,4-Tetrahydro-2-spirocyclohexyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (9i). This compound was prepared in from **8i** (0.126 g, 0.582 mmol) in the manner previously described for **9a**, affording 32 mg (16%) of **9i** (R_f 0.17, hexanes/EtOAc, 5:2). An analytical sample was obtained by recrystallization from MeOH (mp 285−305 °C dec): ^{1}H NMR 11.4 (br s, 1H, CON*H*), 7.36 (s, 1H, 5-H), 6.67 (s, 1H, 7-H), 6.33 (s, 1H, 10-H), 4.68 [br s, 1H, $(CH_3)_2CNH$], 2.82 (t, 2H, J = 6.6, 4-H), 1.77 (t, 2H, J = 6.6, 3-H), 1.65−1.45 (m, 9H, cyclohexyl-H), 1.45−1.35 (m, 1H, cyclohexyl-H); ^{13}C NMR (DMSO-d_6) 160.8, 148.0, 140.3, 136.4 (q, J = 30), 123.5, 122.9

(q, J = 276), 117.3, 112.9 (br), 103.1, 96.3, 50.5, 37.2, 30.4, 25.5, 22.7, 21.2. Anal. ($C_{18}H_{19}F_3N_2O$) C, H, N.

1,2-Dihydro-2,2,4,9-tetramethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (19a). General Procedure for N-Alkylation of 2-Quinolones at N-9: To an oven-dried 50-mL rb flask containing 1,2-dihydro-2,2,4-trimethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (500.0 mg, 1.62 mmol) in 5 mL of THF at 0 °C was added portionwise sodium hydride (71.4 mg of a 60% dispersion in mineral oil, 1.78 mmol, 1.10 equiv). After 30 min, iodomethane (101 μL, 1.62 mmol, 1.00 equiv) was added, and the mixture was allowed to warm to room temperature, and after 4 h, the reaction mixture was cooled to 0 °C, and water (5 mL) was added. The reaction mixture was then diluted with 100 mL of EtOAc, and the organic solution was washed with 50 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, gradient elution) afforded 497 mg (95%) of the desired *N*-methylamide as a bright fluorescent yellow solid (mp 248−250 °C): ^{1}H NMR 7.41 (d, 1H, J = 1.7, 5-H), 6.73 (s, 1H, 7-H), 6.28 (s, 1H, 10-H), 5.42 (s, 1H, 3-H), 4.36 [br s, 1H, $(CH_3)_2CNH$], 3.62 (s, 3H, NCH_3), 2.04 (d, 3H, J = 1.2, 4-CH_3), 1.33 [s, 6H, 2-$(CH_3)_2$]; ^{13}C NMR 161.4, 146.7, 142.5, 137.0 (q), 129.2, 127.1, 121.5, 120.5, 117.8, 114.1, 106.4, 95.9, 52.9, 32.0, 29.8, 18.3. Anal. ($C_{17}H_{17}F_3N_2O$) C, H, N.

1,2-Dihydro-9-ethyl-2,2,4-trimethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (19b). This compound was prepared from **9a** (34.1 mg, 0.111 mmol) and iodoethane in the manner previously described for **19a**, affording 19.8 mg (56%) of **19b** as a yellow solid (mp 231−233 °C): ^{1}H NMR 7.42 (d, 1H, J = 1.6, 5-H), 6.72 (s, 1H, 7-H), 6.32 (s, 1H, 10-H), 5.42 (s, 1H, 3-H), 4.46 [br s, 1H, $(CH_3)_2CNH$], 4.25 (q, 2H, J = 7.2, NCH_2CH_3), 2.04 (d, 3H, J = 1.4, 4-CH_3), 1.36 [s, 6H, 2-$(CH_3)_2$], 1.33 (t, 3H, J = 7.3, NCH_2CH_3); ^{13}C NMR 161.0, 147.1, 141.5, 137.0 (q), 129.4, 126.9, 123.0 (q), 120.5, 117.8, 113.8 (q), 106.5, 95.6, 52.8, 37.7, 32.0, 30.9, 18.3. Anal. ($C_{18}H_{19}F_3N_2O$) C, H, N.

1,2,3,4-Tetrahydro-2,2,4,9-tetramethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (19c). This compound was prepared from **9b** (45.0 mg, 0.145 mmol) in the manner previously described for **19a**, affording 36.7 mg (78%) of **19c** as a fluorescent-yellow solid (mp 235−236 °C): ^{1}H NMR 7.56 (br s, 1H, 5-H), 6.73 (s, 1H, 7-H), 6.31 (s, 1H, 10-H), 4.43 [br s, 1H, $(CH_3)_2CNH$], 3.61 (s, 3H, NCH_3), 2.98 (ddq, 1H, J = 12.8, 12.4, 6.0, 4-H), 1.83 (ddd, 1H, J = 13.0, 5.2, 1.7, 3-H_{eq}), 1.47 (dd, 1H, J = 12.8, 12.8, 3-H_{ax}), 1.40 (d, 3H, J = 6.7, 4-CH_3), 1.32 and 1.26 [2s, 2 × 3H, 2-$(CH_3)_2$]; ^{13}C NMR 161.5, 147.2, 141.2, 136.7 (q), 124.0, 123.0 (q), 122.2, 114.0, 106.2, 96.7, 50.1, 43.8, 31.4, 29.6, 28.5, 27.1, 19.8. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

1,2-Dihydro-2,2,4,9,10-pentamethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (19d). This compound was prepared from **9c** (33.9 mg, 0.105 mmol) in the manner previously described for **19a**, affording 25.5 mg (72%) of **19d** as a fluorescent yellow solid (mp 204−7 °C dec): ^{1}H NMR 7.55 (s, 1H, 5-H), 6.87 (s, 1H, 7-H), 5.56 (s, 1H, 3-H), 4.78 [br s, 1H, $(CH_3)_2CNH$], 4.07 (s, 3H, NCH_3), 2.45 (s, 3H, 10-CH_3), 2.11 (d, 3H, J = 1.2, 4-CH_3), 1.38 [s, 6H, 2-$(CH_3)_2$]; ^{13}C NMR 164.3, 145.9, 144.4, 128.8, 127.3, 124.3, 118.1, 117.8, 114.4, 108.1, 104.2, 52.9, 39.9, 32.3, 29.7, 18.5, 16.2. Anal. ($C_{18}H_{19}F_3N_2O$) C, H, N.

1,2,3,4-Tetrahydro-2,2,4,9,10-pentamethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (19e). This compound was prepared from **9d** (50.0 mg, 0.154 mmol) in the manner previously described for **19a**, affording 38.8 mg (75%) of **19e** as a fluorescent-yellow solid (mp 189-193 °C dec): ^{1}H NMR 7.48 (s, 1H, 5-H), 6.73 (s, 1H, 7-H), 4.13 [s, 1H, $(CH_3)_2CNH$], 3.65 (s, 3H, NCH_3), 3.00 (m, 1H, 4-H), 2.24 (s, 3H, 10-CH_3), 1.84 (dd, 1H, J = 13.6, 4.9, 3-H_{eq}), 1.45 (dd, 1H, J = 12.8, 12.8, 3-H_{ax}), 1.40 (d, 3H, J = 6.7, 4-CH_3), 1.37 and 1.27 [2s, 2 × 3H, 2-$(CH_3)_2$]; ^{13}C NMR 164.3, 146.2, 142.9, 122.3, 121.4, 120.9, 114.2, 107.8, 105.0, 50.2, 43.5, 40.0, 31.8, 29.7, 29.0, 27.5, 20.0, 16.5. Anal. ($C_{18}H_{21}F_3N_2O$) C, H, N.

1,2,3,4-Tetrahydro-2,2,9-trimethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (19f). This compound was prepared from **9e** (830 mg, 2.80 mmol) in the manner previously described for **19a**, affording 735 mg (85%) of **19f** (R_f 0.48, CH_2Cl_2/MeOH, 15:1) as a yellow solid (mp 217−218 °C): ^{1}H NMR 7.35 (s, 1H, 5-H), 6.56 (s, 1H, 7-H), 6.52 (s, 1H, 10-H), 6.10 [s, 1H, $(CH_3)_2CNH$], 3.53 (s, 3H, NCH_3), 2.87 (t, 2H, J = 6.7, 4-H), 1.76 (t, 2H, J = 6.7, 3-H), 1.29 [s, 6H, 2-$(CH_3)_2$]; ^{13}C NMR 161.6, 147.5, 141.4, 136.8 (q, J_{C-F} = 30.8), 126.1, 123.1 (q, J_{C-F} = 275), 117.1, 114.1 (q, J_{C-F} = 5.8), 106.2, 97.0, 49.9, 34.1, 29.8, 29.6, 23.9. Anal. ($C_{16}H_{17}F_3N_2O$) C, H, F, N.

2-Ethyl-1,2,3,4-tetrahydro-2,9-dimethyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (19g). This compound was prepared from **9f** (25 mg, 0.08 mmol) in the manner previously described for **19a**, affording 17 mg (65%) of **19g** as a yellow solid (R_f 0.32, EtOAc/CH_2Cl_2, 9:1). A portion of this material was recrystallized from methanol (mp 234 °C): ^{1}H NMR 7.41 (s, ^{1}H, 5-H), 6.72 (s, ^{1}H, 7-H), 6.34 (s, ^{1}H, 10-H), 4.44 [br s, ^{1}H, $(CH_3)_2CNH$], 3.61 (s, 3H, NCH_3), 2.84 (t, 2H, J = 6.6, 4-H), 1.65−1.85 (m, 2H, 3-H), 1.57 (q, 2H, J = 7.5, CH_2CH_3), 1.22 (s, 3H, 2-CH_3), 0.96 (t, 3H, J = 7.5, CH_2CH_3). ^{13}C NMR 161.4, 147.4, 141.2, 136.6 (q, J = 31), 125.9, 122.9 (q, J = 275), 117.1, 113.9 (q, J = 5.8), 106.0, 96.8, 52.1, 34.3, 31.4, 29.6, 26.2, 23.4, 7.9. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

1,2-Dihydro-1,2,2,4-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (20). To an oven-dried 50-mL rb flask containing **9a** (202 mg, 0.66 mmol) in 5 mL of HOAC at room temperature was added paraformaldehyde (200 mg) and $NaCNBH_3$ (450 mg, 6.60 mmol, 10.0 equiv), and the mixture was allowed to stir overnight. The reaction mixture was then added to 50 mL of saturated $NaHCO_3$ and extracted with EtOAc (2 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexane/EtOAc, 4:1) afforded 191 mg (90%) of the methylated product **20** as a yellow solid (mp 300-302 °C): ^{1}H NMR 11.72 (br s, 1H, CONH), 7.33 (d, 1H, J = 1.4, 5-H), 6.68 (s, 1H, 7-H), 6.28 (s, 1H, 10-H), 5.39 (s, 1H, 3-H), 2.93 (s, 3H, 1-CH_3), 2.02 (s, 3H, 4-CH_3), 1.38 [s, 6H, 2-$(CH_3)_2$]. ^{13}C NMR 163.6, 148.1, 141.8, 138.8 (q), 130.8, 126.7, 122.9 (q), 120.5, 128.7, 113.3 (q), 105.4, 94.8, 57.3, 31.3, 28.5, 18.5. Anal. ($C_{17}H_{17}F_3N_2O$) C, H, N.

1,2-Dihydro-1,2,2,4,9-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (21a). To a 25-mL rb flask containing **9a** (125.8 mg, 0.41 mmol) in 5 mL DMF at room temperature was added 200 mg (ca. 10 equiv) of solid KOH. After 30 min, iodomethane (129 μL, 2.04 mmol, 5.00 equiv) was then added, and the mixture was allowed to stir at room temperature overnight. Ethyl acetate (50 mL) was then added, the biphasic mixture was neutralized to pH 6 with saturated NH_4Cl, and the layers were separated. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, gradient elution) afforded 111 mg (81%) of the desired di-N-methylated product as a bright fluorescent-yellow solid, which could be further purified by recrystallization from EtOAc to give yellow needles (mp 210−212 °C): ^{1}H NMR 7.37 (s, 1H, 5-H), 6.74 (s, 1H, 7-H), 6.21 (s, 1H, 10-H), 5.38 (s, 1H, 3-H), 3.69 (s, 3H, $CONCH_3$), 2.94 [s, 3H, $(CH_3)_2CNCH_3$], 2.03 (s, 3H, 4-CH_3), 1.40 [s, 6H, 2-$(CH_3)_2$]; ^{13}C NMR 161.4, 148.0, 142.8, 136.6 (q), 130.4, 126.5, 122.9 (q), 119.6, 119.2, 113.8, 105.3, 93.9, 57.6, 31.2, 29.8, 28.6, 18.4. Anal. ($C_{18}H_{19}F_3N_2O$) C, H, N.

1,2,3,4-Tetrahydro-1,2,2,9-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (21b). This compound was prepared from **19f** (24.0 mg, 0.08 mmol) in the manner previously described for **20**, affording 24 mg (96%) of **21b** (R_f 0.27, hexane/EtOAc, 1:1) as yellow needles (mp 193−194 °C). ^{1}H NMR 7.35 (s, 1H, 5-H), 6.72 (s, 1H, 7-H), 6.28 (s, 1H, 10-H), 3.67 [s, 3H, $CONCH_3$], 2.96 [s, 3H, $(CH_3)_2CNCH3$], 2.83 (t, 2H, J = 6.7, 4-H), 1.85 (t, 2H, J = 6.7, 3-H), 1.32 [s, 6H, 2-$(CH_3)_2$]; ^{13}C NMR 161.7, 149.2, 141.9, 136.6 (q, J_{C-F} = 31.0), 124.4, 123.2 (q, J_{C-F} = 275), 120.2, 113.8 (q, J_{C-F} = 5.7), 105.1, 94.8, 55.2, 36.7, 31.9, 29.9, 27.0, 24.5. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

2-Ethyl-1,2,3,4-tetrahydro-1,2,9-trimethyl-6-trifluoro-

methyl-8-pyridono[5,6-*g*]quinoline (21c). This compound was prepared from **19g** (18.1 mg, 0.06 mmol) in the manner previously described for **20**, affording 10 mg (51%) of a yellow solid (R_f 0.32, EtOAc/CH_2Cl_2, 9:1). A portion of this material was recrystallized from EtOAc/hexanes (mp 170−171 °C): ^{1}H NMR 7.35 (s, 1H, 5-H), 6.74 (s, 1H, 7-H), 6.31 (s, 1H, 10-H), 3.69 (s, 3H, CONCH_3), 2.95 (s, 3H, CNCH_3), 2.72−2.90 (m, 2H, 4-H), 1.98 (ddd, 1H, J = 13.9, 8.3, 5.6, 3-H), 1.60−1.82 (m, 3H, 3-H, CH_2CH$_3$), 1.29 (s, 3H, 2-CH_3), 0.85 (t, 3H, J = 7.4, CH_2CH_3); ^{13}C NMR 161.6, 149.6, 141.7, 136.4 (q, J = 31), 124.1, 122.9 (q, J = 276), 120.2, 113.5 (q, J = 5.7), 104.9, 94.6, 57.8, 31.9, 31.8, 31.6, 29.7, 25.0, 24.0, 8.2. Anal. ($C_{18}H_{21}F_3N_2O$) C, H, N.

1-(*tert*-Butyloxycarbonyl)-1,2-dihydro-2,2-dimethylquinoline (22). To a flame-dried 500-mL rb flask containing 1,2-dihydro-2,2-dimethylquinoline (5.00 g, 31.4 mmol) in 80 mL anhydrous Et_2O at −78 °C was slowly added *n*-butyllithium (16.3 mL of a 2.5 M solution in hexanes, 40.8 mmol, 1.30 equiv), keeping the temperature below −65 °C. After 10 min, di-*tert*-butyl dicarbonate (8.91 g, 40.8 mmol, 1.30 equiv) was added dropwise as a solution in 20 mL of Et_2O. The mixture was then allowed to warm to room temperature and stirred for an additional 2 h before the reaction was quenched with 100 mL of 1.0 M $NaHSO_4$. The biphasic mixture was then extracted with EtOAc (2 × 100 mL) and washed with brine (150 mL). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to give 6.93 g (85%) of the desired BOC-protected quinoline **22** as a colorless, low-melting solid: ^{1}H NMR 7.19 (d, 1H, J = 9.2, 8-H), 7.09 (ddd, 1H, J = 8.6, 6.9, 1.8, 6-H), 6.97 (dd, 1H, J = 7.5, 1.8, 5-H), 6.92 (ddd, J = 8.2, 7.2, 0.9, 7-H), 6.29 (d, 1H, J = 9.7, 4-H), 5.60 (d, 1H, J = 9.7, 3-H), 1.54 [s, 6H, NC(CH_3)$_2$], 1.53 [s, 9H, COC(CH_3)$_3$].

1-(*tert*-Butyloxycarbonyl)-1,2,3,4-tetrahydro-4-oxo-2,2-dimethylquinoline (23). To a 100-mL rb flask containing a solution of protected quinoline **22** (1.3 g, 5.0 mmol) in 10 mL of THF was added BH_3·THF (10 mL of a 1.0 M solution in THF, 10 mmol, 2.0 equiv), and the mixture was stirred at room temperature for 5 h before the reaction was quenched with 10% KOH (0.5 mL). Hydrogen peroxide (1.0 mL of a 30% solution in water) was added, and the mixture was stirred for 60 min. Water (10 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL), washed with brine (10 mL), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 10:1 to 7:3 gradient elution) afforded a mixture of two regioisomers. The 3-hydroxy isomer (260 mg, 20%), was removed by washing with hexane (2 × 10 mL), giving 0.95 g (68%) of the 4-hydroxy product as a white solid. This material was carried on to the next step without further purification. In a 100-mL rb flask, the 4-hydroxy intermediate (0.95 g, 3.4 mmol) was oxidized with PCC (1.0 g, 4.6 mmol) in CH_2Cl_2 (5 mL) at room temperature for 3 h. Removal of solvent and purification by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) afforded ketone **23** as a white solid (0.83 g, 88%): ^{1}H NMR 7.93 (dd, 1H, J = 7.9, 1.7, 8-H), 7.43 (ddd, 1H, J = 8.6, 6.8, 1.8, 6-H), 7.31 (d, 1H, J = 8.4, 5-H), 7.02 (ddd, J = 8.8, 7.8, 1.1, 7-H), 2.73 (s, 2H, 3-H), 1.56 [s, 9H, COC(CH_3)3], 1.50 [s, 6H, 2-C(CH_3)$_2$].

1,2,3,4-Tetrahydro-2,2,3-trimethylquinoline (27a). To a solution of ketone **23** (0.14 g, 0.50 mmol) and iodomethane (0.25 mL, 4.0 mmol) in DMF (5 mL) was added NaH (60 % in mineral oil, 25 mg, 0.60 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (2 × 15 mL) and concentrated under reduced pressure. The crude reaction mixture was then treated with TFA (1 mL) in 1 mL CH_2Cl_2 at room temperature for 60 min, and then the reaction was quenched with 10% NaOH (10 mL). Extraction with EtOAc (2 × 20 mL) and flash column chromatography of the crude residue (silica gel, hexanes/EtOAc, gradient elution) afforded **24a** (75 mg, 0.40 mmol, 80%) as a colorless oil, which was contaminated with 10% of the 3,3-dimethylated material. The crude material thus obtained was carried on to the next step without further purification. In a 25-mL sealed tube, a solution of **24a** (75 mg, 0.40 mmol) in CH_2Cl_2 (4 mL) was treated with Et_3SiH (1.0 mL) and BF_3·OEt_2 (0.3 mL) at 100 °C for 18 h. The reaction mixture was quenched with 10% KOH (10 mL), extracted with EtOAc (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (silica gel, 2−20% EtOAc/hexanes, gradient) afforded 60 mg (86%) of **27a** as a colorless oil: ^{1}H NMR 7.00−6.91 (m, 2H, 5,6-H), 6.60 (t, 1H, J = 7.3, 7-H), 6.45 (d, 1H, J = 7.3, 8-H), 3.61 (br s, NH), 2.74 (dd, 1H, J = 16.6, 5.3, 4-H$_{eq}$), 2.47 (dd, 1H, J = 16.6, 10.3, 4-H$_{ax}$), 1.82 (m, 1H, 3-H), 1.20 and 1.05 [2s, 2 × 3H, 2-C(CH_3)$_2$], 0.97 (d, 3H, J = 7.2, 3-CH_3).

1,2,3,4-Tetrahydro-2,2,3-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (29a). Quinoline **27a** (60 mg, 0.34 mmol) was subjected to the general three-step nitration−hydrogenation−Knorr sequence described previously for the synthesis of **9e**, affording 37 mg (35% overall) of the desired **29a** as a yellow solid (mp 273−275 °C): IR (KBr) 3437 (m), 2970 (m), 1570 (s), 1529 (s), 1158 (m); ^{1}H NMR 11.46 (br s, 1H, CONH), 7.35 (s, 1H, 5-H), 6.66 (s, 1H, 7-H), 6.31 (s, 1H, 10-H), 4.40 [br s, 1H, (CH$_3$)$_2$CNH], 2.83 (dd, 1H, J = 16.6, 4.8, 4-H$_{eq}$), 2.57 (dd, 1H, J = 16.6, 10.3, 4-H$_{ax}$), 1.83 (m, 1H, 3-H), 1.25 and 1.10 [2s, 2 × 3H, 2-C(CH_3)$_2$], 0.99 (d, 3H, J = 6.9, 3-CH_3); ^{13}C NMR (acetone-d_6) 161.8, 148.8, 141.4, 125.1, 123.0 (q, J = 274), 118.2, 114.2, 105.0, 97.1, 53.0, 36.7, 33.0, 23.4, 16.0. Anal. ($C_{16}H_{17}F_3N_2O$) C, H, N.

3-Ethyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline (27b). Ketone **23** (0.10 g, 0.36 mmol) was subjected to the general alkylation−reduction procedure previously described for **27a** using iodoethane, affording 20 mg (71%) of **27b** as a colorless oil: ^{1}H NMR 6.98 (d, 1H, J = 7.5, 5-H), 6.96 (t, 1H, J = 7.5, 6-H), 6.61 (t, 1H, J = 7.5, 7-H), 6.44 (d, 1H, J = 7.5, 8-H), 3.60 (s, 1H, N*H*), 2.90 (dd, 1H, J = 16.7, 5.2, 4-H$_{eq}$), 2.41 (dd, 1H, J = 16.7, 10.7, 4-H$_{ax}$), 1.68 (m, 1H, 3-H), 1.52 (m, 2H, 3-CH$_2$CH_3), 1.23 (m, 3H, CH$_2$CH_3), 1.22 and 1.05 [2s, 2 × 3H, 2-C(CH_3)$_2$].

3-Ethyl-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (29b). Quinoline **27b** (18.5 mg, 0.10 mmol) was subjected to the general three-step nitration−hydrogenation−Knorr sequence previously described for the synthesis of **9e**, affording 2.0 mg (6% overall) of **29b** as a yellow solid (252−254 °C): ^{1}H NMR (acetone-d_6) 10.65 (s, 1H, CON*H*), 7.31 (s, 5-H), 6.47 (s, 1H, 7-H), 6.41 (s, 1H, 10-H), 6.06 [s, 1H, (CH$_3$)$_2$CN*H*], 3.01 (dd, 1H, J = 16.6, 4.8, 4-H$_{eq}$), 2.53 (dd, 1H, J = 16.6, 11.0, 4-H$_{ax}$), 1.72 (m, 3-H), 1.53 (m, 1H, 3-CH*H*CH$_3$), 1.30 and 1.12 [2s, 2 × 3H, 2-C(CH_3)$_2$], 1.10 (m, 1H, 3-CH*H*CH$_3$), 1.05 (t, 3H, J = 7.2, 3-CH$_2$CH$_3$); ^{13}C NMR (acetone-d_6) 162.1, 148.9, 141.6, 125.2, 124.2 (q, J = 270), 118.4, 114.2 (q, J = 6.0), 105.3, 97.1, 53.3, 44.1, 29.4, 23.9, 23.4, 12.7. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

4-Ethyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline (25c). A 50-mL two-necked rb flask containing cerium(III) chloride heptahydrate under evacuation (0.5 Torr) was immersed in an oil bath and heated gradually with stirring to 140 °C over 3−4 h. Nitrogen gas was then introduced, the flask was then cooled in an ice bath and subsequently charged with THF (5 mL), and finally the flask was allowed to warm to room temperature overnight. The reaction flask was then cooled in an ice bath, and ethyl magnesium bromide (3.0 M in Et_2O, 1.46 mL, 4.38 mmol) was slowly added. After 1.5 h of stirring at 0 °C, ketone **23** (802 mg, 2.92 mmol) in 3 mL of THF was added dropwise, and stirring was continued for 45 min. The reaction mixture was then quenched with 10% HOAc (5 mL), stirring for 10 min. The biphasic mixture was then extracted with EtOAc (3 × 15 mL) and washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2:1) to give 702 mg of an alcohol as a colorless oil, which was carried on to the next step. To a flame-dried 10-mL rb flask containing the alcohol product dissolved in 1:1 EtOAc/EtOH solution (8 mL) was added 10%

Pd on C (ca. 1 mol %) and TFA (20 μL). After flushing and evacuation of the vessel three times with N_2, the mixture was stirred at room temperature under an atmosphere of H_2 overnight. The mixture was then filtered through a pad of Celite, and the eluent was concentrated under reduced pressure to yield a yellow oil which was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:1) to give the BOC-protected tetrahydroquinoline product as a white solid. The BOC-protected tetrahydroquinoline product was then treated with TFA (1 mL) in 2 mL of CH_2Cl_2 at room temperature for 12 h, and the reaction was quenched with anhydrous K_2CO_3 (1 g) and H_2O (10 mL). The biphasic mixture was then extracted with CH_2Cl_2 (3 × 10 mL) and washed with H_2O (5 mL) and saturated $NaHCO_3$ (5 mL). The organic solution was dried (Na_2SO_4), and concentrated under reduced pressure afforded 428 mg (78%) of tetrahydroquinoline **25c** as a colorless oil which required no purification before taken on to the next step: ^{1}H NMR 7.17 (d, 1H, J = 7.6, 5-H), 6.96 (t, 1H, J = 7.6, 6-H), 6.65 (dt, 1H, J = 7.6, 1.1, 7-H), 6.45 (dd, 1H, J = 7.9, 1.0, 8-H), 3.53 (br s, 1H, N*H*), 2.76 (m, 1H, 4-H), 2.03 (m, 1H, 4-C*H*HCH$_3$), 1.78 and 1.43 [d of AB q, 2H, J_{AB} = 12.9, J_A = 6.0, (3-H$_{eq}$), J_B = 12.3, (3-H$_{ax}$)], 1.59 (m, 1H, 4-CH*H*CH$_3$), 1.25 and 1.16 [2s, 2 × 3H, 2-(C*H*$_3$)$_2$], 0.95 (t, 3H, J = 7.5, 4-CH$_2$C*H*$_3$).

4-Ethyl-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (29c). Quinoline **25c** (428 mg, 2.78 mmol) was subjected to the general three-step nitration−hydrogenation−Knorr sequence previously described for the synthesis of **9e**, affording 249 mg (34% overall) of **29c** as a yellow solid (mp 276−278 °C): ^{1}H NMR (CD$_3$OD) 7.49 (d, 1H, J = 1.4, 5-H), 6.48 (s, 1H, 7-H), 6.39 (s, 1H, 10-H), 2.84 (m, 1H, 4-H), 2.06 (m, 1H, 4-CH*H*CH$_3$), 1.86 and 1.39 [d of AB q, 2H, J_{AB} = 12.9, J_A = 5.3, (3-H$_{eq}$), J_B = 12.7, (3-H$_{ax}$)], 1.65 (m, 1H, 4-CH*H*CH$_3$), 1.30 and 1.21 [2s, 2 × 3H, 2-(C*H*$_3$)$_2$], 0.99 (t, 3H, J = 7.5, 4-CH$_2$C*H*$_3$); ^{13}C NMR 164.2, 150.6, 141.3, 140.2, 124.8, 123.6, 123.5, 112.8, 106.4, 97.8, 50.4, 40.8, 34.6, 31.3, 28.5, 27.3, 10.6. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

4-Isopropyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline (25d). Ketone **23** (800 mg, 2.92 mmol) was subjected to the organocerium addition with in situ generation of the Grignard reagent using 2-bromopropene (400 μL, 4.67 mmol) and magnesium (1.13 g, 46.7 mmol), reduction−hydrogenation, and deprotection previously described for the synthesis of **25c**, affording 284 mg (34% overall) of **29c** as a colorless oil: ^{1}H NMR 7.16 (d, 1H, J = 7.7, 5-H), 6.95 (t, 1H, J = 7.5, 6-H), 6.66 (t, 1H, J = 7.1, 7-H), 6.45 (d, 1H, J = 7.9, 8-H), 3.51 (br s, 1H, NH), 2.84 (m, 1H, 4-H), 2.53 (m, 1H, isopropyl-CH), 1.60 and 1.47 [d of AB q, 2H, J_{AB} = 12.8, J_A = 6.1, (3-H$_{eq}$), J_B = 12.6, (3-H$_{ax}$)], 1.26 and 1.14 [2s, 2 × 3H, 2-(CH$_3$)$_2$], 1.06 and 0.71 [2d, 2 × 3H, J = 6.9, 6.9, isopropyl-C(C*H*$_3$)$_2$].

1,2,3,4-Tetrahydro-4-isopropyl-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (29d). Quinoline **25d** (284 mg, 1.41 mmol) was subjected to the general three-step nitration−hydrogenation−Knorr sequence previously described for the synthesis of **9e**, affording 13 mg (3% overall) of **29d** as a yellow solid (mp 278−279 °C dec): ^{1}H NMR (acetone-d_6) 10.90 (br s, 1H, CON*H*), 7.49 (s, 1H, 5-H), 6.49 9s, 1H, 7-H), 6.45 (s, 1H, 10-H), 6.03 [br s, 1H, (CH$_3$)$_2$CN*H*], 2.92 (m, 1H, 4-H), 2.60 (m, 1H, isopropyl-C*H*), 1.76 and 1.45 [d of AB q, 2H, J_{AB} = 12.9, J_A = 5.3, (3-H$_{eq}$), J_B = 12.8, (3-H$_{ax}$)], 1.33 and 1.22 [2s, 2 × 3H, 2-(C*H*$_3$)$_2$], 1.12 and 0.77 [2d, 2 × 3H, J = 7.0, 7.0, isopropyl-C(C*H*$_3$)$_2$]; ^{13}C NMR (acetone-d_6) 162.0, 150.1, 141.2, 138.5, 124.2, 123.3, 121.2, 114.6, 114.5, 105.3, 97.9, 50.1, 38.3, 34.4, 31.4, 28.0, 21.0, 15.7. Anal. ($C_{18}H_{21}F_3N_2O$) C, H, N.

1-(*tert*-Butyloxycarbamoyl)-1,2,3,4-tetrahydro-2,2,3,3-tetramethylquinolin-4-one (24e). In a flame-dried 10-mL rb flask, KH (131 mg, 3.27 mmol) was washed with pentane (3 × 2 mL) and then suspended in THF (5 mL) at 0 °C. To this suspension was added dropwise a solution of ketoquinoline **23** (300 mg, 1.09 mmol) in 2 mL of THF over 10 min. The mixture was allowed to stir for 30 min at 0 °C and then for 30 min at room temperature. Iodomethane (2.04 mL, 32.7 mmol, 10.0 equiv) was added in one portion, and the mixture was allowed to stir at room temperature for 30 min. The reaction was then quenched with saturated NH_4Cl (5 mL), and the mixture was diluted with EtOAc (5 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield a yellow oil. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) afforded 289 mg (87%) of the desired ketone as a white solid: ^{1}H NMR 7.95 (dd, 1H, J = 7.9, 1.7, 5-H), 7.41 (ddd, 1H, J = 8.7, 7.3, 1.8, 7-H), 7.18 (d, 1H, J = 8.5, 8-H), 7.05 (t, 1H, J = 7.8, 6-H), 1.51 [s, 9H, (C*H*$_3$)$_3$CO], 1.44 [s, 6H, 2-(C*H*$_3$)$_2$], 1.21 (s, 6H, 3-(C*H*$_3$)$_2$).

1,2,3,4-Tetrahydro-2,2,3,3-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (29e). The tetramethylated ketone **24e** (153 mg, 0.50 mmol) was subjected to the two-step reduction−deprotection sequence as previously described for **27a**, affording 66 mg (70% overall) of **27e** as a colorless oil. Quinoline **27e** (66 mg, 0.35 mmol) was then subjected to the general three-step nitration−hydrogenation−Knorr sequence previously described for the synthesis of **9e**, affording 40 mg (35% overall) of **29e** as a yellow solid (mp 308-310 °C): ^{1}H NMR (acetone-d_6) 11.20 (br s, 1H, CON*H*), 7.30 (s, 1H, 5-H), 6.52 (s, 1H, H), 6.46 (s, 1H, 10-H), 6.10 [br s, 1H, (CH$_3$)$_2$CN*H*], 2.68 (s, 2H, 4-H), 1.22 [s, 6H, 2-(C*H*$_3$)$_2$], 1.00 [s, 6H, 3-(C*H*$_3$)$_2$]; ^{13}C NMR (acetone-d_6) 162.0, 148.5, 141.4, 125.6, 124 (q, J = 274), 118.1, 114.3, 105.0, 97.1, 55.6, 40.1, 34.0, 25.1, 24.2; IR (KBr) 3342 (m), 3310 (m), 1664 (s), 1628 (s), 1435 (m), 1165 (s), 1134 (s). Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

2,2,3,3,4-Pentamethyl-1,2,3,4-tetrahydroquinoline (26f). To a flame-dried 10-mL rb flask containing methyllithium (1.0 mL of a 1.4 M solution in Et_2O, 1.4 mmol, 1.5 equiv) diluted with Et_2O (2 mL) at −78 °C, a solution of ketone **24e** (289 mg, 0.96 mmol) in Et_2O (2 mL) was added dropwise over 10 min. The mixture was allowed to stir at −78 °C for 30 min and then at 0 °C for 1.5 h. To the reaction mixture was then added saturated NH_4Cl (1 mL) and Et_2O (5 mL). The layers were separated, and aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield a pale yellow oil. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) afforded 215 mg (71%) of 1-(*tert*-butyloxycarbamoyl)-1,2,3,4-tetrahydro-4-hydroxy-2,2,3,3,4-pentamethylquinoline as a white solid: ^{1}H NMR 7.47 (dd, 1H, J = 7.7, 1.4, 5-H), 7.11 (m, 3H, 6,7,8-H), 1.63 (s, 3H, 4-C*H*$_3$), 1.55 [s, 9H, COC(C*H*$_3$)$_3$], 1.44, 1.37, 0.97, and 0.95 [4s, 4 × 3H, 2,3-(C*H*$_3$)$_3$]. The tertiary alcohol thus obtained was then subjected to the catalytic hydrogenation procedure as previously described for the preparation of **25b**, affording 112 mg (82%) of pentamethyl compound **26f** as a pale yellow oil: ^{1}H NMR 7.17 (d, 1H, 5-H), 6.98 (t, 1H, J = 7.5, 7-H), 6.67 (t, 1H, J = 7.1, 6-H), 6.46, dd, 1H, J = 7.9, 0.9, 8-H), 3.54 (br s, 1H, CON*H*), 2.79 (q, 1H, J = 6.9, 4-H), 1.29 (d, 3H, J = 7.1, 4-C*H*$_3$), 1.21, 1.13, 0.99, and 0.76 [4s, 4 × 3H, 2,3-(C*H*$_3$)$_2$].

1,2,3,4-Tetrahydro-2,2,3,3,4-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (29f). Quinoline **26f** (112 mg, 0.560 mmol) was subjected to the general three-step nitration−hydrogenation−Knorr sequence described previously for the synthesis of **9e**, affording 28 mg (14% overall) of **29f** as a yellow solid (mp 300−301 °C dec): ^{1}H NMR 11.92 (br s, 1H, CON*H*), 7.52 (s, 1H, 5-H), 6.66 (s, 1H, 7-H), 6.33 (s, 1H, 10-H), 4.43 [br s, 1H, (C*H*$_3$)$_2$CN*H*], 2.88 (q, 1H, J = 6.4, 4-H), 1.24 (d, 3H, J = 6.8, 4-C*H*$_3$), 1.24, 1.18, 1.03, and 0.71 [4s, 4 × 3H, 2,3-(C*H*$_3$)$_2$]; ^{13}C NMR 163.8, 147.1, 139.1 (q, J = 31.0), 123.5, 122.9 (q, J = 275.4), 112.6 (d, J = 5.2), 106.0, 96.2, 77.2, 55.8, 36.7, 36.0, 26.1, 25.1, 22.5, 16.5, 13.1. Anal. ($C_{18}H_{21}F_3N_2O$) C, H, N.

3-Acetoxy-6-chloro-3-methylhex-1-yne (30). In a 1-L, 3-neck rb flask with an addition funnel, a solution of 5-chloro-2-pentanone (33.1 g, 274 mmol) in THF (140 mL) was treated with ethynylmagnesium bromide (564 mL of a 0.5 M solution in THF, 282 mmol, 1.03 equiv) over 0.5 h at −78 °C. The internal temperature rose to −30 °C during the addition. The mixture was allowed to warm to 0 °C, stirred for 1 h, and then

poured into a cold mixture of Et_2O (400 mL) and 1 N $NaHSO_4$ (400 mL). The aqueous layer was extracted with Et_2O (2 × 200 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to 42 g of a brown oil. This material was transferred to a 250-mL rb flask, whereupon pyridine (27 mL) and acetic anhydride (36.4 g, 356 mmol, 1.30 equiv) were added, and then the flask was cooled to 0 °C. DMAP (1.67 g, 13.7 mmol, 5%) was added, and the solution was stirred for 2 d and then treated with MeOH (10 mL). After 1 h, the solution was poured into a cold mixture of Et_2O (250 mL) and 2 N $NaHSO_4$ (250 mL). The aqueous layer was extracted with Et_2O (250 mL), and the combined organic layers were washed with brine (250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a brown oil. Distillation afforded 30.5 g (59%) of **30** as a colorless oil (bp 79−80 °C at 10 mm Hg): ^{1}H NMR 3.52−3.65 (m, 2H, 6-H), 2.57 (s, 1H, C≡C*H*), 1.85−2.15 (m, 4H, 4,5-H), 2.04 (s, 3H, COCH_3), 1.71 (s, 3H, 3-CH_3).

2-Ethynyl-2-methyl-1-phenylpyrrolidine (31). This compound was prepared from **30** (10.2 g, 54.3 mmol) in a manner similar to that described for **16**, affording 6.35 g (63%) of **31** as a light golden oil (R_f 0.32, hexanes/EtOAc, 19:1): ^{1}H NMR 7.20−7.28 (m, 2H, 3′-H), 6.95 (d, 2H, J = 8.1, 2′-H), 6.72 (t, 1H, J = 7.2, 4′-H), 3.43−3.52 (m, 1H, NC*H*H), 3.35−3.43 (m, 1H, NCH*H*), 2.40−2.50 (m, ^{1}H), 2.40 (s, 1H, C≡C*H*), 2.05−2.17 (m, 2H), 1.92−2.02 (m, ^{1}H), 1.62 (s, 3H, CH_3).

5,6,6a,10-Tetrahydro-6a-methylpyrrolidino[1,2-*a*]quinoline (32). This compound was prepared from **31** (1.85 g, 10.0 mmol) by cyclization in the manner previously described for dihydroquinolines **17**, followed by catalytic hydrogenation as previously described for the synthesis of **18**, affording 1.36 g (99%) of **32**, as a colorless oil, which was used without further purification: ^{1}H NMR 7.07 (t, J = 7.7, 1 H, 2-H), 7.03 (d, J = 7.4, 1H, 4-H), 6.55 (td, J = 7.3, 0.9, 1H, 3-H), 6.41 (d, J = 8.0, 1H, 1-H), 3.46 (td, J = 9.1, 2.1, 1H, NCH), 3.19 (q, J = 9.1, 1H, NCH), 2.86−2.96 (m, 1H, 4-H), 2.72 (ddd, J = 16.5, 5.1, 1.9, 4-H), 2.05−2.20 (m, ^{1}H), 1.88−2.08 (m, 3H), 1.60 (td, J = 12.0, 7.8, ^{1}H), 1.42 (td, J = 13.2, 5.1, ^{1}H), 1.04 (s, 3H, CH_3).

6,7,7a,11-Tetrahydro-7a-methyl-4-trifluoromethyl-2-pyridono[5,6-*g*]pyrrolidino[1,2-*a*]quinoline (33). This compound was prepared from **32** (1.21 g, 6.47 mmol) in three steps by the general nitration−hydrogenation−Knorr procedure previously described for the synthesis of **9e**, affording 130 mg (16% overall) of **33** (R_f 0.15 EtOAc/CH_2Cl_2/hexanes, 1:1:1) as a yellow solid, a portion of which was recrystallized from methanol (mp 289-310 °C dec): ^{1}H NMR (acetone-d_6) 10.54 (s, 1H, CON*H*), 7.34 (s, 1H, 5-H), 6.42 (s, 1H, 3-H), 6.36 (s, 1H, 12-H), 3.52 (t, 1H, J = 9.7, NCH*H*), 3.28 (q, 1H, J = 9.6, NCH*H*), 2.92−3.05 (m, 1H, 4-H), 2.80−2.90 (m, 1H, 4-H), 2.18−2.30 (m, ^{1}H), 2.00−2.20 (m, 3H), 1.68 (td, 1H, J = 12.1, 7.9), 1.46 (td, 1H, J = 13.3, 5.1), 1.14 (s, 3H, CCH_3); ^{13}C NMR (DMSO-d_6) 160.6, 146.2, 140.9, 136.4 (q, J = 30.0), 123.0 (q, J = 276), 122.9, 118.0, 113.0 (q, J = 6.0), 102.6, 94.0, 59.3, 46.5, 32.2, 24.0, 23.4, 21.4; HRMS calcd for $C_{17}H_{17}F_3N_2O$ (M^+): m/z 322.1293, found 322.1277. Anal. ($C_{17}H_{17}F_3N_2O$) C, H, N.

6,7,7a,11-Tetrahydro-1,7a-dimethyl-4-trifluoromethyl-2-pyridono[5,6-*g*]pyrrolidino[1,2-*a*]quinoline (34). This compound was prepared from **33** (73 mg, 0.23 mmol) in a manner similar to that described for **19a**, affording 31 mg (41%) of **34** as a yellow solid (R_f 0.52, CH_2Cl_2/EtOAc/hexanes, 2:1:1), a portion of which was recrystallized from methanol (mp 170-171 °C): ^{1}H NMR 7.44 (s, 1H, 5-H), 6.71 (s, 1H, 3-H), 6.12 (s, 1H, 12-H), 3.67 (s, 3H, NCH_3), 3.56 (t, 1H, J = 9.0, NC*H*H), 3.30 (q, 1H, J = 9.2, NCH*H*), 2.95−3.05 (m, 1H, 4-H), 2.80−2.90 (m, 1H, 4-H), 2.20−2.32 (m, ^{1}H), 2.08−2.20 (m, 2H), 2.03 (dd, 1H, J = 11.9, 6.8), 1.68 (td, 1H, J = 12.2, 7.9), 1.48 (td, 1H, J = 13.3, 5.1), 1.13 (s, 3H, CCH_3); ^{13}C NMR 161.6, 146.6, 141.7, 136.5 (q, J = 31.0), 125.0 (br), 123.0 (q, J = 276), 113 (q, J = 5.8), 104.6, 93.8, 59.8, 46.9, 40.2, 32.9, 29.7, 24.4, 23.6, 22.0, 21.9. Anal. ($C_{18}H_{19}F_3N_2O$) C, H, N.

1-(*tert*-Butyloxycarbonyl)-8-ethoxy-1,2,3,4-tetrahydro-2,2-dimethyl-6-(trifluoromethyl)pyridino[5,6-*g*]quinoline (37). This compound was prepared from **10e** (2.76 g, 8.51 mmol) in the manner previously described for **23**, affording 2.96 g (82%) of the protected dihydroquinoline **37** as pale yellow needles after recrystallization from methanol: ^{1}H NMR 7.57 (s, 1H, 5-H), 6.85 (s, 1H, 7-H), 5.91 (s, 1H, 10-H), 4.51 (q, 2H, J = 7.1, OCH_2CH$_3$), 2.94 (t, 2H, J = 6.8, 4-H), 1.77 (t, 2H, J = 6.8, 3-H), 1.65 [s, 9H, C(CH_3)$_3$], 1.41 (t, 3H, J = 7.0, OCH$_2$CH_3), 1.29 [s, 6H, NC(CH_3)$_2$].

1-(*tert*-Butyloxycarbonyl)-8-ethoxy-1,2,3,4-tetrahydro-2,2-dimethyl-4-oxo-6-(trifluoromethyl)pyridino[5,6-*g*]quinoline (38). To an oven-dried 200-mL rb flask containing **37** (3.02 g, 7.11 mmol) in 70 mL of benzene were added Celite (10 g) and PCC (15.3 g, 71.1 mmol, 10.0 equiv), and the mixture was heated to reflux for 4 h. Upon being cooled to room temperature, the mixture was filtered through a short column of Florisil, washing with CH_2Cl_2. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc, gradient elution), affording 0.94 g (30%) of ketone **38** as an off-white solid: ^{1}H NMR 8.61 (d, 1H, J = 1.8, 5-H), 7.74 (s, 1H, 7-H), 7.08 (s, 1H, 10-H), 4.55 (q, 2H, J = 7.0, OCH_2CH$_3$), 2.82 (s, 2H, 3-H), 1.62 [s, 9H, C(CH_3)$_3$], 1.55 and 1.54 [2s, 2 × 3H, NC(CH$_3$)$_2$], 1.45 (t, 3H, J = 7.0, OCH$_2$CH_3).

1,2,3,4-Tetrahydro-2,2-dimethyl-4-oxo-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (39). To a 10-mL rb flask containing protected ketone **38** (16.0 mg, 0.04 mmol) was added 0.3 mL of TFA, and the mixture was warmed to 60 °C for 5 min. Upon being cooled to room temperature, the mixture was added to 10 mL of saturated $NaHCO_3$ and extracted with 20 mL of EtOAc. The organic layer was concentrated under reduced pressure, and the residue was heated to 80 °C with 1 mL of 57% HI in a 25-mL rb flask for 90 min. Upon being cooled to room temperature, the mixture was added to 10 mL of saturated $NaHCO_3$ and extracted with 20 mL of EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexane/EtOAc, gradient elution) afforded 10.4 mg (92%) of ketone **39** as a pale yellow solid: ^{1}H NMR 11.38 (br s, 1H, CON*H*), 8.33 (s, 1H, 5-H), 6.75 (s, 1H, 7-H), 6.52 (s, 1H, 10-H), 4.70 [br s, 1H, (CH$_3$)$_2$CN*H*], 2.66 (s, 2H, 3-H), 1.36 [s, 6H, 2-(CH_3)$_2$].

1,2-Dihydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono-[5,6-*g*]quinoline (36). To a 5-mL rb flask containing ketone 39 (8.5 mg, 0.03 mmol) in 0.5 mL of MeOH at room temperature was added $NaBH_4$ (mg, mmol, equiv), and the mixture was stirred for 1 h before the reaction was quenched with the addition of 1 mL of water. The MeOH was removed under reduced pressure, and the residue was extracted with EtOAc (10 mL), washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The 4-hydroxy compound thus obtained was homogeneous by TLC and was used without further purification. A portion of the 4-hydroxy compound (5 mg) was treated with 2 mg of *p*-TsOH in 1 mL of benzene at 70 °C for 6 h. Upon being cooled to room temperature, the mixture was added to 5 mL of saturated $NaHCO_3$ and extracted with 10 mL of EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by preparative TLC (silica gel, 250 μm plate, 2% EtOH in EtOAc) afforded 3.9 mg (82%) of olefin **36** as a yellow solid: ^{1}H NMR 11.42 (br s, 1H, CON*H*), 7.23 (d, 1H, J = 0.5, 5-H), 6.66 (s, 1H, 7-H), 6.32 (d, 1H, J = 10.0, 4-H), 6.30 (s, 1H, 10-H), 5.57 (dd, 1H, J = 9.8, 1.9, 3-H), 4.33 [br s, 1H, (CH$_3$)$_2$-CN*H*], 1.36 [s, 6H, 2-(CH_3)$_2$]. Anal. ($C_{15}H_{13}F_3N_2O$) C, H, N.

1-(*tert*-Butyloxycarbonyl)-8-ethoxy-1,2-dihydro-2,2,4-trimethyl-6-(trifluoromethyl)pyridino[5,6-*g*]quinoline (40). This compound was prepared from **10a** (13.0 g, 38.7 mmol) in the manner previously described for **22**, affording 12.9 g (76%) of **40** as a colorless, low-melting solid: ^{1}H NMR 7.56 (d, 1H, J = 1.8, 5-H), 6.84 (s, 1H, 7-H), 6.74 (s, 1H, 10-H), 5.52 (s, 1H, 3-H), 4.47 (q, 2H, J = 7.0, CH$_3$CH_2O), 4.12 [br s, 1H, (CH$_3$)$_2$-CN*H*], 2.09 (d, 3H, J = 1.3, 4-CH_3), 1.59 [s, 9H, C(CH_3)$_3$], 1.42 (t, 3H, J = 7.0, CH_3CH$_2$O), 1.34 [s, 6H, 2-(CH_3)$_2$].

1-(*tert*-Butyloxycarbonyl-8-ethoxy-1,2,3,4-tetrahydro-2,2,4-trimethyl-3-oxo-6-(trifluoromethyl)pyridino[5,6-*g*]-quinoline (41). This compound was prepared from hydroboration−oxidation of **40** (9.69 g, 22.2 mmol) in the manner

previously described for **23**, followed by oxidation of the 3-hydroxy compound (5.47 g, 12.0 mmol) with PDC (5.43 g, 14.4 mmol, 1.20 equiv) in 40 mL of CH_2Cl_2 at room temperature for 8 h. Filtration through a short plug of Florisil, followed by purification by flash column chromatography (silica gel, hexane/EtOAc, gradient elution), afforded 3.31 g (61%) of **41** as a pale yellow solid: ^{1}H NMR 7.81 (s, 1H, 5-H), 7.69 (br d, 1H, J = 1.5, 7-H), 7.16 (s, 1H, 10-H), 4.53 (m, 2H, CH_3CH_2O), 4.03 (q, 1H, J = 5.0, 4-H), 1.80 and 1.46 [2s, 2 × 3H, 2-$(CH_3)_2$], 1.59 (d, 3H, J = 6.6, 4-CH_3), 1.57 [s, 9H, $C(CH_3)_3$], 1.45 (t, 3H, J = 7.2, CH_3CH_2O).

1,2-Dihydro-2,2,3,4-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (42): This compound was prepared from ketone **41** (331 mg, 0.73 mmol) by a three-step addition−elimination−deprotection sequence similar to that previously described for preparation of **25** and **36**, affording 122 mg (52% overall, three steps) of **41** as a yellow solid. ^{1}H NMR 11.66 (br s, 1H, CONH), 7.42 (s, 1H, 5-H), 6.69 (s, 1H, 7-H), 6.35 (s, 1H, 10-H), 4.30 [br s, 1H, $(CH_3)_2CNH$], 2.02 (s, 3H, 4-CH_3), 1.86 (s, 3H, 3-CH_3), 1.33 [s, 6H, 2-$(CH_3)_2$]; ^{13}C NMR (acetone-d_6) 161.9, 148.4, 142.9, 138.8 (q), 130.7, 127.2, 125.4 (q), 119.8, 119.0, 114.4, 104.7, 96.6, 53.2, 50.6, 32.3, 18.4. Anal. ($C_{17}H_{17}F_3N_2O$) C, H, N.

***cis*- and *trans*-1,2,3,4-Tetrahydro-2,2,3,4-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (43 and 44).** To an oven-dried 10-mL rb flask containing olefin **42** (11.2 mg, 0.035 mmol) in 1 mL of 1,2-dichloroethane was added 0.5 mL of TFA and 0.5 mL of triethylsilane, and the mixture was heated to reflux for 8 h. Upon being cooled to room temperature, the mixture was added to 5 mL of saturated $NaHCO_3$ and extracted with 10 mL of EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by semipreparative HPLC (10 mm ODS, MeOH/H_2O, 8:2, 3.0 mL/min) afforded 4.9 mg (43%) of the cis isomer **43** with a retention time of 5.34 min, followed by 4.3 mg (38%) of the trans isomer **44** with a retention time of 6.01 min. The relative stereochemical identity of the respective isomers was confirmed by resynthesis of the *cis* isomer **43** through an alternate route analogous to that used for **29a**−**f**, where the relative stereochemistry at C_3 and C_4 was set through catalytic hydrogenation. **Data for *cis*-1,2,3,4-tetrahydro-2,2,3,4-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (43):** ^{1}H NMR 11.06 (br s, 1H, CONH), 7.55 (s, 1H, 5-H), 6.67 (s, 1H, 7-H), 6.28 (s, 1H, 10-H), 4.35 [br s, 1H, $(CH_3)_2CNH$], 2.54 (m, 1H, 4-H), 1.47 (s, 1H, 3-H), 1.38 (d, 3H, J = 6.6, 4-CH_3), 1.06 [s, 6H, 2-$(CH_3)_2$], 1.05 (d, 3H, J = 6.9, 3-CH_3); ^{13}C NMR 163.2, 146.6, 140.3, 139.1 (q), 124.0, 122.7, 119.8, 112.8, 105.8, 95.9, 49.7, 43.3, 29.9, 28.1, 27.6, 21.1, 18.4. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N. **Data for *trans*-1,2,3,4-tetrahydro-2,2,3,4-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]-quinoline (44):** ^{1}H NMR 11.22 (br s, 1H, CONH), 7.48 (s, 1H, 5-H), 6.68 (s, 1H, 7-H), 6.31 (s, 1H, 10-H), 4.32 [br s, 1H, $(CH_3)_2CNH$], 2.44 (m, 1H, 4-H), 1.57 (m, 1H, 3-H), 1.49 (d, 3H, J = 6.7, 4-CH_3), 1.11 (d, 3H, J = 6.8, 3-CH_3), 1.02 [s, 6H, 2-$(CH_3)_2$]; ^{13}C NMR 163.0, 146.6, 140.2, 138.8 (q), 124.5, 122.4, 120.0, 112.7, 105.6, 95.7, 49.7, 43.2, 31.5, 28.4, 27.6, 22.0, 18.6. Anal. ($C_{17}H_{19}F_3N_2O$) C, H, N.

Cotransfection Assays. Cotransfection assays using hAR and hPR-B were performed in CV-1 cells as described in the literature.[21] CV-1 cells (African green monkey kidney fibroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum then transferred to 96-well microtiter plates one day prior to transfection. Cells were transiently transfected by the calcium phosphate coprecipitation procedure with the following plasmids: pRShAR, MMTV-LUC reporter, pRS-β-Gal, and filler DNA (pRS-CAT). The receptor plasmid, pRShAR, contained the hAR under constitutive control of the Rous Sarcoma Virus promoter. 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 an androgen response element. pRS-β-Gal, coding for constitutive expression of *Escherichia coli* β-galactosidase (β-Gal), was included as an internal control for evaluation of transfection efficiency and compound toxicity. After transfection, media were removed and the cells were washed with phosphate-buffered saline (PBS). Media containing reference compounds (i.e., DHT and 2-hydroxyflutamide) or test compounds in concentrations ranging from 10^{-12} to 10^{-5} M were added to the cells. Three to four replicates were used for each sample. After incubation, the cells were washed with PBS, lysed with a Triton X-100 buffer and assayed for LUC and β-Gal activities using a luminometer or spectrophotometer, respectively. Data evaluation was performed using the Oracle relational database management system with analysis reports and programs designed at Ligand. For each replicate, the normalized response (NR) was calculated as: LUC response/β-Gal rate where β-Gal rate = β-Gal × 1 × 10^{-5}/β-Gal incubation time. The mean and standard error of the mean (SEM) of the NR were calculated. Data were plotted as the response of the compound compared to the reference compounds over the range of the concentration−response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Agonist efficacy (%) was a function of LUC expression relative to the maximum LUC production by the reference agonist, DHT. Antagonist activity was determined by testing the amount of LUC expression in the presence of DHT at its EC_{50} concentration. The concentration of test compound that inhibited 50% of LUC expression induced by progesterone was quantified (IC_{50}). In addition, efficacy of antagonists was determined as a function (%) of maximal inhibition (control without DHT). Cotransfection studies with hPR-B with the MMTV-LUC reporter were carried out as described above to determine cross-reactivity of test compounds.

Receptor Binding Assay. Receptor binding assays for hAR were determined in a whole-cell format using COS-1 cells in 96-well microtiter plates containing DMEM-10% FBS. Cells were transfected as described above with pRShAR (2 ng/well), pRS-β-Gal (50 ng/well), and pGEM (48 ng/well). Six hours after transfection, medium was removed, the cells were washed with PBS, and fresh medium was added. The next day, the media were changed to DMEM-serum free to remove any endogenous ligand complexed with hAR in the cells. After 24 h in serum-free media, either a saturation analysis to determine the K_d for [^{3}H]DHT on hAR or a competitive binding assay to evaluate the ability of test compounds to compete with [^{3}H]DHT for hAR was performed. For the saturation analysis, media (DMEM−0.2% CA-FBS) containing [^{3}H]DHT (12−0.24 nM) in the absence (total binding) or presence (nonspecific binding) of a 100-fold molar excess of unlabeled DHT were added to the cells. For the competitive binding assay, media containing 1 nM [^{3}H]DHT and test compounds in concentrations ranging from 10^{-10} to 10^{-6} M were added to the cells. Three replicates were used for each sample. After 3 h at 37 °C, an aliquot of the total binding media at each concentration of [^{3}H]DHT was removed to estimate the amount of free [^{3}H]-DHT. The remaining media was removed, the cells were washed three times with PBS to remove unbound ligand, and cells were lysed with a Triton X-100-based buffer. The lysates were assayed for bound [^{3}H]DHT and β-Gal activity using a scintillation counter or spectrophotometer, respectively. For the saturation analyses, the difference between the total binding and the nonspecific binding, normalized by the β-Gal rate, was defined as specific binding, which was evaluated by Scatchard analysis to determine the K_d for [^{3}H]DHT. For the competition studies, the data was plotted as the amount of [^{3}H]DHT (% of control in the absence of test compound) remaining over the range of the dose-response curve for a given compound. The concentration of test compound that inhibited 50% of the amount of [^{3}H]DHT bound in the absence of competing ligand was quantified (IC_{50}) after log−logit transformation. The K_i values were determined by application of the Cheng−Prussof equation to the IC_{50} values, where

$$K_i = \frac{IC_{50}}{(1 + \{[^3H]DHT\})/K_d \text{ for } [^3H]DHT}$$

In Vivo Methods; Castrated Rat Model. Male immature rats (60-70 g, 23−25-day-old, Sprague−Dawley, Harlan, five animals/group) were castrated under metofane anesthesia. Five days after castration, animals were divided into groups and dosed for 3 days with one of the following: (1) control vehicle (10% dimethylacetamide (DMA) in 0.2% Tween-80 and 0.25% carboxymethylcellulose) (3 mL/kg/day, orally); (2) TP (1 mg/kg/day, subcutaneous injection in 0.2 mL of sesame oil); (3) TP plus an AR antagonist **1**, **2a**, **3**, **9a**,**d**,**e**, or **19a** (30 mg/kg/day). At the end of treatment, animals were sacrificed, and VPs were collected and weighed. To compare data from different experiments, organ weights were first standardized as mg/100 g of body weight; the increase in organ weight induced by TP (1 mg/kg/day) was taken as the maximum response (100%). One-factor ANOVA followed by the Fisher protected least significant differences test was used for statistical analysis.

Mature Intact Rat Model. Male mature rats (200−250 g, Sprague−Dawley, Harlan; four or five animals/group) received one of the following treatments for 2 weeks. (1) Intact control: oral dosing with vehicle (10% DMA in 0.2% Tween-80 and 0.25% carboxymethylcellulose). (2) Castrated control: oral dosing with vehicle only (surgery done at the time of the first treatment). (3) **2a**, **3**, **9a**, or **9e** to intact rats: oral dosing (20 or 40 mg/kg/day). At the end of treatment, animals were sacrificed and the following occurred: (1) blood was collected by cardiac puncture; serum was separated and stored at −20 °C. T was measured by RIA using SPA technique (Amersham); LH was measured by RIA with kits supplied by Amersham using NIH standards (NIADDK-rat-LH-RP2). (2) Organ wet weights were determined for VP and SV and calculated as before.

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Supporting Information Available: Synthetic procedures and chemical characterization data for compounds **8b**−**d**,**f**−**i**, **16f**−**i**, **17f**−**i**, and **18f**−**i** (4 pages). Ordering information is given on any current masthead page.

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