Nonsteroidal Selective Glucocorticoid Modulators: The Effect of C-10 Substitution on Receptor Selectivity and Functional Potency of 5-Allyl-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinolines

Philip R. Kym,*,† Michael E. Kort,*,† Michael J. Coghlan,†,# Jimmie L. Moore,† Rui Tang,† James D. Ratajczyk,† Daniel P. Larson,† Steven W. Elmore,† John K. Pratt,† Michael A. Stashko,† H. Douglass Falls,† Chun W. Lin,† Masake Nakane,† Loan Miller,† Curtis M. Tyree,‡ Jeffery N. Miner,‡ Peer B. Jacobson,† Denise M. Wilcox,† Phong Nguyen,† and Benjamin C. Lane†

Immunologic Diseases Research, Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064-6061 and New Leads Discovery and Transcription Research, Ligand Pharmaceuticals, Inc., San Diego, California 92121

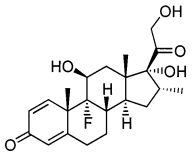
Received July 31, 2002

The preparation and characterization of a series of C-10 substituted 5-allyl-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinolines as a novel class of selective ligands for the glucocorticoid receptor is described. Substitution at the C-10 position of the tetracyclic core with linear, two-atom appendages (OCH_3, OCF_2H, NHMe, SMe, $CH{=}CH_2$, C≡CH, CH_2OH) provided molecules of high affinity ($K_i = 2-8$ nM) for the human glucocorticoid receptor (hGR) with limited cross-reactivity with other steroid receptors (PR, MR, AR, ER). Optimal analogues showed slightly less potent but highly efficacious E-selectin repression with reduced levels of GRE activation efficacy in reporter gene assays relative to prednisolone. Preliminary SAR of analogues containing substitution at the C-9 and C-10 positions identified the 9-OH, 10-OMe analogue **50** and the 9-OH, 10-Cl analogue **58** as compounds that demonstrated potent, GR-mediated inhibition in a conconavalin A stimulated T-cell proliferation assay in both rodent and human whole blood monocytes. When evaluated for their in vivo effects in carrageenan-induced paw edema in rats, **50**, **58**, and 10-OCF_2H analogue **35** showed dose-dependent anti-inflammatory effects (**50**, $ED_{50} = 16$ mg/kg; **58**, $ED_{50} = 15$ mg/kg; **35**, $ED_{50} = 21$ mg/kg vs $ED_{50} = 15$ mg/kg for **18** and $ED_{50} = 4$ mg/kg for prednisolone).

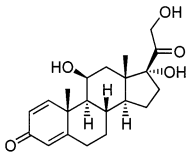
Introduction

Having long been considered among the most potent anti-inflammatory agents known, oral glucocorticoids such as dexamethasone[1] (dex, **1**) and prednisolone[2] (pred, **2**) continue to represent the clinical gold standard for treatment of numerous musculoskeletal, respiratory, gastrointestinal, and dermatological disorders.[3−5] Unfortunately, these beneficial anti-inflammatory and immunomodulatory effects are counterbalanced by a broad spectrum of adverse events, the frequency and severity of which tend to increase with increased dosage, length of therapy, and systemic exposure. These deleterious side effects, which include osteoporosis,[6] glucose intolerance,[7] lipid redistribution, and acute psychosis,[8] have limited a more widespread therapeutic use of synthetic glucocorticoids.

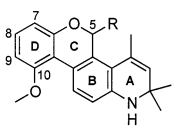
Over the past several years, an understanding of the molecular mechanisms by which corticosteroids exert their biological effects has begun to emerge. Glucocorticoids bind to the glucocorticoid receptor (GR) whereupon the resulting GR/ligand complex can either initiate transcription of specific target genes by binding to consensus sequences on DNA known as glucocorticoid receptor response elements[9] (GREs) or inhibit transcription by repressing the activity of other transcription factors such as NFkB[10] or AP-1.[11] Recently, it has been shown that these are discreet processes, and it has been postulated that molecules that repress transcription without activating GREs may lead to anti-inflammatory drugs with reduced side effect liabilities.[12]



dexamethasone (**1**)



prednisolone (**2**)



3 R = aryl, alkyl

The functional role played by the GR/ligand complex in the initiation or repression of transcriptional events is determined predominantly by its topology, particularly the accessibility of key regions of this complex to interact with various transcription factors, co-promoters, and co-repressor proteins.[13] The conformation of the GR/ligand complex is in turn determined by the manner in which the receptor envelops the ligand, and minor changes in ligand structure can lead to GR/ligand complexes of varied tertiary structure which perform different functions.[14] Our goal is the discovery of structurally novel, nonsteroidal small molecule modulators of GR that mechanistically differentiate transcriptional repression and activation pathways, ultimately providing a superior anti-inflammatory agent with a reduced iatrogenic profile.[15−17]

* To whom correspondence should be addressed: Michael Kort, Abbott Laboratories, D-R4PM Bldg. AP10, 100 Abbott Park Road, Abbott Park, IL 60064-6101; 847-935-4945; michael.e.kort@abbott.com; Philip Kym, Abbott Laboratories, D-R4MF Bldg. AP10, 100 Abbott Park Road, Abbott Park, IL 60064-6061; 847-935-4699; phil.r.kym@abbott.com.

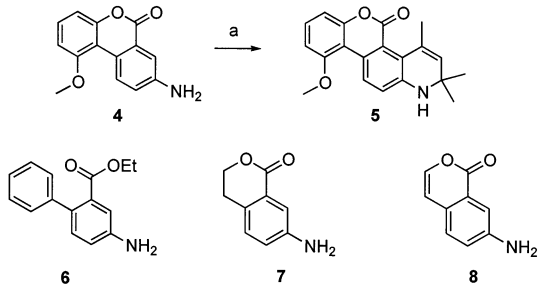
† Abbott Laboratories.

‡ Ligand Pharmaceuticals.

Present address: Eli Lilly and Co., Indianapolis, IN 46285

10.1021/jm020335m CCC: $25.00
Published on Web 02/19/2003

Scheme 1[a]



[a] Reagents: (a) acetone, I_2, 105 °C.

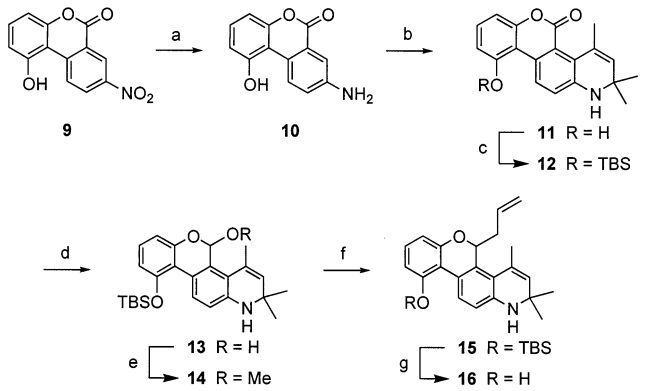
We have recently described the discovery of GR-selective 1,2-dihydro-2,2,4-trimethyl-5H-chromeno-[3,4-f]quinolines (**3**) that are comparable to pred in rodent in vivo models for rheumatoid arthritis and asthma.[15] Introduction of a methyl ether group at the C-10 position of this pharmacophore imparted GR-selective binding accompanied by enhanced GR-specific functional potency for both reporter gene assays of repression and whole cell models of GR function. It was further demonstrated that selective potentiation of GRE activation in this series could be achieved by judicious structural modification of the C-5 substituent.[16] Herein, we describe a more extensive SAR associated with D-ring functionality, concentrated on defining the optimal substitution pattern for potent, GR-selective functional ligands.

Chemistry

For the preparation of analogues bearing the desired substitution pattern, we sought to develop a general method for incorporation of the D-ring involving late-state embellishment of a suitably functionalized AB-ring precursor. To our disappointment, the modified Skraup annulation reaction which provided highly regioselective access to trimethylquinolines when executed with substituted aminocoumarins (e.g., **4** → **5**, Scheme 1)[15,18] was neither selective nor efficient when performed with model substrates **6** or **7**. It was empirically determined that the minimal structural requirement necessary to retain regioselectivity in the Skraup reaction was the presence of an unsaturated C-ring lactone, exemplified by the decisive regioselection (10:1) in the annulation of coumarin **8**. On the basis of this observation, we reasoned that increased diversity of substitution in the D-ring might be best accomplished by installation of functional groups that could be subsequently modified or used to direct the incorporation of additional structural complexity. To this end, our synthetic target became a core structure bearing latent C-10 hydroxyl functionality which could presumably be converted to a large number of C-10 alkyl ethers or further elaborated, via the corresponding trifluoromethanesulfonate derivative, to carbon- and nitrogen-substituted analogues using palladium-catalyzed coupling methodology.

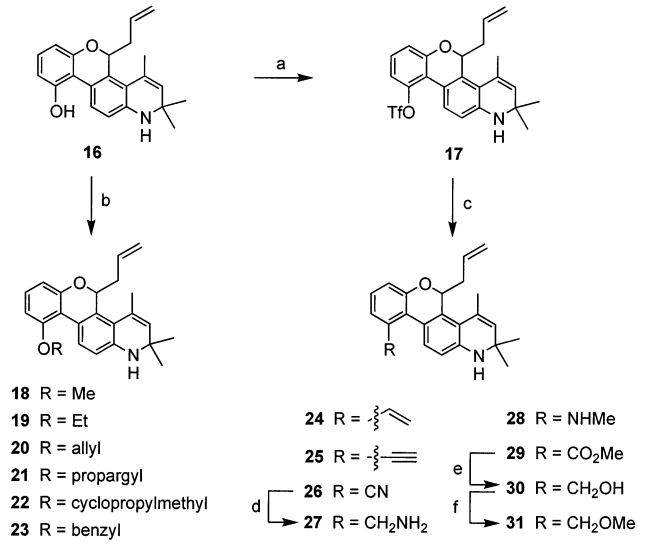
Construction of the desired tetracyclic core made recourse to benzocoumarin **9** (Scheme 2), the synthesis of which has been described elsewhere.[15] Catalytic hydrogenation of the nitroarene afforded aniline **10** which was regioselectively transformed to 1,2-dihydro-2,2,4-trimethylquinoline **11** following in situ conversion to the tris(trimethylsilyl) derivative. Controlled reduction of the corresponding *tert*-butyldimethylsilyl (TBS) protected coumarin **12** and acid-catalyzed acetalization provided versatile intermediate **14**. Exposure of this methyl acetal to allyltrimethylsilane in the presence of BF_3•OEt_2 produced C-5 allylated adduct **15**, which was immediately subjected to tetrabutylammonium fluoride to provide **16** in excellent overall yield.

Scheme 2[a]



[a] Reagents: (a) H_2, 10% Pd/C, THF, 92%; (b) Me_3SiCl, *N*,*O*-bis(trimethylsilyl)acetamide, CH_3CN; acetone, I_2, 105 °C, 73%; (c) TBSCl, imidazole, THF, 23 °C, 60%; (d) Dibal-H, $PhCH_3$, −78 °C; (e) *p*-TsOH·H_2O, MeOH, 23 °C, 66% for 2 steps; (f) allyltrimethylsilane, BF_3·OEt_2, CH_2Cl_2, −78 → 0 °C, 93%; (g) Bu_4NF, THF, 23 °C, 91%.

Scheme 3[a]

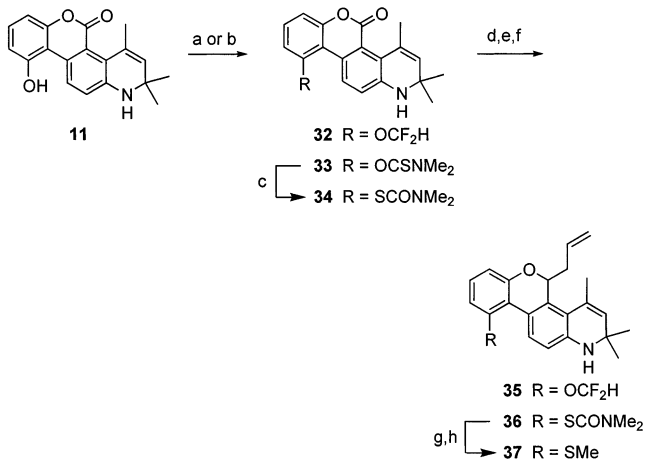


[a] Reagents: (a) Tf_2O, Et_3N, CH_2Cl_2, 78 → 23 °C, 91%; (b) Cs_2CO_3, RX, DMF, 23 °C; (c) Pd(II), R_3P, nucleophile; (d) $LiAlH_4$, Et_2O, 0 → 23 °C, 47%; (e) Dibal-H, CH_2Cl_2, −78 → 0 °C, 93%; (f) KHMDS, MeI, THF, 0 °C, 92%.

To rapidly assess the steric requirements of the "C-10 pocket," a series of alkyl ethers (**18**−**23**) was prepared by treatment of phenol **16** with selected alkylating agents (Scheme 3). Alternatively, **16** could be converted to the triflate derivative **17** (Tf_2O, Et_3N, CH_2Cl_2), which underwent further palladium-catalyzed elaboration to provide **24**−**31**.

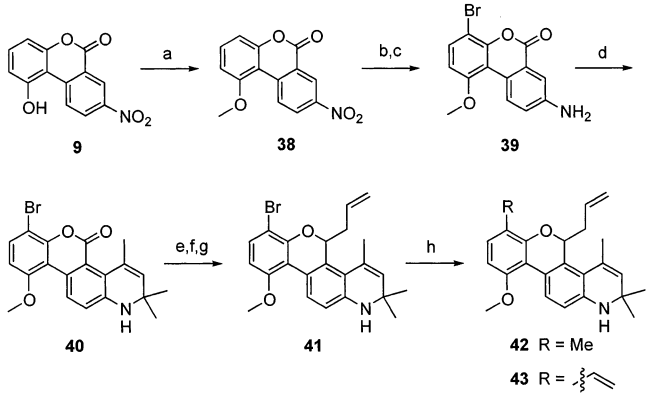
While the C-5 allyl substituted phenol **16** served as a convenient intermediate for the preparation of numerous 10-substituted analogues, transformations demanding especially harsh conditions required backtracking to the more stable 1,2-dihydro-2,2,4-trimethylquinoline **11**. For example, production of a C-10 difluoromethyl

Scheme 4[a]



[a] Reagents: (a) BrF_2CH, K_2CO_3, DMF, 80 °C, 43%; (b) NaH, DMF, 0 °C, Me_2NCSCl, 80 °C, 28%, (c) 275 °C, 59%; (d) Dibal-H, $PhCH_3$, −78 °C; (e) *p*-TsOH·H_2O, MeOH, 23 °C; (f) allyltrimethylsilane, BF_3·OEt_2, CH_2Cl_2, −78 → 0 °C; **35**: 58% for 3 steps; **36**: 18% for 3 steps; (g) KOH, ethylene glycol, 170 °C; (h) Cs_2CO_3, MeI, DMF, 0 °C, 34% for 2 steps.

Scheme 5[a]



[a] Reagents: (a) Cs_2CO_3, MeI, DMF, 23 °C, 99%; (b) Br_2, $CHCl_3$/AcOH, 55 °C; (c) H_2, 10% Pd/C, dioxane, 65 °C, 67% for 2 steps; (d) I_2, acetone, 105 °C, 47%; (e) Dibal-H, $PhCH_3$, −78 °C; (f) *p*-TsOH·H_2O, MeOH, 23 °C; (g) allyltrimethylsilane, BF_3·OEt_2, CH_2Cl_2, −78 → 0 °C; 51% for 3 steps; (h) R'SnR_3, Pd(dppf)Cl_2, NMP, 65 °C; for **42**, 63%; for **43**, 59%.

ether analogue (**11** → **32** → **35**, Scheme 4) necessitated reaction of **11** with difluoromethylcarbene generated from bromodifluoromethane in the presence of potassium carbonate in DMF at 90 °C[19] to generate the desired linkage. Similarly, phenol **11** represented a serviceable entry to sulfur-containing analogues. Pyrolysis of *O*-aryl-*N*,*N*-dimethylthionocarbamate **33** effected Newman-Kwart rearrangement[20,21] to give the *S*-aryl *N*,*N*-dimethylthiocarbamate **34**, which was further converted to **37**.

Oxygen functionality at C-10 also provided a handle for more densely functionalized D-ring derivatives. Regiochemistry enforced by the directing effects of the 10-OMe substituent provided access to 7,10-disubstitution via electrophilic bromination of **38** (Scheme 5). Chemoselective reduction, Skraup reaction,[18] and C-5 elaboration as previously described gave **41**, which reacted efficiently with organostannanes in the presence of palladium catalyst[22] to form C-7 alkyl substituted analogues **42** and **43**.

Analogues bearing 9,10-disubstitution required de novo synthesis from appropriately substituted arylboronic acids, as exemplified by the conversion of 2,3,6-trimethoxyphenylboronic acid (**44**) to 9-hydroxy-10-methoxy derivative **50** (Scheme 6). Selective differentiation of the C-9 and C-10 phenol functionalities was realized by protection of the more accessible 9-OH by treatment with TBSCl and imidazole followed by methylation of the remaining phenol with methyl iodide and cesium carbonate (**48** → **49**). Additional D-ring variants, particularly those decorated with one or more halogen atoms or bearing functional groups at C-8 (**55**−**60**, Figure 1), were similarly available via embellishment of substituted 2-methoxyphenylboronic acids **44** and **51**−**54** using protocols outlined in Schemes 2, 3, and 6. Approaches presented in Scheme 3 applied to **50** provided access to 10-OMe analogues possessing different C-9 substituents (**63**−**70**) designed to probe the "C-9 pocket" (Scheme 7).

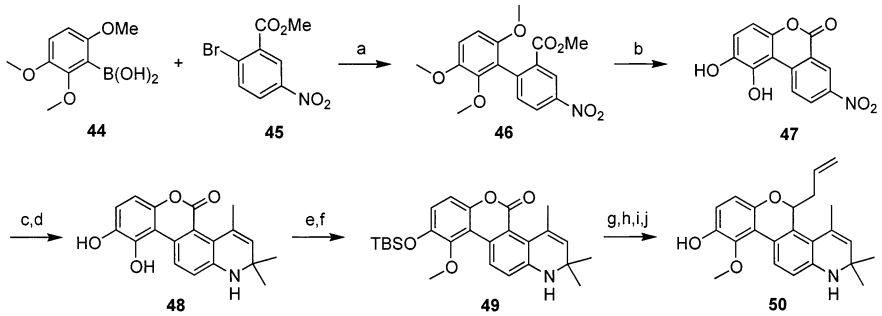
Biological Evaluation

As in our previous studies, receptor binding, E-selectin repression, and glucocorticoid response element (GRE) activation were relied upon for primary screening. Affinity for the α-isoform of hGR was evaluated in a competition binding assay. Selectivity versus other steroid receptors, particularly progesterone receptor,[23,24] was routinely monitored. Each compound was then further probed for its ability to functionally activate or repress transcription in a cellular context using several cotransfection assays.[25,26]

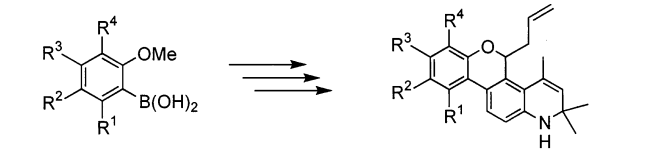
The E-selectin cotransfection assay[25] was used to evaluate compounds for the effect on repression of transcription mediated by nuclear factor κB (NFκB) or activator protein-1 (AP-1). E-selectins are membrane-bound cell adhesion proteins found only on endothelial cells and are upregulated in response to infection or tissue injury. The reporter plasmid used in this assay contains an E-selectin promoter that has binding sites for one NFκB and one AP-1 transcription factor placed upstream of a luciferase expression cassette in HEPG2 cells. NFκB and AP-1 bind to the proximal promoter region and are responsible for transmitting the effects of inflammatory mediators tumor necrosis factor (TNF) and interleukin-1 (IL-1) as well as the subsequent upregulation of E-selectin gene expression. Glucocorticoids act to inhibit the inflammatory process in part by interfering with the binding of both AP-1 and NFκB, thereby repressing the expression of E-selectin and other regulated genes.

The GRE transcriptional activation assay[27] provided a mechanism for determining the facility of formation of a receptor/ligand complex that would bind to GRE signature sequences and initiate transcription. In this cotransfection assay, the reporter plasmid contains a portion of the mouse mammary tumor virus (MMTV) promoter spliced upstream of a luciferase gene expression vector in CV-1 cells. The MMTV promoter contains four GRE sites and the construct has no known affinity for AP-1 or NFκB. Maximal efficacies of compounds in both the E-selectin repression and GRE activation assays are reported as a percentage of the maximal response observed for dexamethasone and potency values are calculated as the concentration at half-maximal response for these curves.

Scheme 6[a]



[a] Reagents: (a) $PdCl_2(PPh_3)_2$, Cs_2CO_3, DMF, 90 °C, 87%; (b) BBr_3, CH_2Cl_2, −78 → 23 °C, 99%, (c) H_2, 10% Pd/C, dioxane, 65 °C; (d) I_2, acetone, 105 °C, 54% for 2 steps; (e) TBSCl, imidazole, THF, 0 °C, 60%; (f) Cs_2CO_3, MeI, DMF, 0 °C, 93%; (g) Dibal-H, $PhCH_3$, −78 °C; (h) p-TsOH·H_2O, MeOH, 23 °C, 61% for 2 steps; (i) Bu_4NF, THF, 23 °C, 99%; (j) allyltrimethylsilane, BF_3·OEt_2, CH_2Cl_2, −78 → 0 °C, 79%.

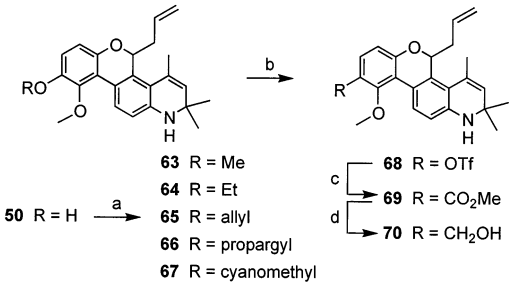


44 $R^1 = R^2 = OMe$, $R^3 = R^4 = H$
51 $R^1 = OMe$, $R^2 = F$, $R^3 = R^4 = H$
52 $R^1 = OMe$, $R^2 = Cl$, $R^3 = R^4 = H$
53 $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = F$
54 $R^1 = Cl$, $R^2 = OMe$, $R^3 = R^4 = H$

50 $R^1 = OMe$, $R^2 = OH$, $R^3 = R^4 = H$
55 $R^1 = OMe$, $R^2 = F$, $R^3 = R^4 = H$
56 $R^1 = OMe$, $R^2 = Cl$, $R^3 = R^4 = H$
57 $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = F$
58 $R^1 = Cl$, $R^2 = OH$, $R^3 = R^4 = H$
59 $R^1 = OMe$, $R^2 = Br$, $R^3 = R^4 = H$
60 $R^1 = Cl$, $R^2 = R^3 = R^4 = H$
61 $R^1 = Cl$, $R^2 = OH$, $R^3 = H$, $R^4 = Br$
62 $R^1 = R^2 = R^3 = R^4 = H$

Figure 1. D-ring disubstituted analogues prepared from functionalized 2-methoxyphenylboronic acids.

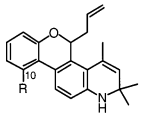
Scheme 7[a]



[a] Reagents: (a) Cs_2CO_3, RX, DMF, 0 °C; (b) Tf_2O, Et_3N, CH_2Cl_2, −78 → 23 °C, 91%; (c) $Pd(OAc)_2$, dppe, CO, Et_3N, MeOH/DMSO, 60 °C, 65%; (d) Dibal-H, CH_2Cl_2, −78 → 0 °C, 61%.

While the aforementioned cotransfection assays were the primary biochemical tools used in compound screening for GR-mediated effects, promising analogues were further evaluated for their effects on down-regulation of T-cell proliferation induced by conconavalin A (con A),[28] an inhibitory process recognized for glucocorticoids.[29] This assay was attractive to us since it could easily be run using either human whole blood or rat spleenocytes, thereby providing a potential measure of species-specific effects. In addition, we have previously observed an excellent correlation between activity in the con A assay run using rat spleenocytes and in vivo activity in the carrageenan paw edema assay,[30] our primary rodent model of inflammation. As before, results are reported as a percentage of the maximal response observed for dexamethasone and potency values are calculated as the concentration at half-maximal response for these curves.

Table 1. Steric Mapping of the C-10 Pocket[a]



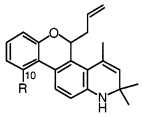
Cmpd	R	GR Ki (nM)	GRE activation		E-selectin repression	
			EC_{50} (nM)[b]	eff (% dex)[c]	EC_{50} (nM)[b]	eff (% dex)[c]
prednisolone	---	2.4±0.3*	8.0±1.1*	89±19*	2.1±0.2*	99±1*
62	H	33.8±1.3	>300	2±1	350	28±9
16	OH	27.6±4.9*	550±5	29±2	250±46	59±5
18	OMe	2.5±0.5*	33±8	68±38	13±6	94±2
35		2.2±0.3*	35±5	70±38	18±1	92±1
19		65±14*	—[d]	0	—	1±1
20		88±19*	—	0	—	7±2
21		4.2±1.1*	>300	9±2	270±70	65±4
22		2100±730*	—	—	—	—
23		6000±3000*	—	—	—	—

[a] Values with standard deviation represent the mean of two experiments with triplicate determinations and values without standard deviation represent a single experiment in triplicate. Values with an asterisk represent the mean value of at least three separate experiments in triplicate with standard error. [b] All EC_{50} values were determined from full seven point, half-log concentration response curves. [c] Efficacies are represented as a percentage of the maximal response of dexamethasone (100%). [d] A hyphen indicates a functional potency that was not calculated due to low efficacy or a functional efficacy <20%.

Results and Discussion

Structure−Activity Relationships. In our previous disclosure, the systematic precession of a methyl ether substituent about the periphery of the 5-aryl-1,2-dihydro-2,2,4-trimethyl-5H-chromeno-[3,4-f]quinoline D-ring demonstrated that C-10 substitution conferred remarkable GR selectivity and functional activity in both in vitro repression assays and in vivo models for asthma.[15] Our present, more rigorous exploration of the C-10 pocket was initiated using a series of C-10 substituted alkyl ethers of varying steric demand (Table 1). It became immediately apparent that GR activity was restricted to a narrowly defined subset of analogues of comparable size: active derivatives **18** and **35**, for instance, differ only in the isosteric replacement of methyl ether with difluoromethyl ether. Introduction of less sterically encumbered functionality at C-10 (H in

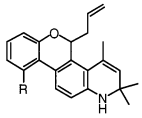
Table 2. Electronic Effect of C-10 Substituent on GR Activity[a]



			GRE activation		E-selectin repression	
cmpd	R	GR Ki (nM)	EC_{50} (nM)[b]	eff (% dex)[c]	EC_{50} (nM)[b]	eff (% dex)[c]
prednisolone		2.4 ± 0.3*	8.0 ± 1.1*	89 ± 19*	2.1 ± 0.2*	99 ± 1*
28	NHMe	7.0 ± 0.1	32 ± 12	60 ± 1	19 ± 9	96 ± 3
37	SMe	5.2 ± 1.2	123 ± 11	60 ± 21	18 ± 8	92 ± 6
24	vinyl	4.4 ± 1.0	17 ± 0	50 ± 4	12 ± 4	95 ± 4
25	−C≡CH	6.9 ± 2.1	130 ± 0	92 ± 4	59 ± 14	89 ± 4
26	CN	9.3 ± 0.7	195 ± 120	87 ± 8	60 ± 6	79 ± 5
27	CH_2NH_2	140 ± 9	–[d]	7 ± 1	467	30 ± 23
30	CH_2OH	2.3 ± 0.6	61 ± 7	69 ± 22	19 ± 5	92 ± 1
31	CH_2OMe	18.0 ± 1.9	–	5 ± 4	305	22 ± 7
29	CO_2Me	400 ± 87	–	–	–	–

[a] Values with standard deviation represent the mean of two experiments with triplicate determinations and values without standard deviation represent a single experiment in triplicate. Values with an asterisk represent the mean value of at least three separate experiments in triplicate with standard error. [b] All EC_{50} values were determined from full seven point, half-log concentration response curves. [c] Efficacies are represented as a percentage of the maximal response of dexamethasone (100%). [d] A hyphen indicates a functional potency that was not calculated due to low efficacy or a functional efficacy <5%.

Table 3. Receptor Cross-Reactivity of GR-Active Analogues[a]



		Ki (nM)				
cmpd	R	GR	PR	MR	AR	ER[c]
prednisolone		2.4 ± 0.3*	–[b]	37 ± 12	2760*	1000†
62	H	33.8 ± 1.3	35.9	–	–	1000†
16	OH	27.6 ± 4.9	330 ± 56	1370 ± 49	2060 ± 1150	1000†
18	OMe	2.5 ± 0.5*	1790 ± 480	46 ± 23	1230 ± 510	1000†
35	OCF_2H	2.2 ± 0.3	349 ± 99	35.8 ± 3.9	96.3 ± 60.1	1000†
28	NHMe	7.0 ± 0.1	2920 ± 700	251 ± 31	2590 ± 270	1000†
37	SMe	5.2 ± 1.2	4740	93.8	2460	1000†
24	vinyl	4.4 ± 1.0*	435 ± 100	57 ± 35	239 ± 27	1000†
25	−C≡CH	6.9 ± 2.1	2400 ± 1060	350 ± 220	650 ± 600	1000†
26	CN	9.3 ± 0.7	1460 ± 490	–	–	1000†
30	CH_2OH	2.3 ± 0.6	192 ± 23	292 ± 49	1320 ± 500	1000†

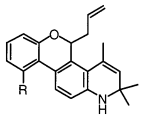
[a] Values with standard deviation represent the mean of two experiments with triplicate determinations and values without standard deviation represent a single experiment in triplicate. Values with an asterisk represent the mean value of at least three separate experiments in triplicate with standard error. [b] A hyphen indicates a binding potency of >5000 nM. [c] Values with a dagger indicate that the mean Ki values of at least three experiments were >1000 nM.

62; OH in **16**) produced markedly decreased GR avidity with concomitant ablation of functional activity in the E-selectin repression and the GRE activation cotransfection assays. An incremental increase in the size of the alkyl ether group produced a similar diminution in GR binding affinity and functional activity. Propargylic substitution (**21**) would appear to represent the steric threshold for acceptable GR binding potency; however, this analogue was essentially inactive in cotransfection assays.

The steric parameters of the C-10 pocket having been established, we next sought to determine the tolerance of hydrophilic substituents with the added objective of improving the physicochemical properties of this otherwise lipophilic pharmacophore. To this end, we prepared molecules containing heteroatoms disposed either α or β to the D-ring at C-10. When the α-position was occupied by C, N, or S (**24**, **28**, or **37**, respectively), GR binding potency and functional activity in cotransfection repression assays were maintained (Table 2). The spatial orientation of the C-10 substituent is also critical for retention of functional agonism, as evidenced by the diminished E-selectin potency of acetylene **25** and nitrile **26**. In short, nonbranched two atom substituents appended to the C-10 position of the 5-allyl-1,2-dihydro-2,2,4-trimethyl-5H-chromeno-[3,4-f]quinoline skeleton provided optimal GR binding potency and E-selectin repression activity. Of note, this subset of analogues demonstrated transcriptional repression activity comparable to pred in the E-selectin assay, but was only partially efficacious and considerably less potent than pred in the GRE-mediated transactivation assay.

We next profiled the steroid receptor cross-reactivity (Table 3) of preferred analogues (hGR Ki < 10 nM, E-selectin EC_{50} > 50%). We have previously documented the crucial role C-10 substitution plays in reducing the affinity of 5-aryl-1,2-dihydro-2,2,4-trimethyl-5H-chromeno-[3,4-f]quinoline analogues for PR[15] and indeed, this appears to be a general feature of this tetracyclic core irrespective of the C-5 substituent. For the C-5 allyl series, C-10 unsubstituted analogue **62** binds GR and PR with equal affinity while methyl ether **18** displays potent GR binding (K_i = 2.5 nM) and very weak PR binding (K_i = 1790 nM). All of the C-10 substituted

Table 4. Species Selectivity in Conconavalin A T-Cell Proliferation Assay[a]



		conconavalin A (rat)		conconavalin A (human)	
cmpd	R	EC_{50} (nM)[b]	eff (% dex)[c]	EC_{50} (nM)[b]	eff (% dex)[c]
prednisolone		19 ± 6*	97 ± 3*	25 ± 2*	95 ± 2*
18	OMe	48 ± 20*	100 ± 2*	780 ± 110*	82 ± 6*
35	OCF_2H	85 ± 15	100 ± 3	563 ± 81	65 ± 9
28	NHMe	48 ± 43	98 ± 0	418 ± 73	83 ± 9
24	vinyl	90 ± 43*	97 ± 3*	>1000*	56 ± 22*

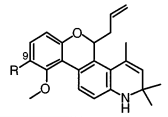
[a] Values with standard deviation represent the mean of two experiments with triplicate determinations and values without standard deviation represent a single experiment in triplicate. Values with an asterisk represent the mean value of at least three separate experiments in triplicate with standard error. [b] All EC_{50} values were determined from full seven point, half-log concentration response curves. [c] Efficacies are represented as a percentage of the maximal response of dexamethasone (100%).

analogues containing two-atom attachments are at least 100-fold selective for GR with **18** and **28** possessing the most favorable cross-reactivity profiles. The C-5 allyl substituent common to all of these analogues also imparts considerable MR affinity (Table 3). In cotransfection assays designed to ascertain MR agonism or antagonism, potent binders of MR were found to not function as MR agonists and had only weak activity as MR antagonists.

Guided by the observed potency in the GR binding assay and the level of GR-mediated transcriptional repression in the E-selectin cotransfection assay, promising analogues were further evaluated using whole blood assays with immunologically relevant endpoints such as the con A-induced T-cell proliferation assay. While demonstrating equivalent potency and comparable efficacy (with 2−5-fold) relative to pred in the rat con A assay, the 10-substituted compounds as a class exhibited a species-selective potency biased toward increased activity (approximately 10-fold) in rat spleenocytes relative to human whole blood (Table 4). As a class, the C-10 substituted compounds demonstrated prednisolone equivalent efficacy, and potency within 2−5-fold of prednislone, but each analogue was less efficacious and about 5−10-fold less potent in the corresponding human experiment.

Toward the development of compounds with parallel rat/human activity and in conjunction with 10-OMe substitution, we reinvestigated the SAR of C-7, C-8, and C-9, potential loci for beneficial interactions with GR. Since it was known from our previous work that the GR did not tolerate C-8 substituents larger than H or F and that polar fucntionality at C-7 resulted in the obliteration of GR activity,[15] our foray with the C-10 substituted compounds was limited (Table 5). Interestingly, halogenation (F, Cl, Br) or introduction of polar substituents (OH, CH_2OH, or CO_2Me) at C-9 led to retention of GR binding potency was with a concurrent increase in PR affinity. Though an improved receptor binding selectivity profile was observed with selected 7,10-disubstituted analogues, this was offset by a loss of E-selectin repression potency (Table 6). Only the C-9 hydroxyl analogue **50** (Table 5) maintained potent GR-specific functional activity in the E-selectin repression assay. Furthermore, **50** was the only example that offered enhanced GR affinity relative to **18**, but at the expense of GR/PR selectivity. With the 10-Cl analogue **58** (Table 6), remarkable increases in GR binding and E-selectin repression potency imparted by the C-9 hydroxyl group were accompanied by an erosion of GR/PR selectivity. In an attempt to restore the desired selectivity for GR by leveraging the favorable cross-reactivity profile afforded by bromination at C-7 (see **41**, Table 6), we prepared trisubtituted D-ring analogue **61**. Though **61** did not increase the GR/PR selectivity ratio as expected, it did retain the potent transcriptional repression activity of the parent 9-hydroxy-10-chloro system. Perhaps the most significant effect of 9-hydroxylation was to overcome the issue of species specificity we had encountered in the con A assays (Table 7). For example, **50** and **58** demonstrated comparable inhibition of con A-induced T-cell proliferation in rat spleenocytes and human whole blood, with the latter analogue exhibiting potency equivalent to pred.

Table 5. Effect of C-9 Substitution in D-Ring on GR Activity[a]

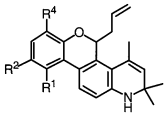


Cmpd	R	GR Ki (nM)	PR Ki (nM)	E-selectin repression EC_{50} (nM)[b]	E-selectin repression eff (% dex)[c]
prednisolone	---	2.4 ±0.3*	—[d]	2.1 ± 0.2*	99±1*
18	H	2.5±0.5*	1790±480*	13±6*	94±2*
55	F	3.8±1.4	200±120	81±18	86±4
56	Cl	5.42±0.99	29±6	94±90	70±8
59	Br	5.32±0.31	34	82	78
50	OH	0.95±0.13	150±41	14±5	96±2
63	OMe	12.1±2.6	610±214	120±21	89±1
64		487±98	—	—	20
65		12.0±3.7	3740±1100	140	83
66		13.9±1.8	1810±350	160	58
67		51.0±3.2	3080±130	130±28	51±11
69	CO_2Me	2.80±0.54	200±92	100	82±6
70	CH_2OH	6.6±3.3	100±28	53±19	82±8

[a] Values with standard deviation represent the mean of two experiments with triplicate determinations and values without standard deviation represent a single experiment in triplicate. Values with an asterisk represent the mean value of at least three separate experiments in triplicate with standard error. [b] All EC_{50} values were determined from full seven point, half-log concentration response curves. [c] Efficacies are represented as a percentage of the maximal response of dexamethasone (100%). [d] A hyphen indicates a binding potency of >5000 nM, a functional potency that was not calculated due to low efficacy, or a functional efficacy <20%.

In Vivo Evaluation. The in vivo activity of **18** in acute and chronic rodent models of inflammation has been previously documented.[15] A comparable profile relative to pred was observed (see Figure 2) upon oral dosing the C-10 difluoromethyl ether **35**, **50**, and the **58** in the rat carrageenan induced paw edema (CPE)

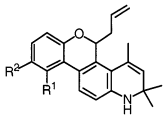
Table 6. Effect of C-9 Substitution in D-Ring on GR Activity[a]



cmpd	R^1	R^2	R^4	GR Ki (nM)	PR Ki (nM)	E-selectin repression EC_{50} (nM)[b]	E-selectin repression eff (% dex)[c]
prednisolone				2.4 ±0.3*	–[d]	2.1 ± 0.2*	99 ± 1*
41	OMe	H	Br	4.1 ± 1.9*	–	59 ± 4	96 ± 1
42	OMe	H	Me	2.0 ± 0.1*	–	81 ± 6	91 ± 7
43	OMe	H	vinyl	34 ± 7*	450	156 ± 10	89 ± 4
60	Cl	H	H	1.9 ± 0.3*	61	45 ± 40	92
58	Cl	OH	H	0.58 ± 0.09*	7.6 ± 2.1*	5.0 ± 2.0*	97 ± 1*
61	Cl	OH	Br	2.3 ± 0.2*	22.0 ± 6.6*	5.0 ± 1.0	95 ± 1

[a] Values with standard deviation represent the mean of two experiments with triplicate determinations and values without standard deviation represent a single experiment in triplicate. Values with an asterisk represent the mean value of at least three separate experiments in triplicate with standard error. [b] All EC_{50} values were determined from full seven point, half-log concentration response curves. [c] Efficacies are represented as a percentage of the maximaw response of dexamethasone (100%). [d] A hyphen indicates a binding potency of >5000 nM, a functional potency that was not calculated due to low efficacy, or a functional efficacy <20%.

Table 7. Effect of D-Ring Substitution on Species Selectivity[a]



cmpd	R^1	R^2	conconavalin A (rat) EC_{50} (nM)[b]	conconavalin A (rat) eff (% dex)[c]	conconavalin A (human) EC_{50} (nM)[b]	conconavalin A (human) eff (% dex)[c]
prednisolone			19 ± 6*	97 ± 3*	25 ± 2*	95 ± 2*
18	OMe	H	48 ± 20*	100 ± 2*	780 ± 110*	82 ± 6*
50	OMe	OH	78 ± 69	105 ± 3	145 ± 61*	87 ± 1*
60	Cl	H	>1000	37 ± 28	440 ± 62	58 ± 11
58	Cl	OH	78 ± 58*	105 ± 3*	29 ± 10	87 ± 6

[a] Values with standard deviation represent the mean of two experiments with triplicate determinations and values without standard deviation represent a single experiment in triplicate. Values with an asterisk represent the mean value of at least three separate experiments in triplicate with standard error. [b] All EC_{50} values were determined from full seven point, half-log concentration response curves. [c] Efficacies are represented as a percentage of the maximal response of dexamethasone (100%).

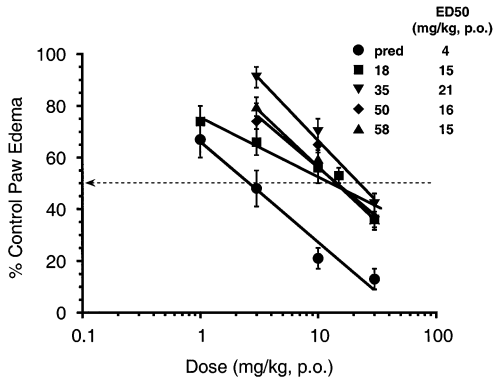


Figure 2. Prednisolone, **18**, **35**, **50**, and **58**, dose-dependently inhibit rat CPE.

assay.[30] An acute inflammatory response was generated in Sprague–Dawley rats following injections of carrageenan in the hind paw; the resulting edema was quantified after 3 h by measuring the increase in volume of the inflamed paw. Each of these compounds dose-dependently inhibited edema in this model (**35**: ED_{50} = 21 mg/kg; **50**: ED_{50} = 16 mg/kg; **58**: ED_{50} = 15 mg/kg) compared to an **18**[16] (ED_{50} = 15 mg/kg) and pred (ED_{50} = 4 mg/kg). Moreover, the efficacy of the 9-hydroxy analogues **58** and **50** is noteworthy given that these two analogues were devoid of species-specific liabilities in vitro (con A assay).

Conclusion

The SAR of D-ring substituted analogues of 5-allyl-1,2-dihydro-2,2,4-trimethyl-5H-chromeno-[3,4-f]quinolines revealed several important effects of C-10 and C-9 substituents on GR-mediated activity. First, the optimal C-10 substituent for obtaining GR-selective binding affinity and potent E-selectin repression activity is a linear appendage of two atoms. The advantageous effect on GR activity conferred by this substitution pattern appears to be linked to the isosteric volume occupied by the substituent rather than its electronic character. This is deduced from the similar profiles for GR activity observed for the C-10 OMe, OCF_2H, NHMe, SMe, vinyl, propargyl, CN, and CH_2OH analogues. Compounds with larger or smaller C-10 substituents exhibit a decrease in GR-mediated activity. Introduction of a 9-OH functionality in combination with a 10-OMe or 10-Cl group increases the potency of GR binding and E-selectin repression, and provides analogues that demonstrate efficacious activity across test species in the conconavalin A assay. It should be noted, however, that this increase in GR potency comes with an apparent decrease in GR/PR selectivity. The most potent and efficacious GR modulators were evaluated in vivo in the rat carrageenan paw edema assay, and several analogues showed an oral ED_{50} comparable to prednisolone. Future work will focus on combining the optimal D-ring substitution patterns with optimal C-5 substituents

with the ultimate goal of providing potent, GR-mediated anti-inflammatory agents.

Experimental Section

General Procedures. Melting points were determined with capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H at 300 MHz and ^{13}C at 75 MHz) were run as dimethyl sulfoxide-d_6 solutions, unless otherwise stated. Dimethyl sulfoxide-d_6 was used as an internal standard. Mass spectra determinations were performed by the Analytical Research Department, Abbott Laboratories. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Optical rotations were measured at 23 °C in chloroform. Analytical thin-layer chromatography was done on 2 × 6 cm Kieselgel 60 F-254 plates precoated with 0.25-mm-thick silica gel distributed by E. Merck. Unless otherwise specified, column chromatography was performed on silica gel (Kieselgel 60, 70−230 mesh) from E. Merck. The term in vacuo refers to solvent removal using a rotary evaporator at 30 mmHg. With the exception of amines, solvents and reagents were purchased from Aldrich Chemical Co. and were used without further purification unless otherwise specified. All amines were dried over molecular sieves (4 Å) for at least 24 h prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl.

Receptor Binding Assays. Cytosol preparations of human glucocorticoid receptor-α (GR-α) isoform and human progesterone receptor-A [PRA] have been described previously.[31] Both receptor cDNAs were cloned into baculovirus expression vectors and expressed in insect SF21 cells. The GRX contains Thr-Met-Glu-Tyr-Met-Pro-Met-Glu-Asp on its N-terminus. [^{3}H]-dexamethasone (Dex) (specific activity 82−86 Ci/mmol) and [3H]-progesterone (Prog) (specific activity 97−102 Ci/mmol) were purchased from Amersham Life Sciences (Arlington Heights, IL).). Glass fiber type C multiscreen MAFC NOB plates were from Millipore (Burlington, MA). Hydroxyapatide Bio-Gel HTP gel was from Bio-Rad Laboratories (Hercules, CA). Tris(hydroxymethyl)aminomethane (Tris), ethylenediaminetetraacetic acid (EDTA), glycerol, dithiothreitol (DTT), and sodium molybdate were obtained from Sigma Chemicals (St. Louis, MO).

Human GR-α and PR-A binding reactions were performed in Millipore multiscreen plates. For GR binding assays, [3H]-Dex (∼35 000 dpm (∼0.9 nM)), GR cytosol (∼35 μg of protein), test compounds and binding buffer (10 mM Tris HCl, 1.5 mM EDTA, 10% glycerol, 1 mM DTT, 20 mM sodium molybdate, pH 7.6 at 4 °C) were mixed in a total volume of 200 μL and incubated at 4 °C overnight in a plate shaker. Specific binding was defined as the difference between binding of [3H]-Dex in the absence and in the presence of 1 μM unlabeled Dex. For PR binding assays, [3H]-Prog (∼36 000 dpm (∼0.8 nM)) and PRA cytosol (∼40 μg of protein) were used. Specific binding was defined as the difference between binding of [^{3}H]-Prog in the absence and in the presence of 1 μM unlabeled Prog. After an overnight incubation, 50 μL of hydroxyapatide (25% weight/volume) slurry were added to each well and plates were incubated for 15 min at 4 °C in a plate shaker. Plates were suctioned with a Millipore vacuum manifold and each well was rinsed with 300 μL of ice-cold binding buffer. Packard Microscint-20 (250 μL) was added to each well and shaken at ambient temperature for 20 min. The amount of radioactivity was determined with a Packard TopCount plate reader. IC_{50}, concentration of test compounds that inhibited 50% of specific binding, was determined from the Hill analysis of the binding curves. K_i of test compounds was determined using the Cheng-Prusoff equation.[32] The following radiolabeled standards were used: dexamethasone (GR), progesterone (PR), aldosterone (MR), testosterone (AR), and estrodiol (ER).

E-Selectin Repression and GRE Activation Assays. Transcriptional repression was evaluated using the E-selectin cotransfection assay as has been previously described.[15] GRE mediated transcriptional activation was determined through a cotransfection assay using a receptor plasmid containing hGR and a reporter plasmid with the mouse mammary tumor virus (MMTV) promoter as we have previously described.[15,27] Maximal efficacies of compounds in the E-selectin repression and the GRE activation assays are reported as a percentage of the maximal response observed for dexamethasone and potency values are calculated as the concentration at half-maximal response for these curves.

Human PBMC-Induced Conconavalin A (Con A) Proliferation Assay.[28] Blood from a human donor (25 mL) was placed in a heparin-treated 50 mL centrifuge tube and diluted 2-fold by adding an equal volume of 3% Dextran T500 (Pharmacia Biotech). After the sample stood for 20 min at ambient temperature, the serum (about 35 mL) was transferred to a fresh 50 mL centrifuge tube. Histopaque-1077 (15 mL, Sigma) was overlaid to the tube and the tube was centrifuged at 1400 rpm for 30 min at 25 °C. An interface was collected and placed into a tube with 5 mL complete medium (RPMI1640 with 10% fetal bovine serum and 50 μM β-mercaptoethanol). The cells were washed and resuspended in complete medium and plated into 96-well culture plates at 50000 cells per well.

After adding compounds to be tested, concanavalin A (con A type IV−S, Sigma) was added to each well at 2.5 μg/mL and incubated for 3 days in a CO_2 incubator. To measure proliferation, 0.5 μCi/well of [^{3}H]-thymidine (NEN Life Science Products) was added and incubated for an additional 6 h at 37 °C. The cells were harvested onto glass fiber filter using a Tomtec Cell Harvester 96. The glass fiber filter was counted via direct β-counting method (Packard Matrix 9600).

Rat Splenocyte-Induced Conconavalin A Proliferation Assay. Sprague−Dawley rat spleens were dissected and the splenocyte suspension was transferred to 50 mL centrifuge tube. After large debris was removed, the cells were collected by centrifugation at 1200 rpm for 10 min at 4 °C. Red blood cells were removed from the splenocyte suspension by osmotic shock, and the resulting cells were suspended in complete medium. The cells were washed and resuspended in complete medium and plated into 96-well culture plates at 50 000 cells per well.

After compounds to be tested were added, con A was added to each well at 2.5 μg/mL and incubated for 3 days in CO_2 incubator. To measure proliferation, 0.5 μCi/well of [^{3}H]-thymidine was added and incubated for additional 6 h at 37 °C. The cells were harvested onto glass fiber filter using a Tomtec Cell Harvester 96. The glass fiber filter was counted via direct β-counting method (Packard Matrix 9600).

In Vivo Evaluation: Carageenan Paw Edema (CPE) Assay.[30] The effectiveness of selected compounds in a rodent model of inflammation was evaluated using the rat carageenan paw edema assay. Sprague−Dawley rats were given injections of carrageenan in their hind paw stimulating an acute inflammatory response. The resulting edema is quantified after 3 h by measuring the increase in the volume of the inflamed paw. The effect of orally dosing our compounds on inhibiting the edema was determined and an ED_{50} dose was calculated.

10-(*tert*-Butyldimethylsiloxy)-5-oxo-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (12). Phenol **11** (2.44 g, 7.55 mmol) was dissolved in of dry THF (125 mL) and the solution was cooled to 0 °C. Imidazole (1.55 g, 22.7 mmol) and TBSCl (1.70 g, 11.3 mmol) were added. A white precipitate formed in the reaction mixture within 1 min of silyl reagent addition. The reaction mixture was stirred overnight without replenishing the cooling bath. The reaction mixture was diluted with EtOAc (100 mL) and washed with 1 N HCl (2 × 50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was purified by chromatography on silica gel (gradient elution: 0−20% EtOAc/hexanes) to give **12** (1.97 g, 4.53 mmol, 60%) as an intensely yellow solid: mp 176−179 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.76 (d, J = 8.7 Hz, 1 H), 7.27 (t, J = 7.9 Hz, 1 H), 6.96 (dd, J = 8.0, 1.1 Hz, 1 H), 6.93 (d, J = 8.6 Hz, 1 H), 6.74 (dd, J = 8.1, 1.0 Hz, 1 H), 5.58 (br d, J = 1.3 Hz, 1 H), 4.23 (br s, 1 H), 2.12 (s, 3 H), 1.33 (s, 6 H), 1.04 (s, 9 H), 0.31 (s, 6 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 158.8, 152.3, 150.9, 145.8, 131.5, 130.1, 127.3, 126.0, 124.0,

121.8, 119.6, 117.3, 115.3, 110.5, 109.5, 49.6, 28.0 (2), 25.8 (3), 21.0, 18.2, −4.0 (2); MS (DCI/NH_3) *m/z* 422 $(M + H)^+$. Anal. ($C_{25}H_{31}NO_3Si$) C, H, N.

General Procedure for C-5 Allylation of Coumarins (Method A). Preparation of 10-(*tert*-Butyldimethylsiloxy)-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]-benzopyrano[3,4-f]quinoline (15). To a solution of lactone **12** (500 mg, 1.26 mmol) in anhydrous toluene (70 mL) at −78 °C under N_2 was added dropwise Dibal-H (2.02 mL of a 1.0 M solution in heptane, 2.02 mmol) maintaining the temperature at −78 °C. The resulting orange-red solution was stirred at −78 °C for 1.5 h at which time TLC analysis of an aliquot (quenched with satd. ammonium chloride) indicated conversion to desired product.. Some lower R_f material (diol resulting from over-reduction) was also observed. EtOAc (10 mL) was added to the solution at −78 °C to quench the excess DIBAL-H reagent (indicated by a color change of the solution from orange-red to light yellow), followed by addition of saturated aq. NH_4Cl solution (15 mL). The reaction mixture was partitioned between EtOAc (150 mL) and aqueous Rochelle's salt (sodium potassium tartrate, 40 mL) and the resulting mixture was stirred vigorously until a clear separation of layers was observed. The layers were separated and the organic layer was washed with brine (20 mL), was dried (Na_2SO_4), and was filtered. Removal of solvent gave the crude lactol **13** (10-(*tert*-butyldimethylsiloxy)-5-hydroxy-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline) as a light yellow foam (512 mg) which was used without further purification: MS (DCI/NH_3) *m/z* 423 $(M- H_2O + H)^+$.

The lactol **13** was dissolved in MeOH (30 mL) at 23 °C and *p*-TsOH•H_2O (50 mg, 25% w/w) was added portionwise as a solid. The mixture was stirred for 14 h at 23 °C and then was quenched with saturated aqueous sodium bicarbonate (10 mL) and was extracted with EtOAc (2 × 50 mL). The organics portions were combined and were washed with brine (20 mL) and were dried (Na_2SO_4). Filtration and concentration provided a yellow residue which was purified by flash chromatography (elution with 5% EtOAc/CH_2Cl_2) to provide 10-(*tert*-butyldimethylsiloxy)-5-methoxy-2,5-dihydro-2,2,4-trimethyl-1H-[1]-benzopyrano[3,4-f]quinoline (**14**) (314 mg, 0.832 mmol, 66% over two steps) as a yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 8.0 Hz, 1 H), 6.62 (d, J = 8.4 Hz, 1 H), 6.54 (t, J = 8.1 Hz, 2 H), 6.09 (br d, J = 1.4 Hz, 1 H), 5.37 (s, 1 H), 3.16 (s, 3 H), 2.08 (s, 3 H), 1.19 (s, 3 H), 0.98 (s, 3 H), 0.83 (s, 9 H), 0.16 (s, 6 H); MS (DCI/NH_3) *m/z* 406 $(M - OCH_3 + H)^+$.

A mixture of **14** (314 mg, 0.832 mmol) and allyltrimethylsilane (286 mg, 2.49 mmol) in CH_2Cl_2 (8 mL) was cooled to −78 °C and treated with BF_3•Et_2O (305 μL, 2.49 mmol) dropwise via syringe. The reaction mixture was allowed to warm to 0 °C in an ice bath. At approximately −50 °C, the solution turned a deep green color that faded upon warming. After 30 min at 0 °C, the yellow-brown mixture was poured into a rapidly stirring mixture of EtOAc (20 mL) and satd. aq. $NaHCO_3$ (10 mL), stirred for 30 min, and partitioned. The aqueous phase was extracted with EtOAc (15 mL) and the combined organic phases washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (gradient elution: 10−20% EtOAc/hexanes to provide **15** (296 mg, 0.774 mmol, 93%) as a colorless foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (d, J = 8.9 Hz, 1 H), 6.95 (t, J = 8.1 Hz, 1 H), 6.61 (d, J = 8.8 Hz, 1 H), 6.53 (d, J = 8.0 Hz, 1 H), 6.30 (d, J = 8.1 Hz, 1 H), 6.17 (br s, 1 H), 5.89−5.72 (m, 2 H), 5.44 (s, 1 H), 5.03 (d, J = 9.0 Hz, 1 H), 4.99 (d, J = 16.0 Hz, 1 H), 2.50−2.40 (m, 1 H), 2.25−2.18 (m, 1 H), 2.08 (s, 3 H), 1.19 (s, 3 H), 0.98 (s, 3 H), 0.83 (s, 9 H), 0.16 (s, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.6, 150.1, 148.3, 142.2, 136.0, 131.8, 128.2, 127.1, 126.7, 123.3, 117.7, 116.6, 115.7, 113.0, 111.9, 105.4, 72.8, 55.6, 49.3, 35.9, 29.2, 28.6, 21.1 (3), 11.0, −4.0 (2); MS (DCI/NH_3) *m/z* 448 $(M + H)^+$; HRMS (FAB) calcd *m/z* for $C_{28}H_{37}NO_2Si$ $(M)^+$ 447.2594, found 447.2588.

10-Hydroxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (16). Silyl ether **15** (507 mg, 1.05 mmol) was dissolved in THF (6 mL) at 23 °C and was treated with tetrabutylammonium fluoride (1.20 mL of a 1 M solution in THF, 1.20 mmol). After 1 h, the reaction mixture was concentrated in vacuo and was resuspended in EtOAc (25 mL). The solution was washed with water (10 mL) and brine (10 mL), then was dried (Na_2SO_4). Filtration through a short plug of silica gel and Celite afforded the phenol **16** (343 mg, 0.960 mmol, 91%) as a pale tan foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.77 (s, 1 H), 8.10 (d, J = 9.0 Hz, 1 H), 6.88 (t, J = 8.0 Hz, 1 H), 6.58 (d, J = 9.0 Hz, 1 H), 6.53 (d, J = 8.0 Hz, 1 H), 6.35 (d, J = 8.0 Hz, 1 H), 6.05 (s, 1 H), 5.89−5.72 (m, 2 H), 5.44 (s, 1 H), 5.03 (d, J = 9.0 Hz, 1 H), 4.99 (d, J = 16.0 Hz, 1 H), 2.50−2.40 (m, 1 H), 2. 25−2.18 (m, 1 H), 2.16 (s, 3 H), 1.16, (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.6, 150.1, 148.3, 142.2, 136.0, 131.8, 128.2, 127.1, 126.7, 123.3, 117.7, 116.6, 115.7, 113.0, 111.9, 105.4, 55.6, 49.3, 35.9, 29.2, 28.6, 23.5; MS (DCI/NH_3) *m/z* 334 $(M + H)^+$; HRMS (FAB) calcd for $C_{22}H_{23}NO_2$ $(M)^+$ 333.1729, found 333.1727.

10-(Trifluoromethanesulfonyloxy)-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (17). To a solution of **16** (134 mg, 0.392 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added triethylamine (165 μL, 1.17 mmol), followed by trifluoromethanesulfonic anhydride (73 μL, 0.43 mmol). The reaction mixture was allowed to slowly warm to 23 °C over a period of 1.5 h. The reaction was quenched with satd. aqueous ammonium chloride (5 mL) and extracted EtOAc (2 × 15 mL). The combined organic layers were washed with brine (5 mL), then were dried (Na_2SO_4) and were concentrated. The resulting tan residue was purified by flash chromatography (elution with 10% EtOAc/hexanes) to provide the triflate (169 mg, 0.357 mmol, 91%) as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 (d, J = 8.6 Hz, 1 H), 7.37 (t, J = 8.3 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 1 H), 7.03 (dd, J = 8.6, 1.1 Hz, 1 H), 6.66 (d, J = 8.6 Hz, 1 H), 6.48 (br s, 1 H), 5.91−5.74 (m, 2 H), 5.48 (br s, 1 H), 5.03 (dd, J = 9.0, 1.1 Hz, 1 H), 4.93 (dd, J = 16.0, 1.1 Hz, 1 H), 2.47−2.26 (m, 2 H), 2.19 (s, 3 H), 1.21 (s, 3 H), 1.18 (s, 3 H);^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 155.4, 151.7, 146.2, 139.6, 135.1, 130.2, 128.0, 127.3, 126.3, 119.2, 117.8, 115.7, 113.0, 110.5, 105.4, 90.8, 55.5, 49.0, 36.1, 29.7, 28.6, 23.8; MS (DCI/NH_3) *m/z* 466 $(M + H)^+$; HRMS (FAB) calcd *m/z* for $C_{23}H_{22}F_3NO_4S$ $(M)^+$ 465.1122, found 465.1127.

General Procedure for C-9 or C-10 Ether Formation: Phenol *O*-Alkylation With Representative Electrophiles (Method B). Preparation of 10-Methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (18). To a solution of **16** (1.79 g, 4.09 mmol) in DMF (200 mL) at 0 °C was added cesium carbonate (2.70 g, 8.19 mmol), followed by the dropwise addition of iodomethane (0.28 mL, 4.50 mmol) over 15 min. The ice bath was removed and the reaction stirred for 1 h. The reaction flask was placed back in the ice bath and quenched with satd. aq. NH_4Cl (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 0.5 M HCl (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo, affording a dark yellow oil. Purification by flash chromatography (elution with 10% EtOAc/hexanes) provided **18** (1.71 g, 3.80 mmol, 93%) as a yellow solid: mp 55−57 °C; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta\delta$ 7.96 (d, J = 8.3 Hz, 1 H), 7.07 (t, J = 8.4 Hz, 1 H), 6.71 (d, J = 8.5 Hz, 1 H), 6.60 (d, J = 8.6 Hz, 1 H), 6.52 (d, J = 8.4 H z, 1 H), 6.12 (br s, 1 H), 5.82 (m, 1 H), 5.76 (dd, J = 10.3, 2.7 Hz, 1 H), 5.44 (br s, 1H), 5.01 (m, 2 H), 3.86 (s, 3 H), 2.44 (m, 1 H), 2.20 (m, 1 H), 2.16 (s, 3 H), 1.17 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.1, 150.8, 145.5, 134.2, 133.5, 132.0, 127.4, 127.1, 126.9, 124.6, 117.1, 116.2, 115.9, 113.2, 110.3, 105.4, 73.3, 55.6, 49.6, 36.4, 28.9 (2), 23.9; MS (DCI/NH_3) *m/z* $(M + H)^+$ 348. Anal. ($C_{23}H_{25}NO_2$) C, H, N.

10-Ethoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (19). Prepared from **16** according to method B using iodoethane as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04 (d, J = 8.81 Hz, 1 H), 7.05 (t, J = 8.14 Hz, 1 H), 6.68 (dd, J = 8.14, 0.7 Hz, 1 H), 6.58 (d, J = 8.81 Hz, 1 H), 6.50 (dd, J = 7.8, 0.7 Hz, 1 H), 6.12 (d, J = 1.36 Hz 1 H), 5.83−5.74 (m, 2 H), 5.44 (d, J = 1.7 Hz, 1 H), 5.05−4.95 (m, 2 H), 4.18−4.02 (m, 2 H), 2.16 (s, 3 H), 1.42 (t, J = 6.8 Hz, 2 H), 1.16 (d, J = 4.4 Hz, 6 H); MS (APCI/

NH_3) *m*/*z* 362 $(M + H)^+$; HRMS calcd for $C_{24}H_{27}NO_2$ (M^+) 361.2042, found 361.2052. Anal. ($C_{24}H_{27}NO_2$) C, H, N.

5-(2-Propenyl)-10-(2-propenyloxy)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (20). Prepared from **16** according to method B using allyl bromide as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.01 (d, J = 8.45 Hz, 1 H), 7.05 (t, J = 8.09 Hz, 1 H), 6.71 (d, J = 8.45 Hz, 1 H), 6.58 (d, J = 8.45 Hz, 1 H), 6.53 (dd, J = 8.82, 0.74 Hz, 2 H), 6.08−6.20 (m, 2 H), 5.89−5.74 (m, 2 H), 5.42−5.48 (m, 2 H), 5.30 (dd, J = 10.8, 1.5 Hz, 1 H), 5.0−4.99 (m, 2 H), 4.73−4.60 (m, 2 H), 2.16 (s, 3 H), 1.16 (d, J = 1.8 Hz 6 H); MS (ESI) *m*/*z* 374 $(M + H)^+$; HRMS calcd for $C_{25}H_{27}NO_2$ (M^+) 373.2042, found 373.2050. Anal. ($C_{25}H_{27}NO_2$) C, H, N.

5-(2-Propenyl)-10-(2-propynyloxy)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (21). Prepared from **16** according to method B using propargyl bromide as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (d, 1H, J = 8.46 Hz), 7.07 (t, 2H, J = 8.0 Hz), 6.78 (d, 1H, J = 7.7 Hz), 6.61 (d, 1H, J = 8.9 Hz), 6.58 (d, 1H, J = 8.9 Hz), 6.15 (d, 1H, J = 2.5 Hz), 5.84 (m, 3H), 5.45 (s, 3H), 5.05 (m, 2H), 4.88 (t, 2H, J = 2.8 Hz), 2.16 (s, 3H), 1.76 (d, 6H, J = 2.2 Hz); MS (DCI) *m*/*z* 372 $(M + H)^+$; HRMS calcd for $C_{25}H_{25}NO_2$ (M^+) 371.1885, found 371.1898. Anal. ($C_{25}H_{25}NO_2$) C, H, N.

10-(Cyclopropylmethyl)oxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (22). Prepared from **16** according to method B using cyclopropylmethyl bromide as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.13 (d, 1H, J = 8.8 Hz), 7.03 (t, 1H, J = 8.1 Hz), 6.64 (dd, 1H, J = 8.5, 1.1 Hz), 6.60 (d, 1H, J = 8.8 Hz), 6.50 (dd, 1H, J = 8.8, 1.1 Hz), 6.10 (d, 1H, J = 1.7 Hz), 5.83−5.74 (m, 2H), 5.44 (d, J = 1.7 Hz), 5.05−4.95 (m, 2H), 4.18−4.02 (m, 2H), 2.17 (s, 3H), 1.42 (t, 2H, J = 6.8 Hz), 1.16 (d, 6H, J = 4.4 Hz), 0.60 (m, 2H), 0.36 (m, 2 H); MS (APCI) *m*/*z* 388 $(M + H)^+$; HRMS calcd for $C_{27}H_{31}NO_2$ (M^+) 387.5141, found 387.5139.

10-Benzyloxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (23). Prepared from **16** according to method B using benzyl bromide as the electrophile: ^{1}H NMR (300 mHz, DMSO-d_6) δ 8.03 (d, 1H, J = 8.81 Hz), 7.45 (d, 2H, J = 7.31 Hz), 7.39 (t, 2H, J = 7.71 Hz), 7.05 (t, 1H, J = 8.06 Hz), 6.80 (d, 1H, J = 8.86 Hz), 6.53 (t, 2H, J = 8.86 Hz), 6.06 (s, 1H), 6.55 (m, 1H), 5.44 (s, 1H), 5.22 (q, 2H, J = 41.7, 12.1 Hz), 5.00−5.04 (m, 2H), 2.16 (s, 3H), 1.16 9s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.0, 150.9, 145.5, 137.0, 134.2, 133.5, 132.1, 128.4, 127.7, 127.5, 127.4, 127.1, 126.9, 117.1, 116.1, 115.8, 113.7, 113.0, 110.6, 107.0, 73.4, 70.1, 49.7, 36.5, 28.9, 23.9; MS (ESI+) *m*/*z* 424 $(M + H)^+$. Anal. ($C_{29}H_{29}NO_2$) C, H, N.

5-(2-Propenyl)-10-vinyl-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (24). A solution of triflate **17** (103 mg, 0.221 mmol) and [1,3-bis(diphenylphosphino)-ferrocene]palladium dichloride dichloromethane complex (22 mg, 0.027 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was treated with vinyl tributylstannane (119 mg, 0.376 mmol). The solution was heated at 65 °C for 24 h, then cooled to 23 °C, treated with satd. KF solution (2 mL), and extracted with EtOAc (10 mL). The organic portion was washed with water (4 mL) and brine (4 mL) then was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (elution with 5% EtOAc/hexanes + 1% triethylamine) to provide **17** (52 mg, 0.13 mmol, 58%) as a pale yellow foam: ^{1}H NMR (300 mHz, DMSO-d_6) δ 7.22 (d, J = 8.5 Hz, 1 H), 7.19−7.13 (m, 2 H), 6.99 (dd, J = 17.3, 10.8 Hz, 1 H), 6.83 (dd, J = 7.0, 2.2 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 1 H), 6.26−6.21 (m, 1 H), 5.87 (dd, J = 10.3, 6.8 Hz, 1 H), 5.77 (dd, J = 10.5, 3.4 Hz, 1 H), 5.76 (dd, J = 17.3, 1.4 Hz, 1 H), 5.49−5.45 (m, 1 H), 5.33 (dd, J = 10.3, 1.4 Hz, 1 H), 5.03 (dd, 1H, J = 10.3, 1.8 Hz, 1 H), 4.98 (br d, J = 17.3 Hz, 1 H), 2.47−2.42 (m, 1 H), 2.32−2.26 (m, 1 H), 2.18 (d, J = 1.4 Hz, 3 H), 1.21 (s, 3 H), 1.15 (s, 3 H); ^{13}CNMR (75 mHz, DMSO-d_6) δ 150.4, 145.8, 137.6, 134.2, 133.5, 128.1, 127.3, 126.7, 123.3, 121.0, 117.0, 116.5, 116.4, 114.4, 113.1, 73.8, 59.6, 49.8, 36.0, 29.4, 28.8, 23.8, 20.6, 14.0; MS (DCI/NH_3) *m*/*z* 344 $(M + H)^+$; HRMS calcd for $C_{24}H_{26}NO$ 344.2014 (M^+), found 344.2011. Anal. ($C_{24}H_{25}NO$) C, H, N.

10-Ethynyl-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (25). A solution of triflate **17** (25 mg, 0.054 mmol), tetrabutylammonium iodide (40 mg, 0.108 mmol), bis(triphenylphosphine)palladium chloride (7.0 mg, 0.010 mmol), copper(I) iodide (3.8 mg, 0.020 mmol), and triethylamine (0.15 mL, 0.717 mmol) in DMF (0.75 mL) was treated with trimethylsilylacetylene (174 mg, 1.76 mmol). The resulting solution was heated at 55 °C for 3 h, then was diluted with EtOAc (20 mL) and filtered. The filtrate was washed with satd. NH_4Cl (6 mL), and the aqueous layer was extracted with EtOAc (10 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative TLC (2× elution with 10% EtOAc/hexanes). Extraction of the silica gel with EtOAc provided the intermediate trimethylsilyl acetylene: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (d, J = 8.5 Hz, 1 H), 7.10−7.04 (m, 2 H), 6.90 (dd, J = 7.8, 1.8 Hz, 1 H), 6.60 (d, J = 8.5 Hz, 1 H), 6.36−6.30 (m, 1 H), 5.83−5.76 (m, 2 H), 5.49−5.43 (m, 1 H), 5.04 (br d, J = 10.5 Hz, 1 H), 4.97 (br d, J = 17.3 Hz, 1 H), 2.39−2.30 (m, 1 H), 2.28−2.20 (m, 1 H), 2.17 (d, J = 1.4 Hz, 3 H), 1.18 (s, 3 H), 1.17 (s, 3 H), 0.26 (s, 9 H); MS (DCI/NH_3) *m*/*z* 414 $(M + H)^+$.

A solution of the silylacetylene in THF (2.5 mL) was treated sequentially with glacial acetic acid (0.005 mL) and tetrabutylammonium fluoride (0.050 mL of a 1.0 M solution in THF, 0.050 mmol). The solution was stirred at 23 °C for 8 h, then was diluted with EtOAc (20 mL) and was washed with satd. NH_4Cl (6 mL). The aqueous layer was extracted with EtOAc (10 mL) and the combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative TLC (2× elution with 10% EtOAc/hexanes) to give **25** (12 mg, 0.029 mmol, 54%) as a pale yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (dd, J = 8.5, 0.7 Hz, 1 H), 7.15 (t, J = 8.5 Hz, 1 H), 7.07 (d, J = 8.5 Hz, 1 H), 6.91 (br d, J = 7.1 Hz, 1 H), 6.62 (d, J = 8.5 Hz, 1 H), 6.38−6.31 (m, 1 H), 5.82−5.77 (m, 1 H), 5.49−5.44 (m, 1 H), 5.03 (br d, J = 10.3 Hz, 1 H), 4.98 (br d, J = 17.1 Hz, 1 H), 4.41 (s, 1 H), 2.49−2.40 (m, 2 H), 2.17 (s, 3 H), 1.18 (s, 6 H); ^{1}H NMR (75 MHz, DMSO-d_6) δ 150.0, 146.5, 134.0, 133.6, 133.0, 128.7, 127.2, 126.5, 126.1, 126.0, 118.3, 117.2, 116.0, 115.9, 112.9, 84.3, 84.2, 73.61, 49.8, 36.6, 29.2, 29.0, 23.8; MS (DCI/NH_3) *m*/*z* 342 $(M + H)^+$; HRMS (FAB) calcd for $C_{24}H_{23}NO$ 341.1780 (M^+), found 341.1788. Anal. ($C_{24}H_{23}NO \bullet H_2O$) C, H, N.

10-Cyano-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (26). A magnetically stirred mixture of **17** (195 mg, 0.419 mmol), tetrakis(triphenylphosphine)palladium(0) (36 mg, 0.031 mmol) and zinc cyanide (36 mg, 0.31 mmol) in dioxane (4.0 mL) and water (1.0 mL) was heated at 80 °C for 48 h under argon atmosphere. The reaction was allowed to cool to ambient temperature, was diluted with EtOAc (25 mL), and was washed with brine (15 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (elution with 10% EtOAc/hexanes) to give product contaminated with starting triflate. The partially pure nitrile further purified by preparative TLC (5× elution with 5% EtOAc/hexanes) and the product isolated by EtOAc extraction to provide **26** (17.3 mg, 0.0505 mmol, 12%) as an off yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, 1H, J = 8.5 Hz), 7.46 (dd, 1H, J = 7.5 Hz, J = 1.5 Hz), 7.27 (t, 1H, J = 7.8 Hz), 7.19 (dd, 1H, J = 8.1 Hz, J = 1.4 Hz), 6.71 (d, 1H, J = 8.5 Hz), 6.57 (m, 1H), 5.90 (dd, 1H, J = 10 Hz, J = 3.6 Hz), 5.82 (m, 1H), 5.49 (m, 1H), 5.04 (dm, 1H, J = 10.5 Hz), 4.98 (dm, 1H, J = 17.3 Hz), 2.38 (m, 1H), 2.30 (m, 1H), 2.19 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.3, 147.4, 133.9, 133.7, 133.3, 128.4, 127.3, 127.2, 127.0, 125.3, 122.3, 119.8, 117.4, 116.1, 113.8, 113.5, 104.4, 73.9, 59.7, 50.0, 36.9, 29.3, 23.7; MS (DCI/NH_3) *m*/*z* 343 $(M + H)^+$; HRMS (FAB) calcd for $C_{23}H_{22}N_2O$ 342.1732 (M^+), found: 342.1730. Anal. ($C_{23}H_{22}N_2O$) C, H, N.

10-Aminomethyl-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (27). To a magnetically stirred solution of the nitrile (40 mg, 0.116 mmol) in Et_2O (1 mL) at 0 °C was added lithium aluminum hydride (140 μL of a 1.0 M solution in Et_2O, 0.140 mmol) under nitrogen. The reaction was warmed to 23 °C and stirred for 6 h, then was quenched by addition to satd. aq. sodium potassium tartrate (2 mL). EtOAc (5 mL) was added and the mixture stirred for 30 min. Water (1 mL) was added and the layers were partitioned. The aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic layers were washed with brine (8 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative TLC (2× elution with 15% EtOAc/hexanes) and the product isolated by EtOAc extraction to provide **27** (19 mg, 0.055 mmol, 47%) of as pale yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (d, J = 8.5 Hz, 1 H), 7.19−7.11 (m, 2 H), 6.80 (dd, J = 7.3, 1.8 Hz, 1 H), 6.64 (d, J = 8.5 Hz, 1 H), 6.19−6.13 (m, 1 H), 5.81 (dd, J = 10.5, 17.1 Hz, 1 H), 5.73 (dd, J = 10.5, 3.4 Hz, 1 H), 5.49−5.43 (m, 1 H), 5.02 (br d, J = 10.5 Hz, 1 H), 4.94 (d, J = 17.1 Hz, 1 H), 4.67−4.60 (m, 2 H), 3.93−3.85 (m, 2 H), 2.35−2.26 (m, 2 H), 2.17 (s, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H); MS (DCI/NH_3) m/z 347 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{26}N_2O$ 346.2045 (M$^+$), found 346.2047. Anal. ($C_{23}H_{26}N_2O\bullet H_2O$) C, H, N.

10-Methylamino-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (28). An ACE-glass high-pressure vessel charged with aryltriflate **17** (165 mg, 0.360 mmol), palladium(II) acetate (1.6 mg, 0.007 mmol), (*S*)−(−)-2,2′-bisphenylphospino)-1,1′-binaphthyl (5.5 mg, 0.008 mmol), sodium *tert*-butoxide (51 mg, 0.53 mmol), methylamine (0.44 mL of 2.0 M solution in THF, 0.88 mmol) and toluene (0.5 mL) was sealed and heated at 90 °C for 4 h. After cooling the reaction to 0 °C, the solution was diluted with EtOAc (5 mL), and washed with 0.5 M HCl (2.5 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated to provide a brown oil. Purification by flash chromatography (gradient elution: 5%→12% EtOAc/hexanes) provided **28** (60 mg, 0.170 mmol, 47%) as light brown oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.83 (d, J = 8.5 Hz, 1 H), 6.94 (dd, J = 7.5, 7.5 Hz, 1 H), 6.62 (d, J = 8.5 Hz, 1 H), 6.28 (dd, J = 7.5, 1.0 Hz, 1 H), 6.25 (dd, J = 7.5, 1.0 Hz, 1 H), 6.05 (d, J = 2.0 Hz, 1 H), 5.86−5.74 (m, 2 H), 5.67 (dd, J = 10.0, 3.0 Hz, 1 H), 5.45 (s, 1 H), 5.40 (q, J = 5.0 Hz, 1 H), 5.03 (dd, J = 9.0, 2.0 Hz, 1 H), 4.98 (dd, J = 15.0, 2.0 Hz, 1 H), 2.72 (d, J = 5.0 Hz, 3 H), 2.60−2.53 (m, 1 H), 2.25−2.18 (m, 1 H), 2.16 (s, 3 H), 1.17, (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.6, 146.2, 145.0, 134.5, 133.6, 132.5, 127.6, 127.5, 124.2, 117.2, 117.0, 117.0, 113.3, 110.7, 106.1, 104.6, 73.5, 49.7, 35.5, 31.1, 29.3, 28.7, 23.9; MS (DCI/NH_3) m/z 347 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{26}N_2O$ 346.2045 (M$^+$), found 346.2049. Anal. ($C_{23}H_{26}N_2O$) C, H, N.

10-Carbomethoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (29). To a deoxygenated solution of **17** (616 mg, 1.33 mmol), bis(diphenylphosphino)ethane (27 mg, 0.066 mmol), triethylamine (241 μL, 1.73 mmol), and methanol (0.5 mL) in DMSO (5.0 mL) was added palladium acetate (15 mg, 0.066 mmol). The solution was saturated with CO by bubbling a stream of gas into the reaction mixture for 4 min at 23 °C. The reaction mixture was then heated at 60 °C under CO atmosphere for 3 h. The reaction was allowed to cool to 23 °C then was partitioned between EtOAc (20 mL) and water (10 mL). The organic portion was washed with water (7 mL) and brine (7 mL) and then dried (Na_2SO_4). Filtration and concentration gave a black residue which was purified by flash chromatography (elution with 15% EtOAc/hexanes) to provide **29** (411 mg, 0.883 mmol, 66%) as a pale yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.19−7.12 (m, 2 H), 7.02 (d, J = 8.5 Hz, 1 H), 6.98 (dd, J = 5.5, 3.7 Hz, 1 H), 6.58 (d, J = 8.5 Hz, 1 H), 6.31−6.27 (m, 1 H), 5.85−5.80 (m, 2 H), 5.45 (s, 1 H), 5.05 (dd, J = 10.5, 1.5 Hz, 1 H), 4.98 (dd, J = 17.3, 1.5 Hz, 1 H), 3.78 (s, 3 H), 2.36−2.28 (m, 2 H), 2.18 (s, 3 H), 1.20 (s, 3 H), 1.16 (s, 3 H); MS (DCI/NH_3) m/z 376 (M + H)$^+$; Anal. ($C_{24}H_{25}NO_3$) C, H, N.

10-Hydroxymethyl-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (30). A magnetically stirred solution of **29** (32 mg, 0.085 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C and Dibal-H (0.400 mL of a 1.0 M solution in cyclohexane, 0.40 mmol) was added in dropwise fashion. The temperature of the reaction was allowed to rise to 0 °C over a period of 30 min. After 3.5 h, the reaction was quenched by addition to aqueous Rochelle's salt (3 mL) and EtOAc (10 mL). Upon warming, the layers were partitioned and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic portions were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by preparative TLC (2× elution with 10% EtOAc/hexanes) and the product isolated by EtOAc extraction to provide **30** (8.0 mg, 0.023 mmol, 20%) as pale yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.47 (d, J = 8.5 Hz, 1 H), 7.17−7.11 (m, 2 H), 6.80 (dd, J = 7.3, 1.8 Hz, 1 H), 6.64 (d, J = 8.5 Hz, 1 H), 6.19−6.12 (m, 1 H), 5.81 (dd, J = 17.1, 10.5 Hz, 1 H), 5.73 (dd, J = 10.5, 3.4 Hz, 1 H), 5.49−5.45 (m, 1 H), 5.32 (dd, J = 6.3, 4.2 Hz, 1 H), 5.02 (br d, J = 10.5 Hz, 1 H), 4.94 (d, J = 17.1 Hz, 1 H), 4.65−4.60 (m, 2 H), 2.34−2.28 (m, 2 H), 2.17 (s, 3 H), 1.19 (s, 3 H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.0, 145.7, 137.1, 134.3, 133.7, 133.5, 128.0, 127.3, 126.2, 124.3, 123.8, 117.0, 116.3, 116.0, 113.3, 73.6, 62.0, 49.8, 35.9, 29.4, 28.9, 23.9; MS (DCI/NH_3) m/z 348 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{25}NO_2$ 347.1885 (M$^+$), found 347.1897. Anal. ($C_{23}H_{25}NO_2$) C, H, N.

10-Methoxymethyl-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (31). To a magnetically stirred solution of the **30** (26 mg, 0.075 mmol) in THF (2.0 mL) at 0 °C was added potassium hexamethyldisilazide (0.14 mL of a 1.0 M solution in hexane, 0.14 mmol). The solution was stirred for 15 min then methyl iodide (13.8 mg, 0.097 mmol) was added and the reaction was allowed to slowly come to ambient temperature. The reaction was quenched with satd aq NH_4Cl (2 mL) and then was extracted with EtOAc (2 × 10 mL). The organic portions were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by preparative TLC (2X elution with 10% EtOAc/hexanes) and the product isolated by EtOAc extraction to provide **31** (25 mg, 0.069 mmol, 92%) as pale yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34 (d, J = 8.5 Hz, 1 H), 7.17−7.11 (m, 2 H), 6.85 (dd, J = 7.4, 2.4 Hz, 1 H), 6.64 (d, J = 8.5 Hz, 1 H), 6.23−6.18 (m, 1 H), 5.81 (d, J = 10.2 Hz, 1 H), 5.77−5.72 (m, 1 H), 5.46 (s, 1 H), 5.02 (br d, J = 10.2 Hz, 1 H), 4.93 (br d, J = 17.3 Hz, 1 H), 4.61 (d, J = 11.2 Hz, 1 H), 4.43 (d, J = 11.2 Hz, 1 H), 3.37 (s, 3 H), 2.37−2.31 (m, 1 H), 2.31−2.25 (m, 1 H), 2.17 (s, 3 H), 1.19 (s, 3 H), 1.17 (s, 3 H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 150.3, 145.8, 134.2, 133.8, 133.6, 132.7, 127.7, 127.3, 126.2, 125.1, 124.7, 117.0, 116.8, 116.7, 116.3, 113.5, 73.6, 72.8, 57.3, 49.8, 36.0, 29.4, 28.9, 23.9; MS (DCI/NH_3) m/z 362 (M + H)$^+$; HRMS (FAB) calcd for $C_{24}H_{27}NO_2$ 361.2042 (M$^+$), found 361.2047. Anal. ($C_{24}H_{27}NO_2$) C, H, N.

10-Difluoromethoxy-5-oxo-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (32). A stirred suspension of **16** (47 mg, 0.127 mmol) and potassium carbonate (53 mg, 0.382 mmol) in DMF (2.5 mL) at 80 °C was treated with bromodifluoromethane by bubbling a stream of the gaseous reagent through the hot, stirred reaction mixture for 4 min. The reaction mixture was heated for an additional 15 min then cooled, diluted with 2:1 hexanes−Et_2O (15 mL) and washed with water (2 × 10 mL). The organic portions were washed with brine (5 mL) and then dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (elution with 10% EtOAc/hexanes) to give **32** (23 mg, 0.055 mmol, 43%) as a white foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (d, J = 9.1 Hz, 1 H), 7.43 (t, J = 7.7 Hz, 1 H), 7.39 (t, J_{H-F} = 74 Hz, 1 H), 7.25 (d, J = 9.1 Hz, 1 H), 7.18−7.12 (m, 2 H), 7.07 (br s, 1 H), 5.48 (br s, 1 H), 1.94 (s, 3 H), 1.24 (s, 6 H); MS (DCI/NH_3) m/z 358 (M + H)$^+$. Anal. ($C_{20}H_{17}FNO_3$) C, H, N.

10-Difluoromethoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (35). Difluoroether **35** was prepared from **32** according to method A:

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (d, J = 9.0 Hz, 1 H), 7.20 (t, J_{H-F} = 74 Hz, 1 H), 7.15 (t, J = 8.0 Hz, 1 H), 6.83 (dd, J = 8.0, 1.0 Hz, 1 H), 6.81 (dd, J = 8.0, 1.0 Hz, 1 H), 6.63 (d, J = 9.0 Hz, 1 H), 6.28 (s, 1 H), 5.89−5.75 (m, 2 H), 5.46 (s, 1 H), 5.04 (dd, J = 11.0, 2.0 Hz, 1 H), 4.96 (dd, J = 17.0, 2.0 Hz, 1 H), 2.48−2.40 (m, 1 H), 2.29−2.20 (m, 1 H), 2.18 (s, 3 H), 1.17 (s, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.4, 147.2, 146.2, 134.0, 133.7, 132.6, 127.2, 127.0, 127.0, 117.3, 116.9, 116.5, 116.2 (t, J_{C-F} = 310.1 Hz), 114.7, 114.2, 113.5, 112.6, 73.7, 49.8, 36.7, 29.2, 29.0, 23.8; MS (DCI/NH_3) m/z 384 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{23}F_2NO_2$ 383.1697 (M^+), found 383.1693. Anal. ($C_{23}H_{23}F_2NO_2$) C, H, N.

5-(2-Propenyl)-10-thiomethoxy-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (37). A suspension of **36** (249 mg, 0.590 mmol) and KOH (90 mg, 1.20 mmol) in ethylene glycol (6 mL) containing water (1.5 mL) was heated at reflux (homogeneous solution) for 1.5 h. The solution was cooled and poured onto ice (10 g). The mixture was acidified (pH 4) with 10% HCl and was then extracted with CH_2Cl_2 (2 × 20 mL). The extracts were dried (Na_2SO_4), were filtered, and were concentrated. The resulting residue was purified by flash chromatography (elution with 5% EtOAc/CH_2Cl_2) to provide nearly homogeneous thiophenol adduct (183 mg) as an off-yellow solid that was used immediately: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.72 (d, J = 8.0 Hz, 1 H), 7.08 (dd, J = 7.6, 1.1 Hz, 1 H), 6.96 (t, J = 7.5 Hz, 1 H), 6.67 (d, J = 8.1 Hz, 1 H), 6.63 (dd, J = 7.5, 1.2 Hz, 1 H), 6.28 (br s, 1 H), 5.88−5.70 (m, 2 H), 5.47 (br s, 1 H), 5.41 (s, 1H), 5.03 (dd, J = 13.2, 1.3 Hz, 1 H), 4.98 (dd, J = 18.4, 1.3 Hz, 1 H), 2.48−2.21 (m, 2 H), 2.17 (s, 3 H), 1.20 (s, 3 H), 1.17 (s, 3 H); MS (DCI/NH_3) m/e 350 (M + H)$^+$.

A solution of the crude thiophenol (183 mg) in DMF (10 mL) at 0 °C was treated with cesium carbonate (50 mg, 0.153 mmol). After 10 min, a solution of iodomethane (25 mg, 0.176 mmol) in DMF (0.7 mL) was added, and the solution was stirred at 0 °C for 30 min then at 23 °C for 2 h. The mixture was diluted with 1:1 EtOAc−hexanes (100 mL) and was washed with water (3 × 25 mL) then washed with brine (25 mL). The organic portion was dried (Na_2SO_4), was filtered, and was concentrated. The resulting residue was purified by flash chromatography (elution with 5% EtOAc/hexanes) to provide **37** (65 mg, 0.179 mmol, 34%) as an off-yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82 (d, J = 8.1 Hz, 1 H), 7.11 (t, J = 7.6 Hz, 1 H), 6.98 (br d, J = 7.7 Hz, 1 H), 6.72 (br d, J = 7.6 Hz, 1 H), 6.62 (d, J = 8.0 Hz, 1 H), 6.27 (br s, 1 H), 5.88−5.70 (m, 2 H), 5.47 (br s, 1 H), 5.03 (dd, J = 13.3, 1.1 Hz, 1 H), 4.99 (dd, J = 18.3, 1.1 Hz, 1 H), 2.47 (s, 3 H), 2.46−2.33 (m, 1 H), 2.32−2.22 (m, 1 H), 2.18 (s, 3 H), 1.21 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.5, 145.9, 134.2, 133.9, 133.6, 133.5, 127.3, 126.9, 126.5, 123.7, 120.5, 117.1, 116.6, 116.3, 114.2, 112.6, 73.9, 49.8, 35.8, 29.5, 28.9, 23.8, 16.5; MS (DCI/NH_3) m/e 364 (M + H)$^+$; HRMS (FAB) calcd m/z for $C_{23}H_{25}NOS$: 363.1657 (M^+), found 363.1663. Anal. ($C_{23}H_{25}NOS$) C, H, N.

7-Bromo-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (41). Prepared from **40** according to method A: ^{1}H NMR (300 MHz, DMSO-d_6) $\delta\delta$ 7.93 (d, J = 8.8 Hz, 1 H), 7.33 (d, J = 9.2 Hz, 1 H), 6.71 (d, J = 9.2 Hz, 1 H), 6.60 (d, J = 8.5 Hz, 1 H), 6.25 (d, J = 1.5 Hz, 1 H), 5.94−5.80 (m, 2 H), 5.45 (s, 1 H), 5.0 (m, 2 H), 3.86 (s, 3 H), 2.17 (d, J = 1.5 Hz, 3 H), 1.17 (s, 6 H). ^{13}C NMR (300 MHz, DMSO-d_6) δ 155.3, 147.0, 146.0, 133.8, 133.6, 131.8, 129.5, 127.3, 127.2, 117.4, 116.0, 115.1, 113.2, 107.1, 102.6, 74.8, 55.9, 49.8, 29.0, 23.8; MS (APCI) m/z 426 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{24}{}^{79}BrNO_2$ 426.3502 (M^+), found 426.3496. Anal. ($C_{23}H_{24}BrNO_2$) C, H, N.

10-Methoxy-7-methyl-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (42). A solution **41** (87 mg, 0.20 mmol) and (1,3-bis(diphenylphosphino)-ferrocene)palladium (II) chloride·dichloromethane complex (20 mg, 0.020 mmol) in DMF (2 mL) was treated with tetramethyltin (63 mg, 0.35 mmol). The solution was heated at 65 °C for 24 h, then cooled to 23 °C, treated with satd. KF solution (2 mL), and extracted with EtOAc (10 mL). The organic portion was washed with water (4 mL) and brine (4 mL) then was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (elution with 5% EtOAc/hexanes) to provide **42** (47 mg, 0.13 mmol, 63%) as a pale yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 8.5 Hz, 1 H), 6.93 (d, J = 8.5 Hz, 1 H), 6.59 (dd, J = 5.5, 2.6 Hz, 1 H), 6.10 (s, 1 H), 5.90−5.76 (m, 2 H), 5.44 (s, 1 H), 5.07−4.90 (m, 2 H), 3.82 (s, 3 H), 2.17 (s, 3 H), 2.08 (s, 3 H), 1.99 (s, 3 H), 1.16 (s, 3 H), 1.15 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 154.2, 148.5, 145.4, 134.5, 133.4, 131.9, 127.8, 127.4, 127.1, 118.2, 117.0, 116.3, 116.0, 113.1, 112.9, 104.8, 73.6, 55.5, 49.6, 36.5, 28.9, 28.8, 23.8, 15.0; MS (ESI) m/z 362 (M + H)$^+$; HRMS (FAB) calcd for $C_{24}H_{27}NO_2$ 361.2042 (M^+), found 361.2045. Anal. ($C_{24}H_{27}NO_2$) C, H, N.

10-Methoxy-7-vinyl-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (43). A solution of **41** (88 mg, 0.21 mmol) and (1,3-bis(diphenylphosphino)-ferrocene)palladium (II) chloride·dichloromethane complex (20 mg, 0.021 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was treated with vinyl tributylstannane (119 mg, 0.376 mmol). The solution was heated at 65 °C for 24 h, then cooled to 23 °C, treated with satd. KF solution (2 mL), and extracted with EtOAc (10 mL). The organic portion was washed with water (4 mL) and brine (4 mL) then was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (elution with 5% EtOAc/hexanes + 1% triethylamine) to provide **43** (46 mg, 0.12 mmol, 59%) as a pale yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82 (d, J = 8.9 Hz, 1 H), 7.23 (d, J = 8.9 Hz, 1 H), 6.78 (dd, J = 11.0, 6.8 Hz, 1 H), 6.61 (d, J = 8.9 Hz, 1 H), 6.49 (d, J = 8.5 Hz, 1 H), 5.99 (d, J = 1.7 Hz, 1 H), 5.74 (dd, J = 7.6, 3.0 Hz, 1 H), 5.71−5.63 (m, 1 H), 5.57 (dd, J = 7.6, 1.7 Hz, 1 H), 5.32 (s, 1 H), 5.00 (dd, J = 9.3, 1.7 Hz, 1 H), 4.92 (dd, J = 10.2, 1.7 Hz, 1 H), 4.83 (dd, J = 16.9, 1.7 Hz, 1 H), 3.75 (s, 3 H), 2.06 (s, 3 H), 1.53−1.41 (m, 2 H), 1.24−1.15 (m, 3 H), 1.05 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 155.66, 147.91, 145.55, 134.17, 133.45, 131.98, 130.77, 127.37, 127.28, 123.88, 119.52, 117.21, 115.99, 115.80, 113.20, 113.18, 112.12, 105.59, 74.01, 55.59, 49.69, 36.40, 29.03, 28.83, 27.67, 26.19, 23.83, 13.55; MS (ESI) m/z 373 (M + H)$^+$; HRMS (FAB) calcd for $C_{25}H_{27}NO_2$ 373.2042 (M^+), found 373.2048. Anal. ($C_{25}H_{27}NO_2$) C, H, N.

9-Hydroxy-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (50). To a solution of lactone **49** (2.75 g, 6.09 mmol) in CH_2Cl_2 (750 mL) at −78 °C under N_2 was added dropwise 1 M DIBAL-H (15.2 mL of a 1.0 M solution in heptane, 15.2 mmol) maintaining the temperature at −78 °C. The resulting orange-red solution was stirred at −78 °C for 1 h at which time a TLC of an aliquot (quenched with satd. NH_4Cl) indicated conversion to desired product.. A small amount of a lower R_f material (diol resulting from over-reduction) was also seen. EtOAc (50 mL) was added to the solution at −78 °C to quench the excess DIBAL-H reagent (indicated by a color change of the solution from orange-red to light yellow). The reaction mixture was partitioned between EtOAc (600 mL) and satd. Rochelle's salt solution (200 mL) and the resulting mixture was stirred vigorously until a clear separation of layers was observed (ca. 2 h). The layers were separated and the aqueous layer extracted with EtOAc (3 × 100 mL). The organics portions were combined, washed with brine (2 × 200 mL), dried (Na_2SO_4), filtered and concentrated to give the lactol as a light yellow oil which was carried on without purification.

The lactol from the previous step was dissolved in MeOH (50 mL) at 0° C and p-TsOH•H_2O (700 mg, 25% w/w) was added portionwise as a solid. The mixture was stirred for 14 h at 23 °C and then quenched with satd. aq. $NaHCO_3$ (20 mL) and extracted EtOAc (2 × 50 mL). The organics portions were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (elution with 10% EtOAc/hexanes) provided the corresponding methylacetal (1.75 g, 3.71 mmol, 61% over two steps) as a white foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.99 (d, J = 8.8 Hz, 1 H), 6.75−6.70 (m, 3 H), 6.27 (d, J = 1.8 Hz, 1 H), 6.15 (s, 1 H), 5.46 (br s, 1 H), 3.63 (s, 3 H), 3.34 (s, 3 H), 2.18 (s, 3

H), 1.28 (s, 3 H), 1.08 (s, 3 H), 1.00 (s, 9 H), 0.22 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.7, 143.6, 143.1, 132.5, 128.2, 127.5, 126.3, 118.1, 117.8, 117.4, 115.9, 114.7, 112.5, 96.0, 59.3, 54.4, 49.7, 30.0, 28.0, 25.6, 22.0, 18.0, −4.6, −4.8; MS (DCI/NH_3) m/z 469 $(M + H)^+$. Anal. Calcd for $C_{27}H_{37}NO_4Si$: C, 69.34; H, 7.97; N, 3.10. Found C, 69.00; H, 8.05; N, 3.03.

To a solution of the crude methylacetal (1.75 g, 3.74 mmol) in THF (100 mL) at 0 °C was added dropwise tetrabutylammonium fluoride (3.74 mL of a 1.0 M solution in THF, 3.74 mmol) over 15 min. The reaction was quenched by the addition of satd ammonium chloride (50 mL) and exracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (2 × 30 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (elution with 30% EtOAc/hexanes) provided the phmethyl acetal (1.30 g, 3.71 mmol, 99%) as a white foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 6.70 (d, J = 8.8 Hz, 1 H), 6.65 (m, 2 H), 6.20, (br s, 1 H), 6.16 (s, 1 H), 5.45 (br s, 1 H), 3.65 (s, 3 H), 3.31 (s, 3 H), 2.18 (s, 3 H), 1.26 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.5, 143.8, 141.3, 132.5, 128.4, 127.6, 126.3, 117.4, 117.4, 116.3, 114.7, 114.0, 112.3, 95.9, 59.3, 54.4, 49.7, 30.1, 28.1, 22.0, 22.0; MS (DCI/NH_3) m/z 354 $(M + H)^+$. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found C, 71.01; H, 6.75; N, 3.71.

Allylation of the methyl acetal was carried out according to method A to provide **50**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.69 (s, 1 H), 7.92 (d, J = 8.5, 1 H), 6.62 (d, J = 8.5 Hz, 1 H), 6.62 (d, J = 8.5 Hz, 1 H), 6.48 (d, J = 8.5, 1 H), 6.16 (d, J = 1.7 Hz, 1 H), 5.81 (ddt, J = 17.3, 10.3, 6.6 Hz, 1 H), 5.67 (dd, J = 9.8, 3.3 Hz), 5.44 (s, 1 H), 5.02 (dd, J = 10.3, 1.8 Hz, 1 H), 4.98 (dd, J = 17.3, 1.8 Hz, 1 H), 2.47−2.41 (m, 1 H), 2.34−2.27 (m, 1 H), 2.16 (s, 3 H), 1.18 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.8, 145.1, 143.9, 142.9, 134.4, 133.4, 132.7, 127.5, 126.5, 117.8, 117.0, 116.3, 116.1, 114.3, 113.6, 112.4, 73.3, 59.3, 49.7, 36.4, 29.2, 28.9, 23.9; MS (DCI/NH_3) m/z 364 $(M + H)^+$. Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

9-Fluoro-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (55). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, J = 8.5 Hz, 1 H), 7.00 (dd, J = 8.8, 2.2 Hz, 1 H), 6.64 (d, J = 8.1 Hz, 1 H), 6.63 (d, J = 8.8 Hz, 1 H), 6.31 (d, J = 1.1 Hz, 1 H), 5.90−5.80 (m, 1 H), 5.79−5.75 (m, 1 H), 5.46 (s, 1 H), 5.05−4.95 (m, 2 H), 3.79 (s, 3 H), 2.17 (d, J = 1.1 Hz, 1 H), 1.17 (s, 6 H); MS (DCI/NH_3) m/z 366 $(M + H)^+$; HRMS (FAB) calcd for $C_{23}H_{24}FNO_2$ 366.1869 (M^+), found 366.1869. Anal. ($C_{23}H_{24}FNO_2$) C, H, N.

9-Chloro-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (56). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 8.5 Hz, 1 H), 7.20 (d, J = 8.5 Hz, 1 H), 6.70 (d, J = 8.5 Hz, 1 H), 6.64 (d, J = 8.5 Hz, 1 H), 6.36−6.33 (m, 1 H), 5.84−5.79 (m, 2 H), 5.48−5.42 (m, 1 H), 5.03 (br d, J = 10.5 Hz, 1 H), 4.98 (br d, J = 17.1 Hz, 1 H), 3.65 (s, 3 H), 2.49−2.39 (m, 1 H), 2.35−2.26 (m, 1 H), 2.18 (s, 3 H), 1.19 (s, 3 H), 1.17 (s, 3 H); MS (ESI) m/z 382 $(M + H)^+$; HRMS (FAB) calcd for $C_{23}H_{24}ClNO_2$ 381.1495 (M^+), found: 381.1488. Anal. ($C_{23}H_{24}ClNO_2$) C, H, N.

8-Fluoro-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (57). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (d, J = 8.5 Hz, 1 H), 7.15−7.09 (m, 2 H), 6.62 (d, J = 8.5 Hz, 1 H), 6.27−6.22 (m, 1 H), 5.83−5.77 (m, 2 H), 5.49−5.44 (m, 1 H), 5.03 (br d, J = 10.0 Hz, 1 H), 4.95 (br d, J = 17.0 Hz, 1 H), 3.65 (s, 3 H), 2.47−2.40 (m, 1 H), 2.33−2.26 (m, 1 H), 2.18 (s, 3 H), 1.20 (s, 3 H), 1.15 (s, 3 H); MS (ESI) m/z 366 $(M + H)^+$; HRMS (FAB) calcd for $C_{23}H_{24}FNO_2$ 365.1791 (M^+), found 365.1795. Anal. ($C_{23}H_{24}FNO_2$) C, H, N.

10-Chloro-9-hydroxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (58). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 1 H), 7.87 (s, J = 8.8 Hz, 1 H), 6.72 (d, J = 8.9 Hz, 1 H), 6.66 (d, J = 8.4 Hz, 1 H), 6.58 (d, J = 8.9 Hz, 1 H), 6.21 (br s, 1 H), 5.81−5.71 (m, 1 H), 5.62 (dd, J = 10.6, 3.0 Hz, 1 H), 5.41 (br s, 1 H), 4.98 (dd, J = 10.5, 2.1 Hz, 1 H), 4.93 (dd, J = 16.9, 2.2 Hz, 1 H), 2.42−2.34 (m, 1 H), 2.26−2.20 (m, 1 H), 2.11 (s, 3 H), 1.16 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.8, 146.2, 145.2, 143.4, 134.3, 134.0, 133.5, 127.3, 127.0, 123.8, 117.1, 116.2, 115.3, 114.0, 112.8, 73.9, 49.9, 49.7, 35.7, 29.5, 28.9, 23.9; MS (DCI/NH_3) m/z 368 $(M + H)^+$; HRMS (FAB) calcd for $C_{22}H_{22}ClNO_2$ 367.1339 (M^+), found 367.1336. Anal. ($C_{22}H_{22}ClNO_2$) C, H, N.

9-Bromo-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (59). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 8.8 Hz, 1 H), 7.33 (d, J = 8.5 Hz, 1 H), 6.67 (d, J = 8.5 Hz, 1 H), 6.65 (d, J = 8.5 Hz, 1 H), 6.36 (d, J = 1.1 Hz, 1 H), 5.88−5.74 (m, 2 H), 5.46 (s, 1 H), 5.05−4.95 (m, 2 H), 3.62 (s, 3 H), 2.18 (d, J = 1.1 Hz, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 152.7, 150.8, 146.5, 134.0, 133.6, 132.1, 130.0, 127.3, 126.1, 119.3, 117.4, 116.2, 115.0, 114.6, 114.0, 109.5, 73.7, 59.6, 49.9, 36.7, 29.4, 29.1, 23.9; MS (DCI/NH_3) m/z 428 $(M + H)^+$; HRMS (FAB) calcd for $C_{23}H_{24}BrNO_2{}^{79}Br$ 425.0990 (M^+), found 425.0998; HRMS (FAB) calcd for $C_{23}H_{24}NO_2{}^{81}Br$ 427.0970 (M^+), found 427.0974. Anal. ($C_{23}H_{24}BrNO_2$) C, H, N.

10-Chloro-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (60). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 8.6 Hz, 1 H), 7.12−7.10 (m, 2 H), 6.90−6.84 (m, 1 H), 6.65 (d, J = 8.8 Hz, 1 H), 6.36 (br s, 1 H), 5.90−5.75 (m, 2 H), 5.47 (br s, 1 H), 5.05 (dd, J = 10.5, 2.1 Hz, 1 H), 4.97 (dd, J = 17.3, 1.7 Hz, 1 H), 2.47−2.26 (m, 2 H), 2.16 (s, 3 H), 1.23 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.6, 146.3, 133.9, 133.6, 133.5, 128.2, 127.2, 127.1, 126.7, 124.5, 123.1, 117.2, 116.5, 116.1, 114.8, 112.9, 74.0, 49.8, 36.1, 29.4, 28.9, 23.8; MS (DCI/NH_3) m/z 352 $(M + H)^+$; HRMS (FAB) calcd for $C_{22}H_{22}ClNO$ 351.1390 (M^+), found 351.1385. Anal. ($C_{22}H_{22}ClNO$) C, H, N.

7-Bromo-10-chloro-9-hydroxy-5-(3-propenyl)-2,2,4-trimethyl-1H-2,5-dihydro-[1]benzopyrano[3,4-f]quinoline (61). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.03 (s, 1 H), 7.90 (d, J = 8.5 Hz, 1 H), 7.00 (app s, 2 H), 6.63 (d, J = 8.4 Hz, 1 H), 6.43 (br s, 1 H), 5.92−5.77 (m, 2 H), 5.47 (br s, 1 H), 5.11−4.97 (m, 1 H), 2.44−2.26 (m, 2 H), 2.19 (s, 3 H), 1.22 (s, 3 H), 1.18 (s, 3 H); MS (DCI/NH_3) m/z 448 $(M + H)^+$; HRMS (FAB) calcd for $C_{22}H_{21}{}^{77}BrClNO_2$ 445.0444 (M^+), found 445.0436; HRMS (FAB) calcd for $C_{22}H_{21}{}^{79}BrClNO_2$ 447.0424 (M^+), found 447.0413. Anal. ($C_{22}H_{21}BrClNO_2$) C, H, N.

5-(2-Propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (62). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (dd, J = 7.7, 1.5 Hz, 1 H), 7.47 (d, J = 8.5 Hz, 1 H), 7.11 (t, J = 7.7 Hz, 1 H), 6.97 (t, J = 7.7 Hz, 1 H), 6.84 (dd, J = 8.1, 1.4 Hz, 1 H), 6.66 (d, J = 8.5 Hz, 1 H), 6.24−6.18 (m, 1 H), 5.86 (dd, J = 9.8, 3.3 Hz, 1 H), 5.84−5.79 (m, 1 H), 5.48−5.42 (m, 1 H), 5.03 (br d, J = 10.3 Hz, 1 H), 4.99 (br d, J = 17.3 Hz, 1 H), 2.47−2.39 (m, 1 H), 2.17 (s, 3 H), 2.15 (m, 1 H), 1.21 (s, 3 H), 1.13 (s, 3 H); MS (ESI) m/z 318 $(M + H)^+$; HRMS calcd for $C_{22}H_{23}NO$ 317.1780 (M^+), found 317.1765. Anal. ($C_{22}H_{23}NO$) C, H, N.

9,10-Dimethoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (63). Prepared from **50** according to method B using methyl iodide as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 8.5 Hz, 1 H), 6.82 (d, J = 8.8 Hz, 1 H), 6.61 (dd, J = 4.4, 4.4 Hz, 2 H), 6.22 (d, J = 1.4 Hz, 1 H), 5.83 (ddt, J = 16.9, 10.3, 3.1 Hz, 1 H), 5.70 (dd, J = 10.3, 3.3 Hz, 1 H), 5.44 (s, 1 H), 5.44−4.96 (m, 2 H), 3.77 (s, 3 H), 3.67 (s, 3 H), 2.16 (s, 3 H), 1.17 (s, 3 H), 1.16 (s, 3 H); MS (ESI) m/z 378 $(M + H)^+$; HRMS (FAB) calcd for $C_{24}H_{27}NO_3$ 377.1991 (M^+), found 377.2001. Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

9-Ethoxy-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (64). Prepared from **50** according to nethod B using iodoethane as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 8.8 Hz, 1 H), 6.79 (d, J = 8.8 Hz, 1 H), 6.60 (d, J = 8.8 Hz, 1 H), 6.55 (d, J = 8.8, 1 H), 6.45 (s, 1 H), 5.85 (ddt, J = 17.3, 10.3, 6.6 Hz, 1 H), 5.43 (d, J = 9.2 Hz), 5.16 (s, 1 H), 5.09 (dd, J = 10.3, 1.1 Hz, 1 H), 5.06 (dd, J = 17.3, 1.1 Hz, 1 H), 4.91 (s, 1 H), 4.06−3.97 (m, 2 H), 2.62−2.52 (m, 1 H), 2.31−2.15 (m, 1 H), 2.24 (s, 3 H), 1.35 (t, J = 7.0 Hz, 3 H), 1.26 (s, 3 H), 1.07 (s, 3 H); MS (DCI/NH_3) m/z 392 $(M + H)^+$; HRMS (FAB) calcd

for $C_{26}H_{27}NO_3$ 391.2147 (M^+), found 391.2138. Anal. ($C_{26}H_{27}NO_3$) C, H, N.

10-Methoxy-5-(2-propenyl)-9-(2-propenyloxy)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (65). Prepared from **50** according to method B using allyl bromide as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 9.0 Hz, 1 H), 6.83 (d, J = 8.8 Hz, 1 H), 6.61 (d, J = 9.0 Hz, 1 H), 6.59 (d, J = 8.8 Hz, 1 H), 6.23 (d, J = 1.5 Hz, 1 H), 6.15−6.02 (m, 1 H), 5.81 (ddt, J = 17.3, 10.3, 6.6 Hz, 1 H), 5.67 (dd, J = 9.8, 3.3 Hz), 5.45 (s, 1 H), 5.44 (dd, J = 16.0, 2.0 Hz, 1 H), 5.27 (dd, 10.6, 2.0 Hz, 1 H), 5.03 (dd, J = 10.3, 1.8 Hz, 1 H), 4.98 (dd, J = 17.3, 1.8 Hz, 1 H), 4.56−4.53 (m, 1 H), 2.47−2.41 (m, 1 H), 2.34−2.27 (m, 1 H), 2.16 (s, 3 H), 1.17 (s, 3 H), 1.16 (s, 3 H); MS (DCI/NH_3) m/z 404 (M + H)$^+$; HRMS (FAB) calcd for $C_{26}H_{29}NO_3$ 403.2147 (M^+), found 403.2150. Anal. ($C_{26}H_{29}NO_3$) C, H, N.

10-Methoxy-5-(2-propenyl)-9-(2-propynyloxy)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (66). Prepared from **50** according to method B using propargyl bromide as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 8.8 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 1 H), 6.62 (d, J = 8.8 Hz, 1 H), 6.61 (d, J = 8.8, 1 H), 6.24 (d, J = 1.7 Hz, 1 H), 5.81 (ddt, J = 17.3, 10.3, 6.6 Hz, 1 H), 5.72 (dd, J = 9.8, 3.3 Hz), 5.44 (s, 1 H), 5.03 (dd, J = 10.3, 1.8 Hz, 1 H), 4.99 (dd, J = 17.3, 1.8 Hz, 1 H), 4.79 (d, J = 2.3 Hz, 2 H), 3.57 (t, J = 2.3 Hz, 1 H), 2.47−2.41 (m, 1 H), 2.34−2.27 (m, 1 H), 2.16 (s, 3 H), 1.17 (s, 3 H), 1.16 (s, 3 H); MS (DCI/NH_3) m/z 402 (M + H)$^+$; HRMS (FAB) calcd for $C_{26}H_{27}NO_3$ 401.1991 (M^+), found 401.1978. Anal. ($C_{26}H_{27}NO_3$) C, H, N.

9-Cyanomethoxy-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (67). Prepared from **50** according to method B using chloroacetonitrile as the electrophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 9.1 Hz, 1 H), 6.95 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1 H), 6.63 (d, J = 9.1 Hz, 1 H), 6.26 (d, J = 2.4 Hz, 1 H), 5.45 (s, 1 H), 5.12 (s, 2 H), 5.05−4.97 (m, 1 H), 5.01 (s, 1 H), 3.69 (s, 3 H), 2.46−2.40 (m, 1 H), 2.30−2.23 (m, 1 H), 2.17 (s, 3 H), 1.18 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.6, 146.2, 145.0, 134.1, 133.6, 133.5, 132.6, 127.3, 126.6, 118.6, 117.2, 116.8, 116.2, 115.2, 114.4, 113.7, 112.4, 73.5, 60.1, 60.1, 55.5, 49.8, 36.7, 29.3, 29.0, 23.9; MS (DCI/NH_3) m/z 403 (M+H)$^+$; HRMS (FAB) calcd for $C_{25}H_{26}N_2O_3$ 402.1914 (M^+), found 402.1947. Anal. ($C_{25}H_{26}N_2O_3$) C, H, N.

10-Methoxy-9-trifluoromethanesulfonyloxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano-[3,4-f]quinoline (68). To a solution of **50** (268 mg, 0.784 mmol) in CH_2Cl_2 (9 mL) at −78 °C was added triethylamine (330 μL, 2.34 mmol), followed by trifluoromethanesulfonic anhydride (146 μL, 0.860 mmol). The reaction mixture was allowed to slowly warm to 23 °C over a period of 1.5 h. The reaction was quenched with satd. aq. NH_4 (0 mL) and extracted EtOAc (2 × 20 mL). The combined organic layers were washed with brine (5 mL), then were dried (Na_2SO_4) and were concentrated. The resulting tan residue was purified by flash chromatography (elution with 10% EtOAc/hexanes) to provide **68** (338 mg, 0.714 mmol, 91%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 (d, J = 8.6 Hz, 1 H), 7.37 (t, J = 8.3 Hz, 1 H), 7.03 (dd, J = 8.6, 1.1 Hz, 1 H), 6.66 (d, J = 8.6 Hz, 1 H), 6.48 (br s, 1 H), 5.91−5.74 (m, 2 H), 5.48 (br s, 1 H), 5.03 (dd, J = 9.0, 1.1 Hz, 1 H), 4.93 (dd, J = 16.0, 1.1 Hz, 1 H), 3.84 (s, 3 H), 2.47−2.26 (m, 2 H), 2.19 (s, 3 H), 1.21 (s, 3 H), 1.18 (s, 3 H);^{13}C NMR (125 MHz, DMSO-d_6) δ 162.7, 153.4, 150.2, 146.2, 140.7, 138.2, 130.6, 127.9, 127.3, 124.1, 118.5, 116.8, 114.4, 113.3, 109.4, 106.7, 74.0, 88.2, 56.0, 47.3, 33.9, 29.4, 26.1, 22.3; MS (DCI/NH_3) m/z 496 (M + H)$^+$; HRMS (FAB) calcd for $C_{24}H_{24}F_3NO_5S$ 362.1756 (M^+, found 362.1749.

9-Carbomethoxy-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (69). To a deoxygenated solution of **68** (308 mg, 0.667 mmol), bis(diphenylphosphino)ethane (14 mg, 0.033 mmol),triethylamine (120 μL, 0.870 mmol), and methanol (0.3 mL) in DMSO (3.0 mL) was added palladium acetate (6 mg, 0.033 mmol). The solution was saturated with CO by bubbling a stream of gas into the reaction mixture for 4 min at 23 °C. The reaction mixture was then heated at 60 °C under CO atmosphere for 3 h. The reaction was allowed to cool to 23 °C then was partitioned between EtOAc (15 mL) and water (5 mL). The organic portion was washed with water (5 mL) and brine (5 mL) and then dried (Na_2SO_4). Filtration and concentration gave a black residue which was purified by flash chromatography (elution with 15% EtOAc/hexanes) to provide **69** (205 mg, 0.442 mmol, 65%) as a pale yellow foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 8.1 Hz, 1 H), 6.48 (d, J = 8.3 Hz, 1 H), 6.75 (d, J = 8.2 Hz, 1 H), 6.65 (d, J = 8.2 Hz, 1 H), 6.33 (br s, 1 H), 5.90−5.75 (m, 2 H), 5.46 (br s, 1 H), 5.04 (dd, J = 10.5, 1.0 Hz, 1 H), 4.98 (dd, J = 15.4, 1.0 Hz, 1 H), 3.82 (s, 3 H), 3.67 (s, 3 H), 2.54−2.42 (m, 1 H), 2.38−2.27 (m, 1 H), 2.18 (s, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 156.5, 154.6, 146.3, 133.9, 133.5, 131.9, 129.0, 127.2, 126.2, 119.1, 118.1, 117.4, 116.2, 114.5, 114.0, 113.0, 74.0, 60.7, 51.8, 49.8, 36.8, 29.4, 29.0, 23.8; MS (DCI/NH_3) m/z 406 (M + H)$^+$; HRMS (FAB) calcd for $C_{25}H_{27}NO_4$ 405.1940 (M^+, found 405.1939. Anal. ($C_{25}H_{27}NO_4$) C, H, N.

9-Hydroxymethyl-10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (70). A magnetically stirred solution of **69** (32 mg, 0.085 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C and Dibal-H (0.400 mL of a 1.0 M solution in cyclohexane, 0.40 mmol) was added in dropwise fashion. The temperature of the reaction was allowed to rise to 0 °C over a period of 30 min. After 3.5 h, the reaction was quenched by addition to aqueous Rochelle's salt (3 mL) and EtOAc (10 mL). Upon warming, the layers were partitioned and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic portions were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by preparative TLC (2× elution with 10% EtOAc/hexanes) and the product isolated by EtOAc extraction to provide **69** (24 mg, 0.069 mmol, 61%) as pale yellow foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, J = 8.2 Hz, 1 H), 7.16 (d, J = 8.3 Hz, 1 H), 6.67 (d, J = 8.1 Hz, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 6.27 (br s, 1 H), 5.87−5.75 (m, 2 H), 5.44 (br s, 1 H), 5.03 (br d, J = 10.3 Hz, 1 H), 4.98 (br d, J = 15.1 Hz, 1 H), 4.97−4.93 (m, 1 H), 4.57−4.48 (m, 2 H), 3.59 (s, 3 H), 2.55−2.46 (m, 1 H), 2.30−2.22 (m, 1 H), 2.19 (s, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H);^{13}C NMR (125 MHz, DMSO-d_6) δ 154.0, 150.2, 145.9, 134.2, 133.4, 132.1, 128.9, 127.4, 126.6, 125.9, 117.2, 116.8, 116.3, 115.6, 113.9, 112.6, 73.6, 60.0, 58.1, 49.8, 36.4, 29.4, 28.9, 23.9; MS (DCI/NH_3) m/z 378 (M + H)$^+$; HRMS (FAB) calcd m/z for $C_{24}H_{27}NO_3$ 377.1991 (M^+, found 377.1985. Anal. ($C_{24}H_{27}NO_3$) C, H, N.

Supporting Information Available: Experimental procedures for the preparation of **9**−**11**, **33**−**34**, **36**, **38**−**40**, **44**, **46**−**49**, and **54** along with characterization data. This information is free of charge via the Internet at http://pubs.acs.org.

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JM020335M