Synthesis and Characterization of Nonsteroidal Glucocorticoid Receptor Modulators for Multiple Myeloma

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Structure−activity relationship studies centered around 3′-substituted (*Z*)-5-(2′-(thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinolines are described. A series of highly potent and efficacious selective glucocorticoid receptor modulators were identified with in vitro activity comparable to dexamethasone. In vivo evaluation of these compounds utilizing a 28 day mouse tumor xenograft model demonstrated efficacy equal to dexamethasone in the reduction of tumor volume.

Introduction

First described in 1848, multiple myeloma is a cancer of bone marrow plasma cells.[1−4] The disease is characterized by proliferation of malignant plasma cells and subsequent overabundance of monoclonal paraprotein, a component of a normal immunoglobulin molecule. Uncontrolled growth of myeloma cells interferes with normal production of blood cells causing leukopenia, anemia, and thrombocytopenia. Destruction and invasion of bone surrounding the bone marrow leads to skeletal issues including spinal cord compression, general bone pain and fractures. Reduction of normal immune function increases the susceptibility to infection. There are approximately 15 000 new cases of myeloma in the United States each year.[5]

There are numerous myeloma treatment options. Glucocorticoids such prednisolone[6] or dexamethasone[7] (Figure 1) are used in first line therapies in combination with Melphalan and thalidomide.[8,9] Prednisolone is also an effective maintenance agent, which can prolong remissions and increase survival rates for myeloma.[10] However, long-term side effects, including osteoporosis, fat redistribution, glucose intolerance, and acute psychosis accompany the beneficial effects and dose reductions are usually necessary. Identifying glucocorticoids with an improved therapeutic index continues to be an active area of research.[11−19]

The human glucocorticoid receptor (GR[a]) is a member of the nuclear receptor superfamily that includes other steroid hormone receptors such as androgen (AR), estrogen (ER), mineralocorticoid (MR), and progesterone (PR).[20] Upon ligand binding, GR is able to modulate gene transcription by one of several general mechanisms.[21,22] First, the receptor can directly bind to specific DNA sequences within the nucleus termed glucocorticoid response elements (GREs) located in the promoters of regulated genes. Once bound, the receptor can recruit specific co-activators that in turn recruit components of the RNA polymerase complex, thereby increasing transcription from the promoter. Transcriptional activation is important for the regulation of glucose homeostasis in the liver and may be responsible

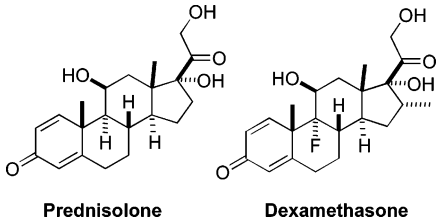

Figure 1.

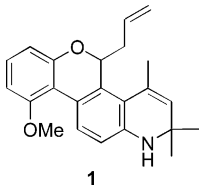

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Figure 2.

for some of the side effects of GCs. Alternatively, the receptor can repress transcription by modulating the activity of other transcription factors, such as NFκB and AP-1. This occurs through either direct interaction with these transcription factors or by competition for other rate-limiting proteins that are crucial for NFkB and AP-1 activity. Note that AP-1 and NFkB are extremely important for the regulation of proinflammatory cytokines, repression of these targets is thought to contribute to the powerful anti-inflammatory effects of steroids.[21]

The nonsteroidal selective GR modulator **1** (AL-438;[14] Figure 2) binds to GR and has been shown to differentially recruit co-activators and co-repressors. Such differential cofactor recruitment results in a receptor capable of regulating only a subset of the genes normally regulated by steroidal GCs and may lead to GCs with a unique activity-side effect profile.[13] However, alterations in the co-activator/co-repressor profile may also reduce the efficacy of a given compound. Herein we describe the design and synthesis of a number of selective glucocorticoid receptor modulators (SGRMs) that exhibit dexamethasone-like antiproliferative activity both in vitro and in vivo in models of multiple myeloma.

Chemistry

The synthesis of core **2** has been previously reported.[14] Lateral lithiation of thiophene **4** with LDA followed by the dropwise addition of the lithio-thiophene to lactone **3** gave hemi-acetal

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[a] Abbreviations: GR, glucocorticoid receptor; GRE, glucocorticoid response element; GC, glucocorticoid; SGRM, selective glucocorticoid receptor modulator; PR, progesterone receptor; MR, mineralocorticoid receptor; AR, androgen receptor.

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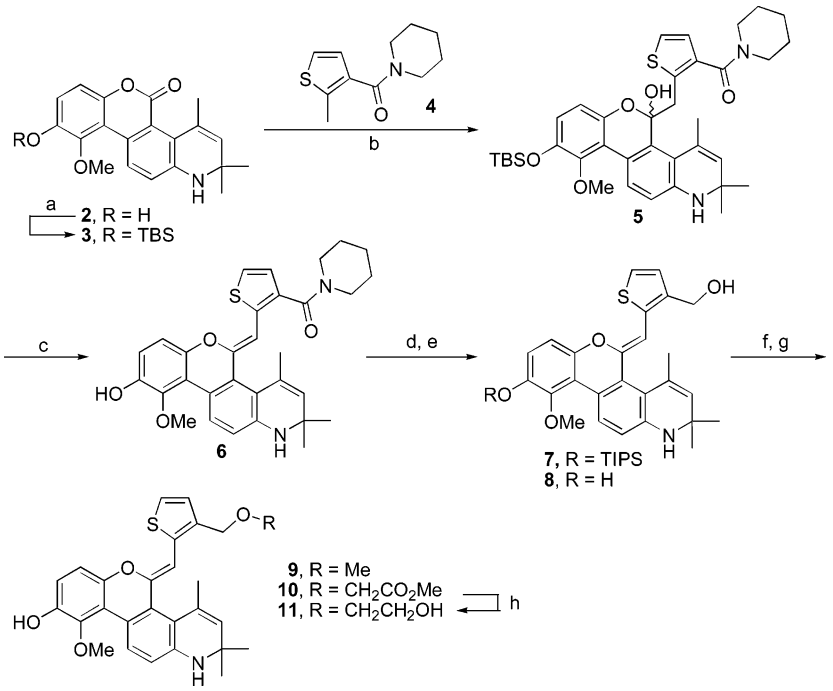
Scheme 1[a]



[a] Reagents and conditions: (a) TBS-Cl, Im, DMF; (b) LDA, THF, **4**, 0 °C; (c) 10% HCl/MeOH; (d) TIPS-OTf, 2,6-lutidine, CH_2Cl_2; (e) $LiEt_3BH$, THF; (f) R = Me, NaH, THF then MeI; R = CH_2CO_2Me, KO*t*-Bu, THF, then $BrCH_2CO_2Me$; (g) TBAF, THF; (h) $NaBH_4$, EtOH.

5. Dehydration of **5** under protic acid conditions gave methylidene **6** in high yield (84%). The synthesis was amenable to multigram quantities of **6** and became a convenient starting point for structure−activity relationship (SAR) studies. Reprotection of the phenol followed by reduction of the amide moiety using excess lithium triethylborohydride (superhydride) gave alcohol **7**. Methylation of the primary alcohol was achieved using standard protocols. Treatment of alcohol **7** with potassium *t*-butoxide followed by addition of methyl bromoacetate gave ester **10**, which was subjected to sodium borohydride reduction to yield alcohol **11** (Scheme 1).

IBX oxidation of **7** gave aldehyde **12**. Reductive amination of aldehyde **12** with trifluoroethylamine provided secondary amine **13**. Nitrile **14** was synthesized via a two-step protocol involving conversion to the intermediate oxime followed by dehydration. Reaction of aldehyde **12** with a number of nucleophiles gave the corresponding secondary alcohols **15** and **16**. IBX oxidation of alcohol **16** followed by deprotection of the TIPS-phenol gave ketone **17** (Scheme 2).

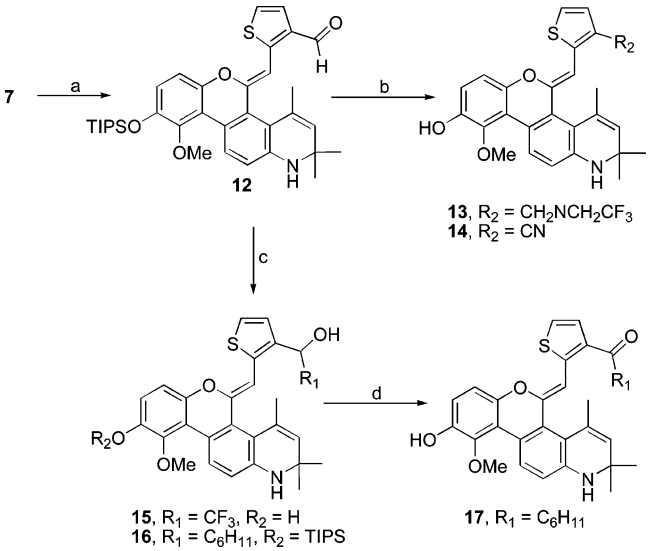
Amide **6** was treated with an excess of the appropriate alkyl lithium reagent to give the corresponding ketones **18** and **19**, which were subsequently reduced with sodium borohydride to provide alcohols **20** and **21**. Ketones **18** and **19** could also be reacted with alkoxyl- or hydroxyl-amine to yield the corresponding *E*-oximes **22**−**24** as the major product (Scheme 3).

Reacting MOM-protected aldehyde **25** with trimethylsilyl cyanide followed by oxidation gave acyl nitrile **26**. Subsequent reaction with methanol in the presence of a catalytic amount of DMAP followed by MOM-group deprotection under acidic conditions gave ester **27**. Wittig reaction with ketone **28** followed by deprotection gave alkene **29** in good yield (Scheme 4).

Results and Discussion

Structure−Activity Relationships. The GR-mediated activity of the compounds was evaluated in a number of biological assays.[23] Direct transcriptional activation by GR was measured

Scheme 2[a]

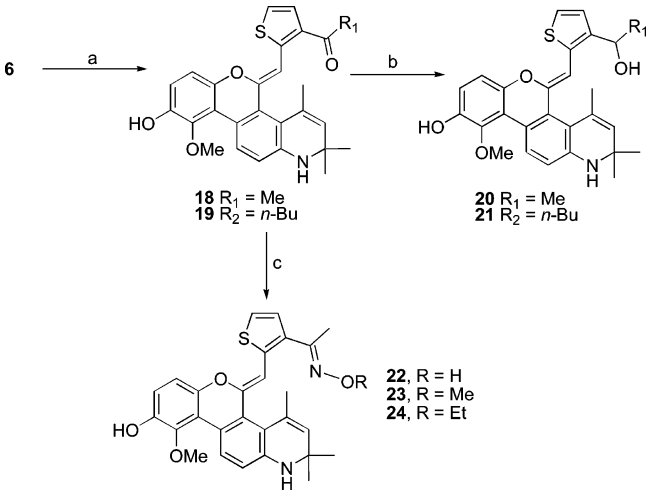


[a] Reagents and conditions: (a) IBX, DMSO/THF; (b) R = $CH_2NHCH_2CF_3$; (i) $NH_2CH_2CF_3$, $NaCNBH_3$, AcOH, MeOH; (ii) TBAF, THF, R = CN; (i) H_2NOH, EtOH; (ii) Im_2CO, THF; (iii) TBAF, THF; (c) R_1 = CF_3, R_2 = H; CF_3TMS, TBAF, THF, R_1 = cyclohexyl, R_2 = TIPS; $C_6H_{11}MgBr$, THF; (d) (i) IBX, THF/DMSO; (ii) TBAF, THF.

in a GRE activation assay using cotransfection.[24] Glucocorticoid-mediated repression of the pro-inflammatory cytokine IL-6 was also measured as further evidence of GR-mediated activity. The antiproliferative activity of the compounds was measured using a steroid-responsive human multiple myeloma cell line (RPMI8226).[25]

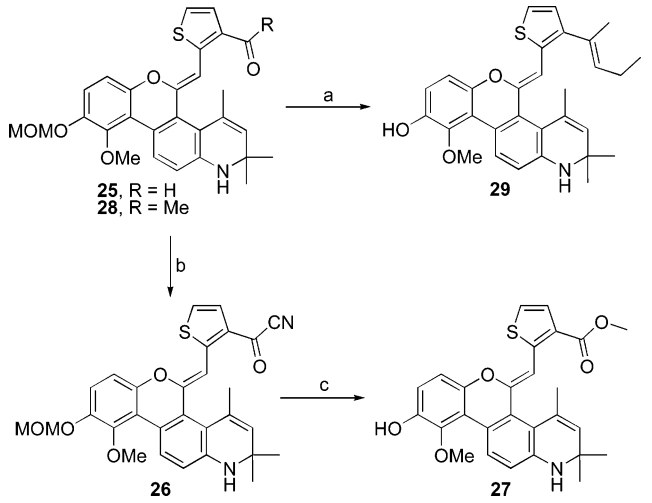
The observation that certain PR agonists[26] displayed a significant degree of GR cross-reactivity led to an SAR effort based upon this scaffold as part of a SGRM program (Figure 3). Incorporation of a C-10 methoxy group substantially improved GR selectivity. A number of C-5 alkyl and aryl analogs were synthesized, which led to the discovery of

Scheme 3[a]



[a] Reagents and conditions: (a) RLi, THF; (b) $NaBH_4$, MeOH; (c) $RONH_2$, EtOH/AcOH.

Scheme 4[a]



[a] Reagents and conditions: (a) NaHMDS, $CH_3CH_2CH_2PPh_3Br$, THF; (b) (i) TMSCN, BF_3OEt, CH_2Cl_2; (ii) IBX, DMSO/THF; (c) (i) MeOH, DMAP; (ii) 10% HCl/MeOH.

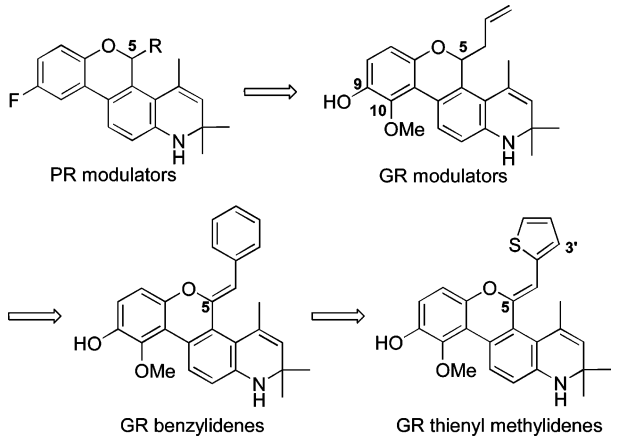


Figure 3.

compound **1**, a glucocorticoid with in vitro and in vivo activity similar to prednisolone. It was later discovered that incorporation of a 9-OH substituent improved the potency of the compounds.[14]

A series of C-5 benzylidene compounds were synthesized that demonstrated greater efficacy and potency compared to their C-5 alkyl- or aryl-counterparts. It was found that the bioisosteric replacement of the C-5 benzylidene with a C-5 thienyl methylidene group lead to a substantial improvement in in vitro antiproliferative activity (Figure 3). An SAR effort was initiated based upon this scaffold to determine the potential of this series of compounds in the treatment of multiple myeloma.

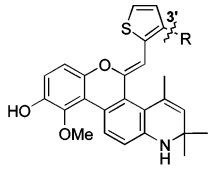
Early SAR studies based on the thiophene methylidene series revealed that the 3-position of the thiophene ring tolerated a number of functional groups yet still retaining excellent antiproliferation activity. We undertook a detailed investigation of this position with the emphasis placed on structural diversity. We were cognizant of the fact that our pharmacophore is relatively lipophilic in nature and, in light of this, incorporated hydrophilic or ionizable groups to enhance the compounds pharmacokinetic characteristics. It was clear the 3-position of the thiophene could tolerate sterically demanding groups while still maintaining excellent GR-mediated functional activity, although we focused most of our attention on relatively small side chains to limit the molecular weight. The 3-position of the thiophene ring also impacted the degree of agonist activity in the GRE activation assay and thus served two important roles, modulating the degree of agonist activity and optimization of the pharmacokinetic properties of the molecules. This allowed us to build up a series of GR modulators in a relatively short amount of time.

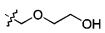
Piperidine amide **6** demonstrated high efficacy and potency in the GRE activation assay, which translated to high antiproliferation activity similar to that of dexamethasone (Table 1). Other compounds, such as oxime analogs **22**−**24**, demonstrated proliferation repression activity equal to dexamethasone while maintaining a partial agonist profile in the GRE activation assay. However, other 3-position analogs displayed low GRE agonist activity yet retained high antiproliferative activity. The degree of agonist activity in the GRE activation assay had no bearing on the antiproliferative activity of the analogs. For example, primary alcohol **8** demonstrated high antiproliferation activity despite exhibiting low agonist efficacy in our GRE activation assay. The in vitro profile displayed by these nonsteroidal GR ligands suggests that they induce a differential gene regulation profile to that of steroidal and nonsteroidal full GRE activation agonist ligands. This is likely mediated by a conformational change in the structure of GR when bound to these ligands that result in an alteration of the recruitment of cofactor proteins, both co-activators and co-repressors, through which GR interacts to regulate gene transcription.[12]

A number of compounds that had no measurable GRE agonist activity but retained strong IL-6 cytokine repression activity were tested in the GRE activation assay in the antagonist mode (Table 2). Interestingly, these compounds behaved as fully efficacious and potent antagonists in the GRE activation assay. This is in contrast to classical GR agonists, such as prednisolone or dexamethasone, which behave as full agonists in the GRE activation assay. Such a profile may be indicative of a separation in transactivation (GRE activation) and transrepression (IL-6 repression). As expected, GR antagonist mifepristone (RU-486)[27] is a strong antagonist in the GRE activation assay but has no measurable GR agonist activity in either the IL-6 repression assay or the antiproliferation assay. Partial agonists, such as oxime **24**, also displayed a significant amount of GR antagonist activity. The enantiomers of alcohol **15** were separated by chiral HPLC and were shown to have comparable activities.

The compounds showed good to excellent receptor selectivity with low to sub-nM binding affinity to GR (Table 3). Affinity

Table 1. hGR Agonist Analogs[a]



		GRE activation agonist mode		IL-6 Repression		RPMI8226 Repression	
Cmpd	R =	Eff (%dex)	EC_{50} (nM)[a]	Eff (abs)	IC_{50} (nM)	Eff (%dex)	IC_{50} (nM)
	Dexamethasone	100 ± 0.3	0.2 ± 0.1	100 ± 0.2	1.4 ± 0.1	100 ± 0.1	6.5 ± 0.1
6		93 ± 6.8	0.3 ± 0.1	94 ± 2.7	1.0 ± 0.4	95 ± 1.1	16 ± 1.1
8		26 ± 1.6	0.2 ± 0.1	94 ± 3.8	0.2 ± 0.1	99 ± 0.7	4.9 ± 0.3
9		58 ± 3.9	0.2 ± 0.1	95 ± 2.1	0.2 ± 0.1	98 ± 0.4	8.5 ±1.0
11		58 ± 9.1	1.6 ± 1.3	98 ± 0.4	1.0 ± 0.2	98 ± 1.1	22 ± 1.8
13		45 ± 4.7	0.5 ± 0.2	98 ± 0.2	0.9 ± 0.4	96 ± 1.1	18 ± 3.1
14		29 ± 2.2	0.2 ± 0.1	97 ± 0.9	0.8 ± 0.1	87 ± 1.2	14 ± 1.1
18		69 ± 9.4	0.6 ± 0.3	97 ± 2.4	0.3 ± 0.2	95 ± 1.5	16 ± 2.1
22		35 ± 5.9	5.0 ± 4.6	99 ± 0.8	1.1 ± 0.6	96 ± 1.0	9.9 ± 2.2
23		40 ± 3.5	0.1 ± 0.1	95 ± 3.3	0.2 ± 0.1	101 ± 0.8	9.5 ± 2.2
24		22 ± 0.9	0.4 ± 0.9	104 ± 4.9	0.5 ± 0.3	98 ± 0.5	16 ± 3.7
27		68 ± 3.7	1.4 ± 0.3	97 ± 1.5	1.8 ± 0.1	95 ±0.5	27 ± 2.1
29		20 ± 1.8	0.5 ± 0.1	91	6.1	94 ± 1.2	22 ± 6.4

[a] EC_{50} values determined from half-log concentration response curves. Efficacies are represented as the percentage maximal response in comparison to dexamethasone (100%). Standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations.

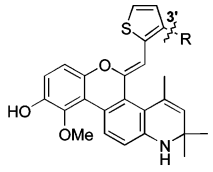
for mineralocorticoid receptor (MR) varied considerably within the series and was monitored. Primary alcohol **8** had vastly diminished MR cross-reactivity in comparison to steroids such as prednisolone or dexamethasone. Methyl ether **9** has an ~100-fold increase in MR binding affinity in comparison to the parent alcohol **8** but behaves as a weak partial agonist in the MR activation assay (agonist 167 nM (25%), antagonist 95 nM (55%)).

In general, lipophilic groups at the 3-position of the thiophene ring tended to show greater affinity to PR. For example, hydroxyl oxime **22** has an ~1315-fold separation in GR/PR binding affinity, whereas methoxy-oxime **23** has only an ~35-fold separation. The lipophilic all-carbon side chain **29** has only an ~13-fold separation in GR/PR binding. Methyl ether **9** had significantly diminished separation between GR and PR binding affinity in comparison to primary alcohol **8**.

An important question that we wanted to answer was whether a GRE activation partial agonist/full anatagonist profile would translate to glucocorticoids with an improved side effect profile. We screened a number of compounds within this series in an activation assay using GREs from the tyrosine aminotransferase (TAT) promoter.[28] The up-regulation of TAT has been related to certain endocrine side effects of GCs and, thus, can be viewed as a measure of potential metabolic side effects. As an example, full GRE activation antagonist **15** demonstrated significantly reduced agonist activity in the TAT GRE activation assay in comparison to dexamethasone (Figure 4). This further emphasizes that these nonsteroidal ligands exhibit differential gene regulation in comparison to the classical steroidal glucocorticoids.

Computational Chemistry. The interaction of our SGRMs with the GR was probed by docking oxime **23** with the crystal structure of GR with dexamethasone (Figure 5).[29] Compound **23** was initially oriented in the ligand binding domain using FlexX.[30] The resulting complex was refined using a simulated annealing procedure in SYBYL[31] with the Tripos force field and Gastiger−Hückel charges. The results are consistent with the principle interactions described for dexamethasone.[29] The phenolic hydroxyl group on the D ring forms hydrogen bonds with ARG 611 and GLN 570, taking the place of the A ring carbonyl from the steroid scaffold. The dihydroquinoline ring hydrogen bonds with ASN 564 and is in proximity to form

Table 2. hGR Antagonist Analogs[a]



		GRE activation antagonist mode		IL-6 Repression		RPMI8226 Repression	
Cmpd	3' substituent	Eff (%dex)	EC_{50} (nM)[a]	Eff (abs)	IC_{50} (nM)	Eff (%dex)	IC_{50} (nM)
	Dexamethasone	–	–	100 ± 0.2	1.4 ± 0.1	100 ± 0.1	6.5 ± 0.01
	Mifepristone	97 ± 0.4	0.6 ± 0.4	–	–	–	–
15		97 ± 0.5	0.3 ± 0.1	97 ± 2.5	0.4 ± 0.1	90 ± 1.4	12 ± 0.8
	(+)-**15**	97 ± 0.3	0.2 ± 0.1	95	0.2	92 ± 0.7	6.1 ± 1.0
	(–)-**15**	93 ± 0.9	1.4 ± 0.7	96	0.6	88 ± 1.1	18 ± 3.6
17		98 ± 0.5	0.4 ± 0.3	94 ± 2.7	1.0 ± 0.2	92 ± 0.4	10 ± 2.6
20		96 ± 2.3	1.3 ± 0.9	99 ± 1.5	1.6 ± 0.1	93 ± 1.5	41 ± 1.0
21		97 ± 0.4	0.6 ± 0.3	93 ± 0.6	0.9 ± 0.6	92 ± 1.5	10 ± 1.4
24		87 ± 2.2	1.9 ± 0.5	104 ± 4.9	0.5 ± 0.3	98 ± 0.5	16 ± 3.7

[a] EC_{50} values determined from half-log concentration response curves. Efficacies are represented as the percentage maximal response in comparison to dexamethasone (100%). Standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations. If no SEM is noted, value is from a single determination. A hyphen (−) denotes an efficacy <10% or potency >1000 nM.

Table 3. Competitive binding Data of C-5 thienyl Methylidene Analogs with PR, MR, and AR[a]

		Binding Ki (nM)			
Cmpd	3' substituent	GR	PR	MR	AR
	dexamethasone	2.1	–	7.2	–
8		0.7 ± 0.1	1400 ± 197	980 ± 74	290 ± 12
9		0.2 ± 0.2	190 ± 36	10 ± 3.0	150 ± 85
15		1.4 ± 0.2	1780 ± 350	670	1900
20		1.2	2290	410	1530
22		0.6 ± 0.1	790 ± 160	21 ± 5.4	290 ± 31
23		1.1 ± 0.4	38 ± 1.6	48 ± 3.1	110 ± 1.6
29		4.4	57	42	346

[a] Standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations. If no SEM is noted, value is from a single determination.

significant electrostatic interactions with GLN 642 and THR 739, the residues that interact with the C-17 hydroxyl function in dexamethasone. This binding orients the substituted thiophene ring toward helix 12. It is this interaction with helix 12 that

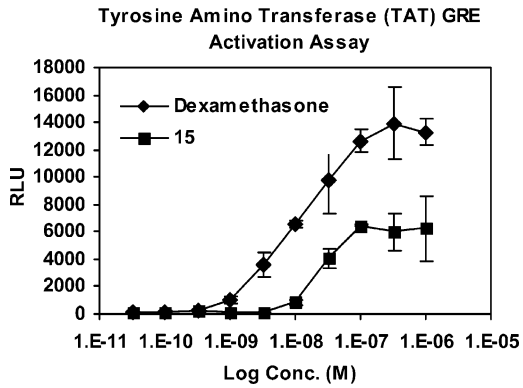


Figure 4. Glucocorticoid-mediated up-regulation of the TAT promoter. H4IIEC3 cells were transfected with TAT3/LUC[28] using fugene-6 transfection reagent. After 24 h, the cells were harvested, and the assay was carried out as described.[28]

correlates with the observed antagonist properties of compounds within this series.

In Vivo Evaluation. A number of compounds were profiled in a four-week tumor xenograft model (Figure 6), and the results are summarized (Table 4). Administration of dexamethasone reduced tumor burden, whereas the untreated (control) animal's tumor burden increased over a 30 day period. Compounds **8** and **23** were as efficacious as dexamethasone in reducing the tumor burden at the highest dose (100 mg/kg). At 30 mg/kg, compounds **8** and **23** were 80% and 82% efficacious in comparison to dexamethasone, respectively. Compound **15** was as efficacious as dexamethasone at the lower dose of 30 mg/kg and 89% efficacious at the low dose (10 mg/kg). A single dose PK experiment showed that compound **15** had relatively good exposure via oral administration (30 mg/kg CD-1 mice, C_{max} 0.65 μg/mL, AUC 4.92 $\pm$ 2.22 μg.hr/mL).

Conclusion

The SAR of the 3-position of the C-5 thienyl methylidene analogs revealed a number of SGRMs with in vitro antiproliferative efficacy comparable to dexamethasone. Their in vivo activity was also demonstrated in a tumor xenograft model in which a number of compounds showed dexamethasone-like efficacy. Studies relating to the in vivo side effect profile of these compounds will be reported in due course.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Inova 500 MHz or a Varian Mercury 300 MHz spectrometer using TMS (0.00 ppm 1H, 0.00 ppm ^{13}C) as an internal standard, unless otherwise noted. Chemical shifts are given in parts per million (ppm), and coupling constants (*J*) are given in hertz (Hz). Selected data are reported in the following order: chemical shift, coupling constant, and assignment. Infrared (IR) spectra were recorded on a Nicolet Impact 400 FT infrared spectrometer. Liquid samples were measured as neat films on NaCl plates; solid samples were measured as dichloromethane solutions. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Melting points were taken on an Electrothermal IA9100 digital apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. Flash column chromatography refers to the method of Still using Merck 230−400 mesh silica gel. Analytical thin-layer chromatography (TLC) was performed using Merck 60-F-254 0.25 mm precoated silica gel plates. Analytical HPLC was performed on an Agilent HP1100 system. Preparative HPLC was performed on a Waters Delta Prep 4000 or Waters Fraction Lynx System using mass trigger collection. Electron spray mass spectrometry (ESI) was carried out on a Micromass ZQ2000 or LCT instrument. Solvents were purchased from Aldrich as anhydrous and used without further purification. HPLC purity was determined on two systems: method A, Peeke Kromasil, 100 Å, 5 μm C_{18} (reverse phase), 90:10 CH_3CN/H_2O, 1 mL/min; method B, Beckman ultrasphere, 5 μm Si, normal phase, 80:20 hexanes/ethanol, 1 mL/min. Purity runs are reported as retention time in minutes, with the percentage purity in parentheses. Unless otherwise specified, solutions of common inorganic salts used in workups are aqueous solutions. Reactions were conducted under a nitrogen atmosphere unless otherwise noted. Reported yields are not optimized.

(*Z*)-5-(2′-(3′-Piperidinocarbonyl)thienylmethylidene)-1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 6. *n*-BuLi (2.5 M) in hexanes (35.1 mL, 87.8 mmol) was added dropwise to a solution of diisopropylamine (12.3 mL, 87.8 mmol) in THF (150 mL) at 0 °C under a nitrogen atmosphere, and the solution was stirred for 0.2 h. A solution of amide **4** (15.3 g, 73.2 mmol) in THF (60 mL) was cooled to 0 °C and added dropwise over 0.5 h to the LDA solution via cannula. After complete addition, the dark-red solution was stirred for an additional 0.2 h. This solution was added dropwise over 1.5 h to a precooled (0 °C) solution of lactone **3** (11.0 g, 24.4 mmol) in THF (100 mL) via cannula. On complete addition, the reaction was stirred at room temperature for 15 h. The reaction was quenched with a saturated ammonium chloride solution (30 mL), ethyl acetate (200 mL) was added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated ammonium chloride solution (3 × 300 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The oily foam was taken up in 1:1 hexanes/dichloromethane (400 mL), and the volume was reduced (to ~300 mL) slowly with cooling. The resulting precipitate was filtered under reduced pressure and washed with hexanes (100 mL) to yield lactol **5** as an off-white powder (13.5 g, 84%).

Note: This is a light-sensitive product, and the reaction should be performed in the dark. Lactol **5** (5.0 g, 7.6 mmol) was dissolved in 10% v/v concd HCl/MeOH (25 mL) and stirred at room temperature for 15 h. Water (125 mL) was added, the suspension was stirred for 0.1 h, and the slurry was filtered under reduced pressure. The precipitate was washed with water (50 mL) and ethyl acetate (100 mL). The off-white precipitate was taken up in 1:1 ethyl acetate/water (100 mL) and vigorously stirred for 1 h. The layers were separated, and the organic layer was washed with saturated sodium hydrogencarbonate solution (100 mL) and saturated ammonium chloride solution (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield **6** as a bright yellow powder (3.6 g, 87%); mp 174−175 °C; IR cm^{-1} (film) 3054, 1622, 1422, 1265, 895, 741; ^{1}H NMR (500 MHz, acetone) δ 8.32 (d, J = 8.6 Hz, 1H), 7.85 (s, 1H), 7.42 (dd, J = 5.2, 0.8 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 5.2 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.07 (d, J = 0.8 Hz, 1H), 5.91 (s, 1H), 5.51 (m, 1H), 3.76 (s, 3H), 3.63 (m, 2H), 3.27 (m, 2H), 2.05 (d, J = 1.3 Hz, 3H), 1.62 (m, 2H), 1.57 (m, 2H), 1.42 (m, 2H), 1.31 (s, 6H); ^{13}C NMR (125 MHz, acetone) δ 170.0, 165.4, 146.9, 146.3, 146.2, 145.7, 144.5, 135.0, 134.7, 131.9, 130.0, 125.7, 125.6, 125.5, 125.0, 118.7, 118.3, 115.3, 115.1, 114.4, 111.7, 107.2, 59.7, 59.3, 49.9, 24.4, 20.7, 20.0, 13.6; MS (ESI) m/z 529 $(M + H)^+$. Anal. ($C_{31}H_{32}N_2O_4S$) C, H, N.

All subsequent chemistry was conducted in subdued lighting due to the potential for isomerization to the *E*-isomer upon prolonged exposure of compound solutions to light. Nonphotolytic isomerization was not observed.

Alcohol 7. 2,6-Lutidine (5.0 mL, 43 mmol) was added to a solution of alcohol **6** (5.0 g, 9.5 mmol) in dichloromethane (200 mL). Triisopropylsilyl trifluoromethanesulfonate (5.9 mL, 22 mmol) was added dropwise at room temperature, and the reaction solution was stirred for 72 h. The reaction was quenched with a saturated solution of ammonium chloride (100 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with a 1 M hydrochloric acid solution (300 mL) and a saturated solution of ammonium chloride (300 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography,

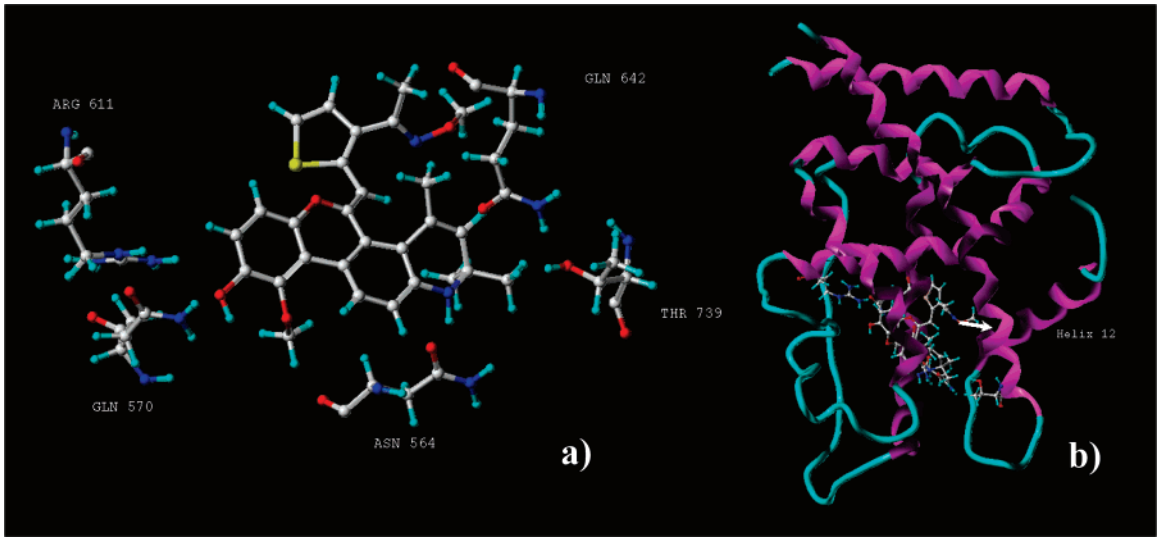


Figure 5. (a) Hydrogen-bonding close contacts for compound **23** in the refined glucocorticoid receptor structure. (b) The GR tertiary structure showing the interaction of the substituted thiophene ring with helix 12.

eluting with ethyl acetate/hexanes gave the silyl ether (5.2 g, 80%) as a yellow oil.

Lithium triethylborohydride (1 M) in THF (43.9 mL, 43.9 mmol) was added dropwise to a solution of the amide (6.0 g, 8.76 mmol) in THF at 0 °C. The reaction solution was allowed to warm to room temperature and stirred for an additional 4 h. The reaction was quenched with the dropwise addition of a saturated solution of sodium hydrogencarbonate (200 mL) and diluted with ethyl acetate (200 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), the combined organics were washed with a saturated solution of ammonium chloride (500 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexanes, gave alcohol **7** (4.2 g, 80%) as a bright yellow powder; ^{1}H NMR (500 MHz, Acetone) δ 10.08 (s, 1H), 8.48 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 5.4 Hz, 1H), 7.43 (dd, J = 5.4, 0.6 Hz, 1H), 7.19 (d, J = 0.6 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.03 (s, 1H), 5.58 (m, 1H), 3.84 (s, 3H), 2.07 (d, J = 1.3 Hz, 3H), 1.36 (s, 6H), 1.35 (sept, J = 7.4 Hz, 3H), 1.16 (d, J = 7.4 Hz, 18H).

(*Z*)-5-(2′-(3′-Hydroxymethylthienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 8. Amide **6** (500 mg, 0.95 mmol) was treated with lithium triethylborohydride (9.5 mL, 9.5 mmol) as per previous discussion to yield alcohol **8** (322 mg, 76%) as a yellow powder; ^{1}H NMR (500 MHz, acetone) δ 8.30 (d, J = 8.7 Hz, 1H), 7.78 (s, 1H), 7.32 (dd, J = 5.3, 0.5 Hz, 1H), 7.06 (d, J = 5.3 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 6.20 (d, J = 0.5 Hz, 1H), 5.88 (s, 1H), 5.53 (q, J = 1.2 Hz, 1H), 4.62 (s, 2H), 3.76 (s, 3H), 2.06 (d, J = 1.2 Hz, 3H), 1.33 (s, 6H). MS (ESI) m/z 448 $(M + H)^+$. Anal. ($C_{26}H_{25}NO_4S \cdot 0.2H_2O$) C, H, N.

(*Z*)-5-(2′-(3′-Methoxymethylthienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 9. Sodium hydride (60%) dispersion in mineral oil (165 mg, 4.1 mmol) was added in one portion to a solution of alcohol **7** (500 mg, 0.83 mmol) in THF (40 mL) at 0 °C. The reaction suspension was allowed to warm to room temperature, stirred for 0.5 h, and recooled to 0 °C before the addition of methyl iodide (0.52 mL, 8.3 mmol). The reaction was allowed to warm to room temperature and stirred for 4 h, a saturated solution of ammonium chloride (40 mL) was added, ethyl acetate (40 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with a saturated solution of ammonium chloride (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure.

Tetrabutylammonium fluoride (1 M) in THF (0.14 mL, 0.14 mmol) was added dropwise to a solution of the silyl ether (30 mg, 0.049 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction solution was stirred for 0.2 h at this temperature, a saturated solution of ammonium chloride (10 mL) was added, ethyl acetate (10 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with a saturated solution of ammonium chloride (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexanes gave ether **9** (14 mg, 62%) as a yellow powder. ^{1}H NMR (500 MHz, acetone) δ 8.32 (d, J = 8.6 Hz, 1H), 7.78 (s, 1H), 7.33 (dd, J = 5.3, 0.5 Hz, 1H), 7.00 (d, J = 5.3 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.22 (d, J = 0.5 Hz, 1H), 5.88 (s, 1H), 5.55 (q, J = 1.3 Hz, 1H), 4.42 (s, 2H), 3.77 (s, 3H), 3.30 (s, 3H), 2.07 (d, J = 1.3 Hz, 3H), 1.34 (s, 6H). MS (ESI) m/z 462 $(M + H)^+$. Anal. ($C_{27}H_{24}NO_4S \cdot 0.3H_2O$) C, H, N.

(*Z*)-5-(2′-(3′-(2″-Hydroxyethoxymethyl)thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno-[3,4-*f*]quinoline 11. *t*-BuOK in THF (1 M, 5.0 mL, 5.0 mmol) was added dropwise to a solution of alcohol **7** (610 mg, 1.01 mmol) in THF (10 mL) at 0 °C over 0.2 h. The reaction was stirred at 0 °C for 0.1 h before the dropwise addition of ethyl bromoacetate (0.95 mL, 10.0 mmol). After the addition was complete, the reaction was allowed to warm to room temperature and stirred for 4 h. A saturated ammonium chloride solution (20 mL) and ethyl acetate (20 mL) were added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexanes, yielded the ester as a yellow oil (320 mg, 46%).

Sodium borohydride (267 mg, 6.9 mmol) was added to a solution of the ester (320 mg, 0.47 mmol) in ethanol (15 mL), and the reaction stirred at room temperature for 2 h. The reaction was quenched with saturated ammonium chloride (40 mL), 1 M HCl (20 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with a saturated solution of ammonium chloride (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude reaction was treated with 1 M TBAF in THF (1.30 mL, 1.30 mmol) as per previous discussion. Purification by flash chromatography, eluting with ethyl acetate/hexanes, gave alcohol **11** as a yellow powder (124 mg, 54%).^{1}H NMR (500 MHz, acetone) δ 8.31 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H), 7.34 (dd, J = 5.2, 0.6 Hz, 1H), 7.03 (d, J = 5.2 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.20 (d, J = 0.6 Hz, 1H), 5.90 (s, 1H), 5.55 (q, J = 1.3 Hz, 1H), 4.52 (s, 2H), 3.77 (s, 3H), 3.66 (m,

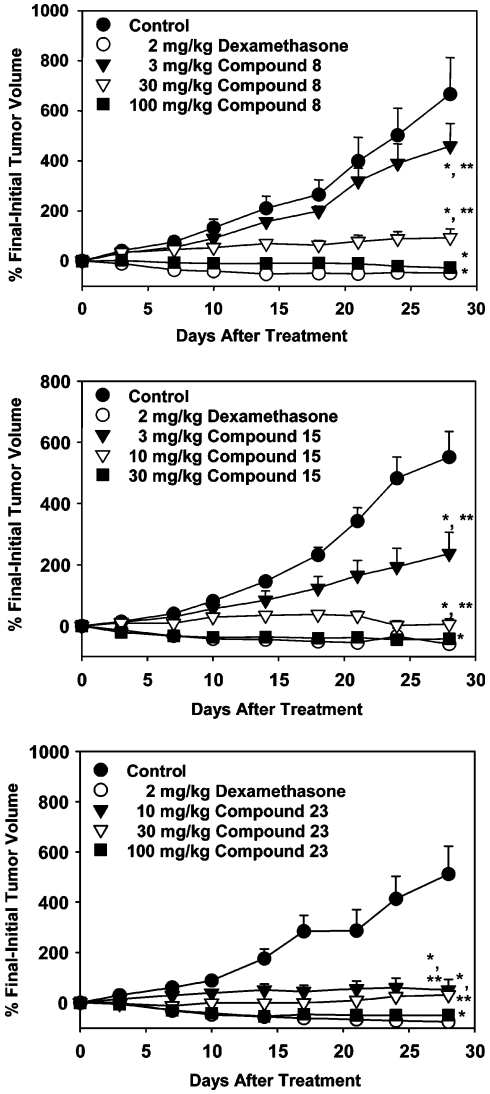


Figure 6. Tumor volume plotted against days after treatment of nude mice at multiple dosages. Nude mice bearing palpable RPMI8226 tumors were treated with vehicle, dexamethasone, and study compound at various doses via oral administration for 4 weeks. Drug effect on tumor growth was determined twice a week (mean ± SEM, $n = 6$ animals per group bearing two tumors per animal). *Significantly different from vehicle control at $p < 0.05$; **significantly different from dexamethasone at $p < 0.05$.

Table 4

	tumor volume (eff % vs 2 mg/kg dex)			
cmpd	3 mg/kg	10 mg/kg	30 mg/kg	100 mg/kg
8	29	−	80	97
15	52	89	97	−
23	−	78	82	95

2H), 3.58 (m, 1H), 3.54 (t, $J = 5.2$ Hz, 2H), 2.07 (d, $J = 1.3$ Hz, 3H), 1.34 (s, 6H). MS (ESI) m/z 492 $(M + H)^+$. Purity (A) 2.00 min (98.2%); (B) 11.1 min (99.4%).

Aldehyde 12. 1-Hydroxy 1,2-benziodoxal-3(*1H*)-one-1-oxide (7.75 g, 27.7 mmol) was added in one portion to a solution of alcohol **7** (5.5 g, 9.12 mmol) in 1:1 THF/DMSO (300 mL) at 0 °C. The suspension was allowed to warm to room temperature and stirred for 1 h. The reaction was poured into ice−water (900 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with a saturated solution of ammonium chloride (600 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexanes, gave aldehyde **12** (4.2 g, 77%) as a bright red powder; ^{1}H NMR (300 MHz, CD_3OD) δ 8.36 (d, $J = 8.8$ Hz, 1H), 7.26 (d, $J = 5.2$ Hz, 1H), 7.04 (d, $J = 5.2$ Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 1H), 6.75 (d, $J = 8.8$ Hz, 1H), 6.73 (d, $J = 8.8$ Hz, 1H), 6.13 (s, 1H), 5.51 (m, 1H), 4.58 (s, 2H), 3.75 (s, 3H), 2.05 (m, 3H), 1.30 (s, 6H), 1.29 (m, 3H), 1.12 (d, $J = 7.2$ Hz, 18H).

(*Z*)-5-(2′-(3′-((2″,2″,2″-Trifluoroethylamino)methyl)thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 13. Trifluoroethylamine (0.53 μL, 0.66 mmol) was added to a solution of aldehyde **12** (40 mg, 0.067 mmol) in methanol (2 mL) at room temperature. The solution was allowed to warm to room temperature and stirred for 1 h. Methanol (2 mL), acetic acid (50 μL, 0.66 mmol), and sodium cyanoborohydride (62 mg, 0.99 mmol) were added sequentially, and the solution was stirred at room temperature for 0.2 h. A saturated solution of ammonium chloride (20 mL) was added, ethyl acetate (20 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organics were washed with a saturated solution of ammonium chloride (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexanes, yielded amine **13** as a yellow powder (13 mg, 37%). ^{1}H NMR (500 MHz, acetone) δ 8.31 (d, $J = 8.8$ Hz, 1H), 7.78 (s, 1H), 7.35 (dd, $J = 5.3$, 0.6 Hz, 1H), 7.07 (d, $J = 5.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 1H), 6.81 (d, $J = 8.8$ Hz, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 6.19 (d, $J = 0.6$ Hz, 1H), 5.89 (s, 1H), 5.54 (q, $J = 1.2$ Hz, 1H), 3.90 (m, 2H), 3.77 (s, 3H), 3.26 (m, 2H), 2.25 (m, 1H), 2.07 (d, $J = 1.2$ Hz, 3H), 1.34 (s, 6H). MS (ESI) m/z 529 $(M + H)^+$. Anal. ($C_{28}H_{27}F_3N_2O_3S \cdot 0.5H_2O$) C, H, N.

(*Z*)-5-(2′-(3′-Cyanothienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 14. Aldehyde **12** (50 mg, 0.083 mmol) was reacted with hydroxylamine hydrochloride (14 mg, 0.21 mmol) as per general method 1 to yield the oxime as a yellow powder (38 mg, 74%).

1,1′-Carbonyldiimidazole (65 mg, 0.40 mmol) was added to a solution of the oxime (25 mg, 0.04 mmol) in THF (2 mL) at room temperature. The solution was heated to reflux and stirred for 2 h. The reaction was allowed to cool to room temperature, the reaction was partitioned between ethyl acetate (20 mL) and water (20 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with a saturated sodium chloride solution (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude reaction was treated with 1 M tetrabutylammonium fluoride in THF (0.12 mL, 0.12 mmol) as per previous discussion. Purification by flash chromatography, eluting with ethyl acetate/hexanes, yielded nitrile **14** as a yellow powder (9.3 mg, 52%); ^{1}H NMR (500 MHz, acetone) δ 8.41 (d, $J = 8.7$ Hz, 1H), 7.94 (s, 1H), 7.55 (dd, $J = 5.3$, 0.7 Hz, 1H), 7.30 (d, $J = 5.3$ Hz, 1H), 7.05 (d, $J = 8.7$ Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 1H), 6.87 (d, $J = 8.7$ Hz, 1H), 6.35 (d, $J = 0.7$ Hz, 1H), 6.06 (s, 1H), 5.58 (q, $J = 1.3$ Hz, 1H), 3.80 (s, 3H), 2.08 (d, $J = 1.3$ Hz, 3H), 1.34 (s, 6H). MS (ESI) m/z 443 $(M + H)^+$. Purity (A) 2.29 min (97.4%); (B) 5.12 min (98.3%).

(±)-(*Z*)-5-(2′-(3′-(1″-Hydroxy-2″,2″,2″-trifluoroethyl)thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 15. Trifluoromethyltrimethylsilane (1.97 mL, 13.3 mmol) was added to a solution of aldehyde **12** (650 mg, 1.33 mmol) in THF (120 mL). The solution was cooled to 0 °C before the dropwise addition of 1 M tetrabutylammonium fluoride in THF (6.7 mL, 6.7 mmol) over 0.2 h. The reaction solution was stirred for an additional 0.2 h, a saturated solution of ammonium chloride (100 mL) was added, ethyl acetate (100 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with a saturated solution of ammonium chloride (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexanes gave alcohol **15** (405 mg, 55%) as a yellow oil. ^{1}H NMR (500 MHz, acetone) δ 8.32 (d, $J = 8.8$ Hz, 1H), 7.82 (s, 1H), 7.43 (d, $J = 5.5$ Hz, 1H), 7.21 (d, $J = 5.5$ Hz, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.22 (s, 1H), 5.93 (s,

1H), 5.79 (d, $J = 5.7$ Hz, 1H), 5.52 (q, $J = 1.6$ Hz, 1H), 5.30 (dq, $J = 5.7$, 7.2 Hz, 1H), 3.77 (s, 3H), 2.05 (m, 3H), 1.32 (s, 6H). MS (ESI) *m*/*z* 516 $(M + H)^+$. Anal. Calcd for $(C_{27}H_{24}F_3NO_4S \cdot H_2O)$: C, 60.78; H, 4.91; N, 2.63. Found: C, 60.84; H, 4.45; N, 2.44.

The enantiomers of racemate **15** were separated by chiral HPLC using a chiracel OD column (1 cm × 25 cm, 3.5 mL/min), eluting with 92/8 hexanes/ethanol; first enantiomer $t = 43.5$ min, $[\alpha]^{0.1}_D$ +23.0; second enantiomer $t = 56.0$ min, $[\alpha]^{0.1}_D$ −21.0.

(*Z*)-5-(2′-(3′-(Cyclohexylcarbonyl)thienylmethylidene))-1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 17. Cyclohexylmagnesium chloride solution (2.0 M) in THF (37 μl, 0.073 mmol) was added to a solution of aldehyde **12** (40.0 mg, 0.064 mmol) in THF (5 mL) at −78 °C. The reaction was allowed to warm to room temperature over 2.5 h then poured into a saturated ammonium chloride solution (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organics were washed with a saturated sodium chloride solution (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

The alcohol (22 mg, 0.033 mmol) was treated with 1-hydroxy 1,2-benziodoxal-3(1*H*)-one-1-oxide (27 mg, 0.098 mmol) as per previous discussion to yield the ketone as a red powder (18 mg, 82%).

Acetic acid in THF (1.0 M; 1.0 mL, 0.10 mmol) was added to a solution of the ketone (18 mg, 0.026 mmol) at −78 °C. TBAF in THF (1.0 M; 0.10 mL, 0.10 mmol) was added dropwise at −78 °C and the reaction was stirred for 1.5 h. The reaction was poured into saturated sodium hydrogencarbonate solution (10 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with a saturated sodium chloride solution (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexanes, yielded ketone **17** as a red solid (10.5 mg, 62%). ^{1}H NMR (300 MHz, CD_3-OD) δ 8.35 (d, $J = 8.7$ Hz, 1H), 7.45 (d, $J = 5.4$ Hz, 1H), 7.31 (d, $J = 5.4$ Hz, 1H), 7.17 (s, 1H), 6.99 (d, $J = 8.6$ Hz, 1H), 6.78 (d, $J = 8.6$ Hz, 1H), 6.76 (d, $J = 8.7$ Hz, 1H), 5.54 (m, 1H), 3.76 (s, 3H), 3.09 (m, 1H), 2.01 (m, 3H), 1.89−1.65 (m, 4H), 1.47−1.37 (m, 4H), 1.33 (s, 6H), 1.31−1.22 (m, 2H). MS (ESI) *m*/*z* 528 $(M + H)^+$. Anal. $(C_{32}H_{33}NO_4S \cdot 0.2H_2O)$ C, H, N.

(*Z*)-5-(2′-(3′-Acetylthienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 18. Methyllithium in diethyl ether (1.6 M; 95 mL, 152 mmol) was added dropwise to a solution of amide **6** (8.0 g, 15.2 mmol) in 1:1 tetrahydrofuran/diethyl ether (150 mL) at 0 °C over 0.3 h. The reaction slurry was allowed to warm to ambient temperature over 5 h and quenched with an aqueous solution of saturated ammonium chloride (150 mL). The aqueous layer was extracted with ethyl acetate (3 × 75 mL), and the combined organics were washed with a saturated sodium chloride solution (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with dichloromethane, yielded ketone **18** as an orange powder (5.01 g, 72%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (d, $J = 8.8$ Hz, 1H), 7.50 (d, $J = 5.6$ Hz, 1H), 7.42 (d, $J = 0.6$ Hz, 1H), 7.29 (dd, $J = 5.6$, 0.6 Hz, 1H), 6.99 (d, $J = 8.8$ Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 1H), 6.76 (d, $J = 8.8$ Hz, 1H), 5.53 (q, $J = 1.2$ Hz, 1H), 3.76 (s, 3H), 2.52 (s, 3H), 2.01 (d, $J = 1.2$ Hz, 3H), 1.33 (s, 6H); MS (ESI) *m*/*z* 460 $(M + H)^+$. Anal. $(C_{27}H_{25}NO_4S \cdot 0.3H_2O)$ C, H, N.

(±)-(*Z*)-5-(2′-(3′-(1″-Hydroxyethyl)thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline 20. Sodium borohydride (6 mg, 0.158 mmol) was added to a solution of ketone **18** (35 mg, 0.076 mmol) in methanol (3 mL) at 0 °C. The reaction was stirred for 0.5 h then poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with a saturated sodium chloride solution (1 × 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with 2:1 hexanes/ethyl acetate, yielded alcohol **20** as a powder (33 mg, 93%). ^{1}H NMR (500 MHz, CD_3-OD) δ 8.30 (d, $J = 8.8$ Hz, 1H), 7.27 (d, $J = 5.3$ Hz, 1H), 7.10 (d, $J = 5.3$ Hz, 1H), 6.93 (d, $J = 8.8$ Hz, 1H), 6.74 (d, $J = 8.8$ Hz, 1H), 6.73 (d, $J = 8.8$ Hz, 1H), 6.10 (s, 1H), 5.52 (q, $J = 1.2$ Hz, 1H), 4.97 (q, $J = 6.4$ Hz, 1H), 3.75 (s, 3H), 2.05 (d, $J = 1.2$ Hz, 3H), 1.42 (d, $J = 6.4$ Hz, 3H), 1.30 (s, 6H). MS (ESI) *m*/*z* 462 $(M + H)^+$. Purity (A) 2.11 min (98.5%); (B) 8.42 min (96.6%).

(±)-(*Z*)-5-(2′-(3′-(1″-Hydroxypentyl)thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno-[3,4-*f*]quinoline 21. *n*-Butyllithium in cyclohexane (2.0 M; 0.7 mL, 1.40 mmol) was added to a solution of amide **6** (50.0 mg; 0.095 mmol) in THF (4 mL) at 0 °C over 5 min. The reaction was allowed to warm to room temperature and stirred for 5 h. A saturated solution of ammonium chloride (10 mL) was slowly added and the reaction mixture was stirred for an additional 5 min. The layers were separated and the aqueous layer extracted with ethyl acetate (2 × 10 mL). The combined organics were washed with a saturated sodium chloride solution (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

Sodium borohydride (3.1 mg, 0.0819 mmol) was added to a solution of the residue in methanol (4 mL) at 0 °C. After 1 h, the reaction was quenched by the addition of water (10 mL) and ethyl acetate (10 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organics were washed with a saturated sodium chloride solution (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography, eluting with dichloromethane, yielded alcohol **21** as a yellow powder (27 mg, 57%); ^{1}H NMR (300 MHz, CD_3OD) δ 8.31 (d, $J = 8.8$ Hz, 1H), 7.27 (d, $J = 5.4$ Hz, 1H), 7.07 (d, $J = 5.4$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 6.74 (d, $J = 8.8$ Hz, 1H), 6.73 (d, $J = 8.8$ Hz, 1H), 6.06 (s, 1H), 5.50 (q, $J = 1.1$ Hz, 1H), 4.77 (t, $J = 6.7$ Hz, 1H), 3.76 (s, 3H), 2.05 (d, $J = 1.1$ Hz, 3H), 1.80 (m, 1H), 1.65 (m, 1H), 1.37−1.26 (m, 10H), 0.88 (t, $J = 7.3$ Hz, 3H). MS (ESI) *m*/*z* 504 $(M + H)^+$. Purity (A) 3.06 min (97.1%;) (B) 5.69 min (96.7%).

General Method 1. Hydroxyl- or alkoxyamine hydrochloride (2.5 equiv) was added to a solution of the carbonyl compound (1 equiv) in absolute ethyl alcohol (10 mL/mmol) and warmed to 40 °C until complete consumption of the starting material. The reaction was concentrated under reduced pressure, and the resulting solid was taken up in ethyl acetate/water (1:1, 30 mL/mmol). The aqueous phase was extracted with ethyl acetate (3 × 10 mL/mmol), and the combined organics were washed with a saturated sodium chloride solution, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with dichloromethane, yielded the desired oxime.

(*Z*)-5-(2′-(3′-((*E*)-1″-Hydroxyiminoethyl)thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno-[3,4-*f*]quinoline 22. Reacting ketone **18** (100 mg, 0.22 mmol) with hydroxyamine hydrochloride as per general method 1 yielded oxime **22** as a yellow powder (66 mg, 64%). ^{1}H NMR (500 MHz, CD_3-OD) δ 8.30 (d, $J = 8.8$ Hz, 1H), 7.35 (dd, $J = 5.3$, 0.8 Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 1H), 6.89 (d, $J = 5.3$ Hz, 1H), 6.73 (d, $J = 8.8$ Hz, 2H), 5.86 (d, $J = 0.8$ Hz, 1H), 5.49 (q, $J = 1.2$ Hz, 1H), 3.75 (s, 3H), 2.06 (s, 3H), 2.02 (d, $J = 1.2$ Hz, 3H), 1.28 (s, 6H). MS (ESI) *m*/*z* 475 $(M + H)^+$Anal. $(C_{27}H_{26}N_2O_4S \cdot 0.2H_2O)$ C, H, N.

(*Z*)-5-(2′-(3′-((*E*)-1″-Methoxyiminoethyl)thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno-[3,4-*f*]quinoline 23. Reacting ketone **18** (100 mg, 0.22 mmol) with methoxyamine hydrochloride as per general method 1 yielded oxime **23** as a yellow powder (69 mg, 65%). ^{1}H NMR (500 MHz, CD_3-OD) δ 8.30 (d, $J = 8.8$ Hz, 1H), 7.32 (dd, $J = 5.4$, 0.8 Hz, 1H), 7.08 (d, $J = 5.4$ Hz, 1H), 6.97 (d, $J = 8.8$ Hz, 1H), 6.74 (d, $J = 8.8$ Hz, 1H), 6.73 (d, $J = 8.8$ Hz, 1H), 6.55 (d, $J = 0.8$ Hz, 1H), 5.49 (q, $J = 1.2$ Hz, 1H), 3.92 (s, 3H), 3.75 (s, 3H), 2.15 (s, 3H), 2.06 (d, $J = 1.2$ Hz, 3H), 1.29 (s, 6H); MS (ESI) *m*/*z* 489 $(M + H)^+$. Purity (A) 3.52 min (99.2%); (B) 4.31 min (98.3%).

(*Z*)-5-(2′-(3′-((*E*)-1″-Ethoxyiminoethyl)thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno-[3,4-*f*]quinoline 24. Reacting ketone **18** (100 mg, 0.22 mmol) with ethoxyamine hydrochloride as per general method 1 yielded oxime **24** as a yellow powder (77 mg, 71%). ^{1}H NMR (500 MHz, CD_3-

OD) δ 8.30 (d, J = 8.7 Hz, 1H), 7.32 (dd, J = 5.4, 0.8 Hz, 1H), 7.09 (d, J = 5.4 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 0.8 Hz, 1H), 5.47 (q, J = 1.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 2.16 (s, 3H), 2.05 (d, J = 1.3 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.29 (s, 6H); MS (ESI) m/z 503 $(M + H)^+$. Purity (A) 4.33 min (99.4%); (B) 3.95 min (99.8%).

(*Z*)-5-(2′-(3′-(Methoxycarbonyl)thienylmethylidene))-1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-quinoline 27. Methoxymethyl chloride (4 mL), tetrabutylammonium hydroxide (8 mL), and 6 M sodium hydroxide solution (8 mL) were added sequentially to a solution of phenol **6** (500 mg, 0.95 mmol) in dichloromethane (80 mL), and the reaction was stirred at room temperature for 1 h. The reaction was diluted with water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with 1 M hydrochloric acid (150 mL), a saturated ammonium chloride solution (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure.

The crude amide was reacted with lithium triethylborohydride (8.7 mL, 8.7 mmol) as per previous discussion. Purification by flash chromatography, eluting with ethyl acetate/hexanes, yielded the alcohol as a yellow powder (390 mg, 83%). The resultant alcohol (390 mg, 0.79 mmol) was treated with 1-hydroxy 1,2-benziodoxal-3(1*H*)-one-1-oxide (7.75 g, 27.7 mmol) as per previous discussion. $BF_3{\cdot}OEt_2$ (0.025 mL, 0.20 mmol) was added dropwise to a solution of the crude product and trimethylsilylcyanide (0.13 mL, 0.96 mmol) in dichloromethane (50 mL) at −45 °C. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with saturated sodium hydrogencarbonate (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with saturate ammonium chloride (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography, eluting with hexanes/ethyl acetate, yielded cyanohydrin **26** (340 mg, 83%) as a yellow oil.

Cyanohydrin **26** (340 mg, 0.66 mmol) was treated with 1-hydroxy 1,2-benziodoxal-3(1*H*)-one-1-oxide (556 mg, 1.98 mmol) as per previous discussion. The crude reaction was dissolved in methanol (5 mL), DMAP (1 crystal) was added, and the reaction was stirred for 15 h. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with a saturated ammonium chloride solution (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure.

The crude mixture was treated dissolved in 10% v/v hydrochloric acid/methanol (10 mL) and stirred at room temperature for 15 h. Water (20 mL) was added and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography, eluting with hexanes/ethyl acetate, yielded ester **27** as a yellow powder (100 mg, 31%). ^{1}H NMR (500 MHz, acetone) δ 8.37 (d, J = 8.6 Hz, 1H), 7.87 (s, 1H), 7.45 (d, J = 5.4 Hz, 1H), 7.38 (dd, J = 5.4, 0.7 Hz, 1H), 7.30 (d, J = 0.7 Hz, 1H), 7.05 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 5.99 (s, 1H), 5.58 (q, J = 1.3 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.07 (d, J = 1.3 Hz, 3H), 1.37 (s, 6H). MS (ESI) m/z 476 $(M + H)^+$. Anal. ($C_{27}H_{25}NO_5S{\cdot}0.4H_2O$) C, H, N.

(*Z*)-5-(2′-(3′-(*E*-Methylbutenyl)thienylmethylidene))-1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-quinoline 29. NaHMDS solution in THF (1 M; 1.29 mL, 1.29 mmol) was added to a stirred solution of *n*-propyltriphenylphosphonium bromide (495 mg, 1.29 mmol) in THF (10 mL) at −78 °C. The reaction mixture was warmed to −40 °C and stirred for 30 min and recooled to −78 °C before the dropwise addition of a solution of ketone **28** (108 mg, 0.21 mmol) in THF (10 mL). The reaction was allowed to warm up to room temperature and stirred for 15 h. Water (20 mL) was added, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure.

The resulting crude material was treated with 10% v/v HCl in methanol (2 mL) as per previous discussion. Purification by flash chromatography, eluting with ethyl acetate/hexanes, yielded alkene **29** as an off-white powder (57 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 1H), 7.24 (dd, J = 5.2, 0.8 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 5.2 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 0.8 Hz, 1H), 5.60 (s, 1H), 5.48 (tq, J = 7.4, 1.4 Hz, 1H), 5.47 (q, J = 1.3 Hz, 1H), 4.18 (s, 1H) 3.77 (s, 3H), 2.04 (d, J = 1.3 Hz, 3H), 1.90 (q, J = 1.4 Hz, 3H), 1.77 (m, 2H), 1.31 (s, 6H), 0.81 (t, J = 7.4 Hz, 3H). MS (ESI) m/z 486 $(M + H)^+$. Anal. ($C_{30}H_{31}NO_3S{\cdot}0.1H_2O$) C, H, N.

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Supporting Information Available: Additional details of both in vitro and in vivo biological testing and a table of combustion analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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