Synthesis and Structure−Activity Relationships of a Novel Series of 2,3,5,6,7,9-Hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide K_{ATP} Channel Openers: Discovery of (−)-(9*S*)-9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (A-278637), a Potent K_{ATP} Opener That Selectively Inhibits Spontaneous Bladder Contractions

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Structure−activity relationships were investigated on a novel series of sulfonyldihydropyridine-containing K_{ATP} openers. Ring sizes, absolute stereochemistry, and aromatic substitution were evaluated for K_{ATP} activity in guinea pig bladder cells using a fluorescence-based membrane potential assay and in a pig bladder strip assay. The inhibition of spontaneous bladder contractions in vitro was also examined for a select group of compounds. All compounds studied showed greater potency to inhibit spontaneous bladder contractions relative to their potencies to inhibit contractions elicited by electrical stimulation. In an anesthetized pig model of myogenic bladder overactivity, compound **14** and (−)-cromakalim **1** were found to inhibit spontaneous bladder contractions in vivo at plasma concentrations lower than those that affected hemodynamic parameters. Compound **14** showed approximately 5-fold greater selectivity than **1** in vivo and supports the concept that bladder-selective K_{ATP} channel openers may have utility in the treatment of overactive bladder.

Introduction

Overactive bladder (OAB) is defined by the occurrence of spontaneous detrusor contractions during bladder filling.[1] Clinically, OAB is manifested by the symptoms of urgency, frequency, and incontinent episodes. The origin of spontaneous contractions has been linked to the hyperexcitability of diseased bladder smooth muscle cells.[1−4] Whereas normal human micturition is primarily mediated by the parasympathetic nervous system, there is evidence that diseased bladder contractile activity has both cholinergic and noncholinergic components.[5−7] Thus, evidence showing efficacy of anticholinergic drugs against urodynamically proven involuntary contractions is limited.[2,7,8] Ideally, pharmacotherapy for OAB would suppress disease-related bladder contractions while leaving normal voiding function intact, since excessive inhibition of the latter could lead to undesirable urinary retention.

Due to the ability of K_{ATP} channel openers[9] to dampen smooth muscle excitability by lowering cellular membrane potential and inhibiting calcium influx, there has been considerable interest in exploring K_{ATP} openers as therapeutic agents in the treatment of OAB.[3,10] Cromakalim (**1**) (Figure 1) entered a small pilot trial for OAB where promising results were seen; however, its further development was terminated due to unspecified animal toxicity in long-term studies.[11] Although definitive clinical data is lacking, it is a widely held notion that **1** possesses insufficient bladder selectivity relative to its K_{ATP}-mediated cardiovascular (CV) effects to be useful for OAB. Since K_{ATP} channel openers relax both bladder and vascular smooth muscle, the primary objective of recent efforts in this area has been the identification of K_{ATP} openers with improved bladder/CV selectivity.

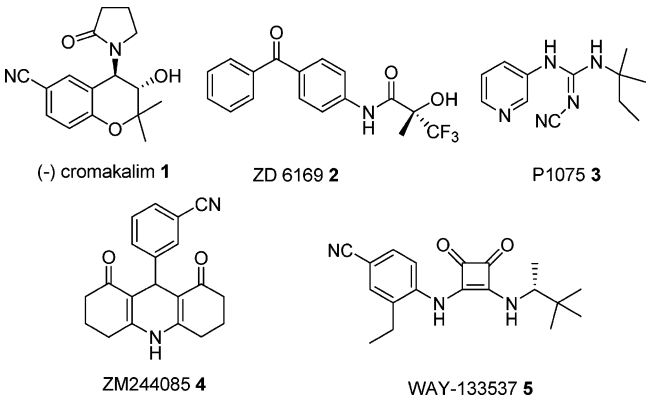

Figure 1. K_{ATP} Opener Standards.

The more recent K_{ATP} openers ZD6169 (**2**), ZM244085 (**4**), and WAY-133537 (**5**) have been reported to possess varying degrees of bladder selectivity on oral dosing in rat and dog models[12−16] Interestingly, none of these

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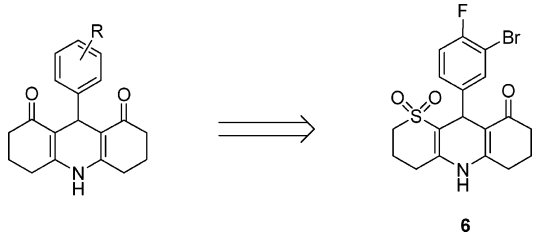


Figure 2.

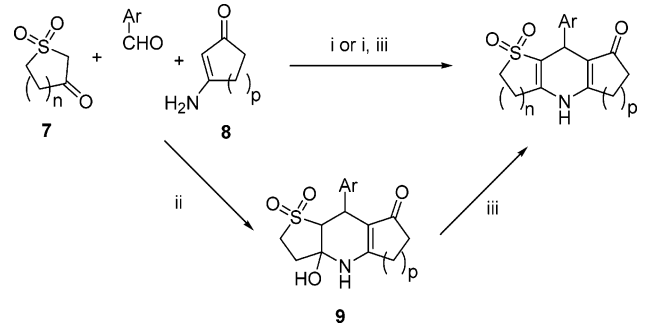
agents has demonstrated any intrinsic selectivity for bladder over cardiovascular tissues in vitro. Although ancillary pharmacology[17] and pharmacokinetic considerations[15] on oral dosing have emerged as potential explanations, the true basis for the reported in vivo selectivities of these agents remains to be completely elucidated.

The reported bladder-selective actions of **4** make it an attractive lead from which to design novel K_{ATP} openers. Compared to the benzopyran class of K_{ATP} opener like **1**,[18,19] far less is known about what structural features influence the K_{ATP} activity of acridinediones such as **4**. It has been reported that optimal potency in this series is achieved with meta and para disubstitution of electron-withdrawing groups or halogens on the aromatic ring.[20] Monosubstitution in the meta or para positions does retain K_{ATP} opening activity, however with reduced potency. Surprisingly, little additional SAR information has appeared on this ring system, despite the exhaustive studies that have been carried out on structurally related dihydropyridine calcium channel antagonists. We were interested therefore in investigating the K_{ATP} opening activity of novel ring systems containing the dihydropyridine nucleus imbedded within. It had previously been shown in SAR studies around **2** that replacement of the benzophenone carbonyl by a sulfonyl group resulted in an improvement in K_{ATP} potency in vitro.[13] As a starting point for our own SAR studies, this switch was applied to the acridinedione system of **4** (Figure 2). Indeed, the 3,4,6,7,8,10-hexahydro-2*H*-thiopyrano[3,2-*b*]quinolin-9(5*H*)-one 1,1-dioxide ring system (compound **6**) was found to possess potent in vitro K_{ATP} opening activity in guinea pig bladder smooth muscle cells (pEC_{50} = 6.42), when substituted by a 3-bromo-4-fluorophenyl in the 10 position. In this paper, we describe extensive SAR investigations around the core ring system examining ring size effects, ring-opening effects, stereochemistry, and aromatic ring substitution. In addition, several compounds were profiled for effects on spontaneous versus electrically stimulated bladder contractions. (−)-(9*S*)-9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-dioxide (**14**, A-278637) and **1** were further examined for their ability to inhibit spontaneous contractions in vivo in the pig. The results of these studies have led us to offer an hypothesis for the bladder-selective actions of K_{ATP} openers observed in animal studies.

Chemistry

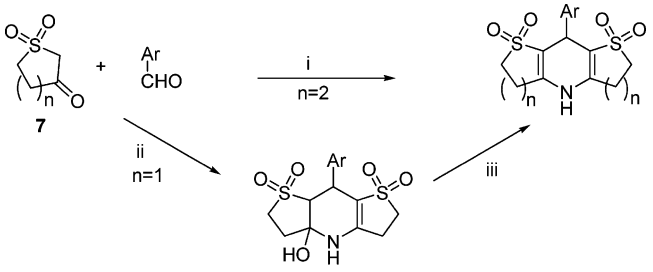
Unsymmetrical tricyclic analogues were assembled using the modified Hantzsch reaction of Scheme 1, wherein a cyclic ketosulfone **7** was condensed with a 3-amino-2-cycloalken-1-one **8** and an aromatic aldehyde

Scheme 1[a]



[a] Conditions: (i) EtOH, 80 °C; (ii) EtOH, Et_3N, 80 °C; (iii) HCl, EtOH, 80 °C.

Scheme 2[a]



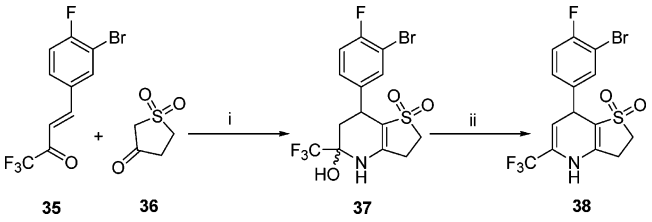
[a] Conditions: (i) NH_3, EtOH, 80 °C; (ii) NH_3, EtOH, 80 °C; toluene 110 °C; (iii) HCl, EtOH, 80 °C.

under conditions of heating in ethanol. In the cases where $n = 1$ and $p = 2$, this reaction was complicated by the formation of up to 10% of the corresponding acridinedione as an impurity. Addition of triethylamine to the reaction mixture suppressed the formation of the acridinedione impurity and allowed isolation of an intermediate hemiaminal **9**. For other ring sizes, varying amounts of the hemiaminal intermediate were observed either with or without added triethylamine. Dehydration of the hemiaminal was accomplished by heating in the presence of acid.

Synthesis of the symmetrical tricyclic bis-sulfones was carried out in a similar fashion with the exception that 2 equiv of **7** was heated with the aldehyde and ammonia in the Hantzsch reaction (Scheme 2). Where $n = 1$, an intermediate hemiaminal **10** was produced that could be dehydrated with acid treatment. Where $n = 2$, Hantzsch conditions similar to those above provided a complex reaction mixture that appeared to consist of the desired product plus other double bond isomers. The appearance of such double bond regioisomers has previously been observed in the Hantzsch reaction with larger ring ketosulfones.[21] Fortunately, simply heating the crude reaction product in toluene was sufficient to convert all the reaction constituents to the desired product.

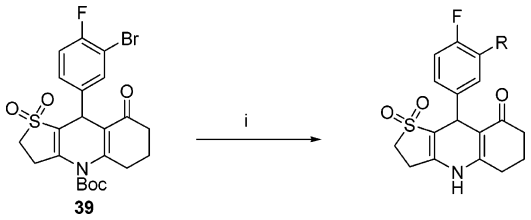
The above-described methods were also used for the preparation of most of the bicyclic analogues investigated (see the Experimental Section for details). The trifluoromethyl-substituted analogue **38**, however, was synthesized in a stepwise manner starting with the aldol condensation of trifluoroacetone with 3-bromo-4-fluorobenzaldehyde followed by condensation of the resultant enone **35** with 3-oxotetrahydrothiophene 1,1-dioxide **36** and ammonia (Scheme 3). Two diastereo-

Scheme 3[a]



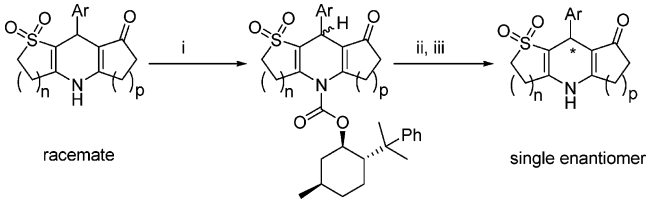
[a] Conditions: (i) NH_3, EtOH, reflux; (ii) *p*-TsOH, toluene, reflux.

Scheme 4[a]



[a] Conditions: (i) Bu_3SnR, $Pd(PPh_3)_4$, DMF, 110 °C.

Scheme 5[a]



[a] Conditions: (i) (−)-8-phenylmenthylchloroformate, KtOBu, THF; (ii) silica gel chromatography; (iii) NaOMe, MeOH.

meric hemiaminals **37** were isolated and subjected to dehydration with *p*-TsOH to obtain the final product **38**.

A number of novel aromatic ring substituents were introduced using palladium-mediated coupling reactions on the Boc-protected intermediate **39** or the corresponding (*S*)-enantiomer (Scheme 4). Typical conditions for effecting this transformation consisted of heating **39** with an organostannane reagent in DMF to 110 °C in the presence of $Pd(PPh_3)_4$. The Boc protecting group was also removed by the conditions of the coupling reaction.

Single enantiomers of the target compounds were prepared by two different methods: (i) resolution with a chiral auxiliary (Scheme 5) or (ii) preparative chiral HPLC. Several different chiral auxiliaries, attached at the dihydropyridine nitrogen, were investigated, but chromatographically separable diastereomers were obtained only through the carbamates of commercially available (−)-8-phenylmenthol. Once the diastereomers were separated, the carbamate group was cleaved with catalytic NaOMe in MeOH to provide the single enantiomer. Chiral chromatographic separation of the enantiomers was accomplished using Regis (*R*,*R*)-Whelk-O1 or Whelk-O2 columns. Although both methods were comparable with regard to the enantiomeric purity achievable, the HPLC method proved more efficient than the auxiliary method in terms of substrate generality and scalability. The absolute stereochemistries were determined for several different ring systems by X-ray crystal analysis. The stereochemistries of analogues with simple variations of the aromatic ring substitution (Table 5) were assigned on the basis of rotation and/or elution order in analogy with compounds **13** and **14**. In this ring system, the less polar enantiomer by HPLC invariably possessed a negative rotation and was assigned the (*S*)-stereochemistry.

Biological Assays

Guinea Pig Bladder (GPB) Assay.[22] Membrane potential changes elicited by test compounds were measured using a fluorometric imaging plate reader (FLIPR). Dose−response curves were generated for changes in fluorescence with the membrane potential sensitive dye $DiBAC_4(3)$. Potencies are expressed as the negative logarithm of the EC_{50} (pEC_{50}), and efficacies were determined relative to the standard P1075 (**3**).

Field-Stimulated Landrace Pig Detrusor (FS-LPD) Assay.[23] Compounds were evaluated for bladder K_{ATP} activity using tissue strips from Landrace pig bladders. Low-frequency stimulation (0.05 Hz, 0.5 ms at 20 V) produced a stable twitch response, the amplitude of which was reduced by increasing concentrations of test agents. These field-stimulated contractions have both cholinergic and noncholinergic components and are partially sensitive to muscarinic blockers such as tolterodine.

Spontaneous Landrace Pig Detrusor (SLPD) Assay.[24] Spontaneously contracting bladder strips were obtained from the area closer to the trigonal region of the bladder in Landrace pigs. The reduction of the area under the curve (AUC) by increasing concentrations of test agents was measured. These spontaneous contractions are purely of myogenic origin, have no cholinergic component, and thus are insensitive to the effects of muscarinic blockers such as tolterodine.

Concentration−response curves were generated for each agent with the potency expressed as the pEC_{50}. Confirmation of a K_{ATP} mechanism was demonstrated for all compounds by reversal of the bladder relaxant effect following addition of glyburide at the end of each experiment. In both tissue strip models, the test compounds were fully efficacious when compared to the control **3**. Because of the different sensitivities of the two assays to muscarinic antagonists, each may model bladder overactivity of distinct etiology.

Obstructed Pig Urodynamics.[25] Compounds were tested in vivo in a disease model of overactive bladder. Female Landrace/Yorkshire swine (∼12 weeks old; 14−20 kg) were obstructed with a 7.5 mm silver omega ring placed around the proximal urethra. Seventeen to 20 weeks later, the pigs were instrumented with telemetry transducer/transmitters for the measurement of carotid arterial pressure and intravesical (bladder) pressure. Animals were allowed to recover for 10−14 days before testing.

For urodynamic testing, pigs were anesthetized with telazol/xylazine, intubated, and maintained on isoflurane/oxygen in the supine position. Anesthesia level and bladder volume were adjusted to establish a regular pattern of unstable bladder contractions. The isoflurane/oxygen mixture inhibits normal parasympathetically mediated voiding contractions but not disease-related spontaneous contractions of myogenic origin. The anticholinergic tolterodine is not efficacious in this model. After a 30 min baseline data acquisition period, two increasing doses of test compounds were administered intravenously (3 min infusion) at 30 min intervals.[26] Blood samples were obtained from the opposite ear at

15 min after each dose for subsequent determination of plasma concentrations by liquid chromatography/mass spectroscopy. Bladder contraction AUC was averaged over each 30 min postdosing period and expressed as percent change from baseline. From the concentration−response relationship, an EC_{50} to inhibit bladder contractions was determined.

Conscious Pig Hemodynamics. For conscious mean arterial pressure (MAP) and heart rate (HR) evaluation, pigs obstructed and telemeterized as described above were placed into a stainless steel restraint cage, and 20 gauge venous catheters were placed in both ears to provide vascular access for dosing and blood sampling. Drug administration and plasma sampling were conducted as above. Arterial pressure and heart rate data were averaged in 5 min bins for each 30 min postdosing period and expressed as percent change from baseline.

Results and Discussion

In Vitro K_{ATP} SAR. SAR investigations around compound **6** first focused on ring size effects and stereochemistry, and the data are summarized in Table 1. In three of the four pairs of enantiomers, one enantiomer possessed at least 10-fold greater potency than the antipode. In two of these three cases, the more potent analogue had the (*R*)-stereochemistry (**11** and **15**). For the third case, a suitable crystal was not obtained for X-ray analysis; however, the more active enantiomer **17** displayed the same sign of rotation as compound **15**, the other analogue containing a six-membered ring sulfone. For **13** and **14**, the difference in potency between the enantiomers was only 3-fold, presumably due to the pseudosymmetrical nature of these compounds where the five-membered sulfur-containing ring and the six-membered carbocyclic ring have similar steric properties. Among the analogues with the (*R*)-configuration, there were no major differences in potency in GPB, although there appeared to be some preference for the five-membered sulfone ring analogues **11** and **13** in FSLPD. Compounds **11** and **13** are highly potent K_{ATP} openers, essentially equivalent with the standard **3**. Larger ring sizes such as in examples **19** and **20** markedly reduced the potency. Of the two symmetrical bis-sulfone analogues **21** and **22**, the five-membered rings provided the greater potency. Both **21** and **22**, however, were less potent than the most potent unsymmetrical analogues in Table 1, indicating that the sulfonyl and carbonyl groups are not totally interchangeable.

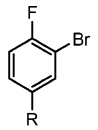
Dimethyl substitution was investigated on the carbocyclic ring of the 2,3,5,6,7,9-hexahydrothieno[3,2-*b*]-quinolin-8(4*H*)-one 1,1-dioxide ring system (Table 2). The *gem*-dimethyl group adjacent to the dihydropyridine nitrogen (5-position) reduced the potency for both enantiomers (**23** and **24**), with the (*S*)-enantiomer being the more potent of the two. On the other hand, substitution adjacent to the carbonyl at the 7-position had little effect on potency (**27** and **28**) in GPB; however, the potency was significantly reduced in FSLPD. Installation of the *gem*-dimethyl at the 6-position greatly attenuated potency (**25** and **26**).

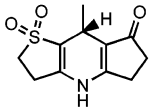
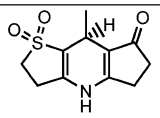
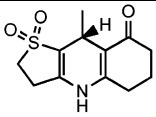
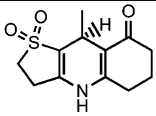
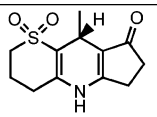
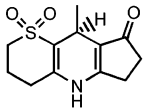
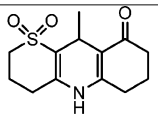
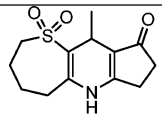
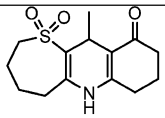
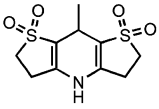
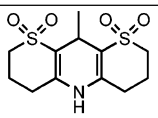
A number of bicyclic variations of the core structure were investigated (Table 3). The cyano **29** and methyl ester **30** analogues proved to be the most potent, essentially equivalent to the most potent tricyclic compounds. The K_{ATP} opening activity of **30** was somewhat surprising, since ester groups are more known for imparting calcium channel blocking activity. However, this result was not totally unexpected, since the preferred aromatic ring substitution patterns for Ca^{2+} channel blocking (ortho and/or meta)[27] and K_{ATP} opening (meta and/or para) activities were known to be divergent. Increasing the size of the ester to ethyl, however, did diminish the potency by 10-fold (**31**). Replacement of the methyl by CF_3 in the case of the ethyl ester served to reduce the potency still further (**32**). The carboxylic acid analogue **33** also showed weak potency relative to the esters. Interestingly, removal of the ester group with retention of the CF_3 in the 2-position increased the potency significantly (**38**).

Using the tricyclic core of compound **14**, extensive SAR investigations were conducted on the aromatic ring substitution (Table 4). At the meta position, a clear preference was found for the larger halogens. Groups such as 3-CF_3 (**55**), 3-NO_2 (**49**), 3-CN (**53**), and 3-(2-furyl) (**60**) were similar to 3-Cl, whereas other substituents such as 3-F (**43**, **52**), 3-Me (**54**), 3-MeS (**56**), 3-$MeSO_2$ (**57**), 3-acetyl (**58**), and 3-vinyl (**59**) were less potent. Aromatic groups other than 2-furyl attached at the 3-position were essentially inactive up to 10 μM (**61**−**63**). At the para position the following substituents gave very comparable potencies: F, Me, Cl, Br, CF_3. A larger alkyl group like Et was less well tolerated (**50**). The benzoxadiazole (**64**) was found to be a suitable replacement for a 3,4-dichlorophenyl group; however, the benzothiadiazole **65** was substantially less active. Surprisingly, addition of an ortho hydroxy group as in examples **66** and **67** did not reduce potency relative to the des-hydroxy analogues. These are the first examples of substitution in a position other than meta or para providing K_{ATP} opening activity. These are also the first examples of active dihydropyridine analogues possessing an electron-donating group on the aromatic ring. Chain extension of the hydroxyl to a benzylic alcohol (**68**), however, resulted in a complete loss in activity. In agreement with the previous literature, the mono-substituted analogues **69**−**71** were significantly less active. Parallel synthesis techniques were used to prepare 130 additional aromatic substitutions from diverse commercially available aromatic aldehydes. With the exception of the discovery of the novel 2-OH 5-Br substitution, this exercise served to confirm earlier findings that electron-donating groups and substitution patterns other than those already discussed eliminate K_{ATP} activity. Heterocyclic aromatic replacements for the substituted phenyl were also investigated (Table 5). In general these gave disappointing results. Unsubstituted pyridines, thiophenes, and furans all showed poor activity (data not shown). With the exception of example **75** (potency similar to the carbocyclic analogue **69**), none of the substituted pyridines possessed a pEC_{50} greater than 5. Substitution with either bromo or nitro on either thiophene regioisomer improved activity relative to **61** as anticipated (**76**−**79**).[20]

In Vitro and in Vivo Selectivity. Compounds **13**, **14**, **1**, **2**, **5**, and **3** were evaluated for K_{ATP} opening activity in vitro in both spontaneously contracting (SLPD) and electrically stimulated (FSLPD) pig bladder

Table 1

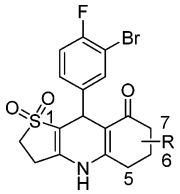


cpd no.	R	Stereochemistry	GPB pEC_{50}[a,e]	FSLPD pEC_{50}[b,f]
11		R (+)	7.48 (0.32)[d]	7.51 ± 0.27
12		S (-)	6.24 (0.56)[d]	6.47 ± 0.20
13		R (+)	7.36 (0.46)[d]	7.16 ± 0.09
14		S (-)	6.91 (0.32)[d]	6.63 ± 0.15
15		R (-)	7.28 (0.16)[d]	6.55 ± 0.05
16		S (+)	4.83 (0.31)[d]	4.58 ± 0.23
17		(-)	7.42 (0.30)[d]	6.44 ± 0.08
18		(+)	5.92 (0.058)[c]	5.17 ± 0.13
19		racemate	5.65 (0.20)[c]	4.93 ± 0.57
20		racemate	5.48 (0.26)[d]	NT
21		-	6.47 (0.35)[d]	6.57 ± 0.15
22		-	5.50 (0.074)[c]	4.93 ± 0.27
4			5.42 (0.22)[d]	5.01 ± 0.08
1			6.37 (0.25)[d]	6.59 ± 0.16
2			6.41 (0.30)[d]	5.56 ± 0.13
3			7.35 (0.42)[d]	7.07 ± 0.10
5			6.60 (0.07)[c]	6.17 ± 0.13

[a] GPB = guinea pig bladder cells. [b] FSLPD = field-stimulated Landrace pig detrusor strips. [c] Number of determinations = 2. [d] Number of determinations ≥ 3. [e] Standard deviation in parentheses. [f] Number of determinations ≥ 4; standard error shown. NT = not tested.

strips (Table 6). All of the compounds displayed greater potency (5−10-fold) to relax spontaneous bladder contractions than to inhibit those elicited by electrical stimulation. Both **13** and **14** were more potent than **1**,

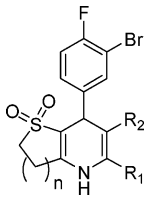
Table 2



compd	R	stereochem	pEC50 GPB[a,e]	pEC50 FSLPD[b,f]
23	5,5-diMe	R	<5[c]	NT
24	5,5-diMe	S	6.20(0.09)[c]	5.57 ± 0.18
25	6,6-diMe	R	4.75(0.36)[c]	NT
26	6,6-diMe	S	5.15(0.01)[c]	NT
27	7,7-diMe	R	6.97(0.30)[d]	6.01 ± 0.07
28	7,7-diMe	S	7.08(0.32)[d]	5.25 ± 0.12

[a] GPB = guinea pig bladder cells. [b] FSLPD = field-stimulated Landrace pig detrusor strips. [c] Number of determinations = 2. [d] Number of determinations ≥ 3. [e] Standard deviation in parentheses. [f] Number of determinations ≥ 4; standard error shown. NT = not tested.

Table 3



compd	n	R_1	R_2	pEC50 GPB[a,e]	pEC50 FSLPD[b,f]
29	1	Me	CN	7.56(0.24)[d]	NT
30	1	Me	CO_2Me	7.27(0.20)[d]	NT
31	1	Me	CO_2Et	6.30(0.32)[d]	NT
32	1	CF_3	CO_2Et	<5[d]	NT
33	1	Me	CO_2H	5.74(0.20)[d]	5.06 ± 0.21
34	2	Me	COMe	6.67(0.17)[c]	6.10 ± 0.13
38	1	CF_3	H	6.35(0.19)[c]	5.65 ± 0.29

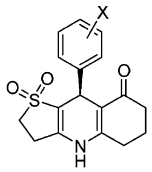
[a] GPB = guinea pig bladder cells. [b] FSLPD = field-stimulated Landrace pig detrusor strips. [c] Number of determinations = 2. [d] Number of determinations ≥ 3. [e] Standard deviation in parentheses. [f] Number of determinations ≥ 4; standard error shown. NT = not tested.

2, and **5**. The in vitro selectivity for spontaneous contractions may be relevant to potential clinical selectivity for diseased bladder contractions of purely myogenic origin.

Since **14** showed the most selectivity to inhibit spontaneous contractions in vitro, it was chosen for evaluation in the obstructed pig assay, and its properties were compared to those of **1** (Figure 3). The pig was employed as the anatomy, physiology, and pharmacology of the lower urinary tract are considered similar to humans.[28] Both compounds inhibited spontaneous bladder contractions in a dose- and concentration-dependent fashion, while **14** showed greater potency than **1**.

To assess selectivity for bladder versus cardiovascular in vivo, the effects of **14** and **1** on MAP and HR were evaluated and compared. Since the anesthesia isoflurane is known to affect cardiovascular function and act additively with K_{ATP} openers such as **1** to lower blood pressure,[29] MAP and HR were determined in conscious pigs similar to those used for the measurement of bladder function. Both compounds reduced MAP in a dose- and concentration-dependent fashion over a simi-

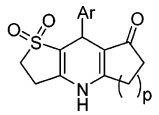
Table 4

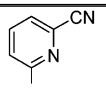
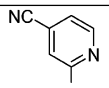
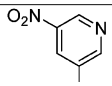
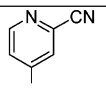
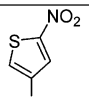
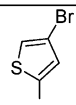


cpd no.	X	GPB pEC50[a,e]	FSLPD pEC50[b,f]
41	3-I, 4-F	7.55 (0.41)[d]	6.35 ± 0.12
14	3-Br, 4-F	6.91 (0.32)[d]	6.63 ± 0.15
42	3-Cl, 4-F	6.86 (0.06)[d]	6.67 ± 0.11
43	3-F, 4-F	5.69 (0.04)[c]	NT
44	3-I, 4-Me	7.66 (0.02)[c]	6.51 ± 0.32
45	3-Br, 4-Me	6.74 (0.24)[d]	6.96 ± 0.33
46	3-Br, 4-Cl	7.59 (0.49)[d]	6.14 ± 0.11
47	3-Br, 4-Br	7.26 (0.45)[d]	6.27 ± 0.14
48	3-Br, 4-CF_3	6.66 (0.11)[c]	5.02 ± 0.13
49	3-NO_2, 4-Me	6.55 (0.16)[c]	6.27 ± 0.16
50*	3-NO_2, 4-Et	5.64 (0.39)[c]	NT
51	3-Cl, 4-Cl	6.57 (0.22)[d]	6.48 ± 0.21
52	3-F, 4-Cl	5.88 (0.13)[d]	NT
53	3-CN, 4-F	6.33 (0.07)[d]	NT
54*	3-Me, 4-F	5.55 (0.12)[c]	NT
55	3-CF_3, 4-F	6.81 (0.06)[c]	6.01 ± 0.20
56*	3-MeS, 4-F	5.59 (0.13)[d]	NT
57*	3-SO_2Me, 4-Me	<5	NT
58*	3-acetyl, 4-F	5.98 (0.02)[d]	NT
59	3-vinyl, 4-F	5.87 (0.08)[c]	5.61 ± 0.27
60	3-(2-furyl), 4-F	6.67 (0.37)[d]	5.77 ± 0.25
61*	3-(2-thienyl), 4-F	<5	NT
62*	3-(3-pyridyl), 4-F	<5	NT
63*	3-Ph, 4-F	4.92 (0.03)[d]	NT
64		6.67 (0.25)[d]	5.63 ± 0.11
65		5.62 (0.10)[c]	NT
66*	2-OH, 4-F, 5-Br	6.68 (0.01)[c]	6.17 ± 0.13
67*	2-OH, 5-Br	6.24 (0.24)[c]	4.69 ±
68	2-CH_2OH, 4,Cl, 5-Cl	4.21 (0.53)[c]	NT
69	3-CN	5.23 (0.20)[d]	4.89 ± 0.09
70	3-Br	5.82 (0.28)[c]	NT
71	4-Br	<5	NT

[a] GPB = guinea pig bladder cells. [b] FSLPD = field-stimulated Landrace pig detrusor strips. [c] Number of determinations = 2. [d] Number of determinations ≥ 3. [e] Standard deviation in parentheses. [f] Number of determinations ≥ 4; standard error shown. NT = not tested. *racemate.

Table 5



cpd no.	p	Ar	GPB pEC_{50}[a,e]	FSLPD pEC_{50}[b,f]
72	1		<5	NT
73	1		<5	NT
74	1		<5	NT
75	1		5.50 (0.16)[a]	NT
76	1		6.62 (0.14)[a]	6.18 ± 0.10
77	1		5.73 (0.24)[a]	NT
78	1		6.82 (0.06)[a]	6.32 ± 0.19
79	1		6.13 (0.15)[a]	NT

[a] GPB = guinea pig bladder cells. [b] FSLPD = field-stimulated Landrace pig detrusor strips. [c] Number of determinations = 2. [d] Number of determinations ≥ 3. [e] Standard deviation in parentheses. [f] Number of determinations ≥ 4; standard error shown. NT = not tested.

Table 6. In Vitro Bladder Relaxation[a]

compd	pEC_{50} FSLPD[a,c]	pEC_{50} SLPD[b,c]	selectivity SLPD:FSLPD
13	7.16 ± 0.09	7.90 ± 0.11	5.5
14	6.63 ± 0.15	7.64 ± 0.08	10
1	6.59 ± 0.19	7.46 ± 0.20	7.4
2	5.56 ± 0.13	6.53 ± 0.32	9.3
5	6.17 ± 0.13	6.99 ± 0.06	6.6
3	7.07 ± 0.10	7.66 ± 0.16	3.9

[a] FSLPD = field-stimulated Landrace pig detrusor strips. [b] SLPD = spontaneous Landrace pig detrusor strips. [c] Number of determinations ≥ 4; standard error shown.

lar concentration range (Figure 3). Reflex HR increases were observed for both compounds in parallel with the reductions in MAP, although the magnitude of the HR effects were considerably more variable (Table 7). Importantly, the correlation of plasma concentration with HR effects observed here is in accord with published clinical results for **1**.[30]

Both **14** and **1** inhibited spontaneous bladder contractions at plasma concentrations lower than those that affected blood pressure. Compound **14** displayed greater

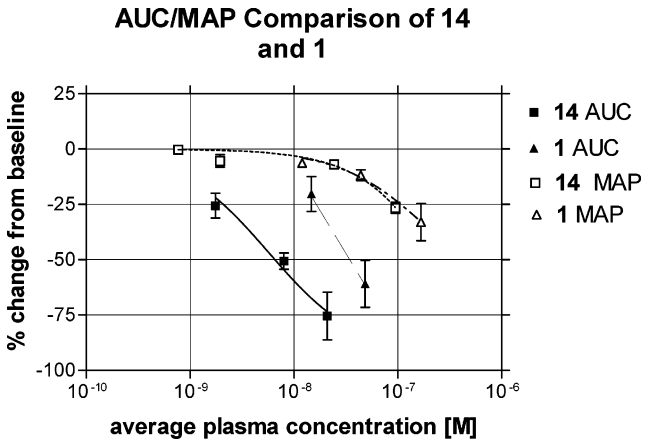


Figure 3. Reductions in AUC (area under the curve) and MAP (mean arterial pressure) with ascending concentrations. ■, **14** AUC (doses: 3, 10 and 30 nmol/kg); □, **14** MAP (doses: 1, 3, 10 and 30 nmol/kg); ▲, **1** AUC (doses: 10 and 30 nmol/kg); △, **1** MAP (doses: 10, 30 and 100 nmol/kg). Plasma concentrations are the average of 2−4 experiments. **14** AUC EC_{50} = 8 nM. (−)-**1** AUC EC_{50} = 39 nM.

Table 7. Cardiovascular Effects of **14** and **1**

compound **14**			compound **1**		
plasma concn[a] (nM)	%Δ MAP[b]	%Δ HR[c]	plasma concn[a] (nM)	%Δ MAP[b]	%Δ HR[c]
1.9	−5.4 ± 2.8	6.2 ± 8.2	12	−6.3 ± 0.5	13 ± 22
24	−6.9 ± 1.9	3.5 ± 8.6	44	−12 ± 2.4	38 ± 10
95	−27 ± 2.5	56 ± 14	167	−33 ± 8.4	47 ± 14

[a] Average plasma concentration (n = 2−4). [b] MAP = mean arterial pressure. Percent MAP change from baseline in mmHg is shown. [c] HR = heart rate. Percent HR change from baseline in beats per minute is shown.

selectivity than **1** due to its approximately 5-fold greater potency to reduce AUC and equivalent potency to affect MAP (Figure 3). For **14**, bladder AUC was reduced up to 75% at plasma concentrations that were without significant effects (<10%) on MAP in conscious pigs. Since the compounds were administered intravenously and the AUC and CV effects were measured over the same time period, these results are less dependent on pharmacokinetic considerations such as nonlinear effects that can occur on oral dosing.

In what appears to be a general property of K_{ATP} openers, all compounds examined in this study showed selectivity for spontaneous over electrically stimulated bladder contractions in vitro. Although in vivo selectivity for diseased versus normal bladder function was not measured in this study, the in vitro selectivity for spontaneous contractions suggests that this may be a property of K_{ATP} openers. Similar to results from other studies,[13,15] all agents from Table 1 showed no absolute selectivity in vitro against vascular tissue preparations such as the rat aorta or portal vein[31] (data not shown). Nonetheless, the in vivo data suggests an inherent selectivity of K_{ATP} openers for disease-related bladder contractions as both **1** and **14** inhibited spontaneous bladder contractions over concentration ranges that had minimal effects on cardiovascular parameters. Compound **14** displayed improved selectivity relative to **1**; however, it remains to be determined whether its efficacy at nonhypotensive concentrations would translate to symptom relief.

Conclusion

In conclusion, these SAR studies have significantly expanded the understanding of the dihydropyridine pharmacophore as it relates to K_{ATP} opening activity. Specifically, we examined the effects of absolute stereochemistry, ring sizes, and novel aromatic substitutions. The analogues **11** and **13** displayed equivalent potency to the standard **3**. We have also demonstrated novel methods for the preparation of single enantiomers in this structural class. In addition, we found that compound **14** potently inhibited spontaneous bladder contractions in the pig both in vitro and in vivo in addition to demonstrating greater selectivity than **1**. Since the spontaneous contractions measured in this study lack a cholinergic component, compound **14** may have utility in the treatment of diseased bladder contractions that are resistant to antimuscarinic drugs.

Experimental Section

Chemistry. General. Proton NMR spectra were obtained on a General Electric QE 300 or QZ 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Unless otherwise indicated in the individual experimentals, melting points of final compounds were all greater than 260 °C. Elemental analyses were performed by Robertson Microlit Laboratories. Column chromatography was carried out on silica gel 60 (230−400 mesh). Thin-layer chromatography (TLC) was performed using 250 mm silica gel 60 glass-backed plates with F_{254} as indicator. HPLC separations were done using a Gilson system with a 215 liquid handler and a UV detector. Optical rotations were measured with a Perkin-Elmer 541 polarimeter. X-ray crystal structures were obtained on a Bruker SMART system.

(+)-(9*R*)-9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (13) and (−)-(9*S*)-9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (14). (Method A). A solution of dihydrothiophen-3(2*H*)-one 1,1-dioxide (4.82 g, 36 mmol), 3-bromo-4-fluorobenzaldehyde (4.00 g, 36 mmol), Et_3N (2.5 mL, 18 mmol), and 3-aminocyclohex-2-en-1-one (7.67 g, 37.8 mmol) in EtOH (50 mL) was heated to reflux for 72 h and cooled, and 11.6 g of the intermediate hemiaminal was collected as a white precipitate. The precipitate in EtOH (120 mL) was heated to reflux, treated with 1.0 M HCl/Et_2O (2 mL), reacted for 15 min, and cooled, and the solid precipitate was collected to provide 10.56 g of the racemic title compound as a white solid: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 1.88 (m, 2H), 2.23 (m, 2H), 2.56 (m, 2H), 2.83 (dtd, 1H), 3.03 (dt, 1H), 3.33 (t, 2H), 4.85 (s, 1H), 7.22 (m, 2H), 7.40 (dd, 1H), 9.78 (br s, 1H); MS (APCI) *m*/*e* 410 $(M - H)^-$, 412 $(M - H)^-$.

9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-dioxide (0.50 g), obtained from method A above, was chromatographed on a 5 × 25 cm Regis WhelkO 2 chiral column with 280 g of packing, eluting with hexane:MeOH:CH_2Cl_2 (77.5/15/7.5) as the mobile phase with a flow rate of 117 mL/min to provide 220 mg of compound **13** as the more polar enantiomer, the absolute stereochemistry of which was determined by X-ray crystal structure analysis (see Supporting Information): $[\alpha]^{23}_D$ +50.24° (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 1.72−1.98 (m, 2H), 2.22 (m, 2H), 2.55 (m, 2H), 2.8 (m, 1H), 3.1 (m, 1H), 3.32 (m, 2H), 4.82 (s, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 9.8 (s, 1H); MS (APCI$^+$) *m*/*z* 414 $(M + H)^+$. Anal. ($C_{17}H_{15}BrFNO_3S$) C, H, N. From the chiral chromatography described above was obtained 210 mg of compound **14** as the less polar enantiomer: $[\alpha]^{23}_D$ −48.8 (CH_3CN);^{1}H NMR (DMSO-d_6) δ 1.72−1.98 (m, 2H), 2.22 (m, 2H), 2.52 (m, 2H), 2.8 (m, 1H), 3.1 (m, 1H), 3.31 (m, 2H), 4.82 (s, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 9.8 (s, 1H); MS (APCI$^+$) *m*/*z* 414 $(M + H)^+$. Anal. ($C_{17}H_{15}BrFNO_3S$) C, H, N.

(−)-(9*R*)-(3-Bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydrocyclopenta[*b*]thiopyrano[2,3-*e*]pyridin-8(2*H*)-one 1,1-Dioxide (15) and (+)-(9*S*)-9-(3-Bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydrocyclopenta[*b*]thiopyrano[2,3-*e*]pyridin-8(2*H*)-one 1,1-Dioxide (16). A solution of dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide (888 mg, 6.00 mmol), 3-bromo-4-fluorobenzaldehyde (1.2 g, 6.0 mmol), and 3-aminocyclopent-2-en-1-one (583 mg, 6.0 mmol) in EtOH (10 mL) was heated to reflux for 72 h and cooled. The solid that precipitated was collected, washed with EtOH, and dried to provide 1.476 g of the racemic title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.25 (m, 4H), 2.60 (m, 4H), 3.20 (m, 2H), 4.83 (s, 1H), 7.25 (m, 2H), 7.41 (dd, 1H), 9.96 (br s, 1H); MS (APCI) *m*/*e* 412 $(M + H)^+$, 414 $(M + H)^+$.

Method B. The racemic product from above (1.476 g, 3.58 mmol) as a slurry in THF (20 mL) under N_2 at 5 °C was treated dropwise with a solution of 1.0 M KO^{t}Bu in THF (3.9 mL), allowed to warm to room temperature over 20 min, treated with a solution of (−)-8-phenylmenthylchloroformate (1.17 g, 3.97 mmol) in THF (5 mL), stirred at room temperature overnight, quenched in aqueous $NaHCO_3$, extracted with Et_2O (2×). The organics were dried with Na_2SO_4 and filtered, and solvent was evaporated to provide a mixture of diastereomeric carbamates. This mixture was flash chromatographed over a 6 × 36 cm column of silica gel, eluting with Et_2O:hexane (85/15) to provide 746 mg of the less polar diastereomer. This material, as a slurry in MeOH (10 mL) under N_2, was treated with catalytic NaOMe, stirred at room temperature for 24 h, and treated with glacial AcOH (3 drops). The solid precipitate was collected, washed with EtOH, and dried to provide 227 mg of compound **16** as a white solid (see Supporting Information for X-ray structure report): $[\alpha]^{23}_D$ +63.9 (MeCN); ^{1}H NMR (DMSO-d_6) δ 2.15−2.35 (m, 4H), 2.46−2.70 (m, 4H), 3.23 (m, 2H), 4.83 (s, 1H), 7.25 (m, 2H), 7.42 (dd, 1H), 9.96 (br s, 1H); MS (APCI$^-$) *m*/*z* 410 $(M - H)^-$. Anal. ($C_{17}H_{15}BrFNO_3S$) C, H, N. From the chromatography of diastereomers described above was obtained 824 mg of the impure more polar diastereomer. This material was flash chromatographed over a 6 × 36 cm column of silica gel, eluting with Et_2O:hexane (9/1) to provide 695 mg of the more polar diastereomer. This diastereomer, as a slurry in MeOH (10 mL) under N_2, was treated with catalytic NaOMe, stirred at room temperature for 5 d, and treated with glacial AcOH (3 drops). The solid precipitate was collected, washed with EtOH, and dried to provide 120 mg of the title compound as a white solid. The filtrate was flash chromatographed (5−15% EtOH/CH_2Cl_2) and the product triturated with EtOAc to provide an additional 186 mg of compound **15**. $[\alpha]^{23}_D$ −60.8 (MeCN); ^{1}H NMR (DMSO-d_6) δ 2.15−2.30 (m, 4H), 2.47−2.70 (m, 4H), 3.20 (m, 2H), 4.83 (s, 1H), 7.25 (m, 2H), 7.41 (dd, 1H), 9.96 (br s, 1H); MS (APCI$^-$) *m*/*z* 410 $(M - H)^-$. Anal. ($C_{17}H_{15}BrFNO_3S$) C, H, N.

(−)-(9*S*)-(3,4-Dichlorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (51). 3,4-Dichlorobenzaldehyde (1.05 g, 6.00 mmol) was treated according to method A to provide 1.72 g of the racemic title compound: ^{1}H NMR (DMSO-d_6) δ 1.75−2.0 (m, 2H), 2.23 (m, 2H), 2.57 (m, 2H), 2.85 (dt, 1H), 3.03 (dt, 1H), 3.38 (m, 2H), 4.84 (s, 1H), 7.17 (dd, 1H), 7.35 (d, 1H), 7.50 (d, 1H), 9.85 (br s, 1H); MS (APCI) *m*/*e* 384 $(M + H)^+$.

Method C. The racemic title compound (1.65 g, 4.30 mmol) as a slurry in THF (20 mL) under nitrogen at 5 °C was treated dropwise with a solution of 1.0 M KO^{t}Bu in THF (3.9 mL), allowed to warmed to room temperature over 20 min, treated with a solution of (−)-8-phenylmenthylchloroformate (4.3 mmol) in THF (5 mL), stirred at room temperature overnight, quenched in aqueous $NaHCO_3$, and extracted with Et_2O (3×). The organics were dried (Na_2SO_4) and filtered, and solvent was evaporated to provide a mixture of diastereomeric carbamates. This mixture was flash chromatographed (2×) over a 6 × 40 cm column of silica gel, eluting with $CHCl_3$:hexane:Et_2O(7:2:1) to provide 628 mg of the pure more polar diastereomer. This diastereomer, as a slurry in MeOH (10 mL) under N_2, was treated with catalytic NaOMe, stirred at room temperature overnight, and treated with glacial AcOH (2 drops). The solid

precipitate was collected, washed with EtOH, and dried to provide 228 mg of compound **51** as a white solid: $[\alpha]^{23}_D$ −68.8° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.75−1.95 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 2.73 (dt, 1H), 3.03 (dt, 1H), 3.35 (m, 2H), 4.84 (s, 1H), 7.17 (dd, 1H), 7.35 (d, 1H), 7.50 (d, 1H), 9.85 (br s, 1H); MS (APCI$^-$) *m/z* 382 (M − H)$^-$. Anal. ($C_{17}H_{15}Cl_2NO_3S$) C, H, N.

(9*S*)-(3-Ethenyl-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (59). (9*S*)-1,1-Dimethylethyl 9-(3-bromo-4-fluorophenyl)-8-oxo-3,5,6,7,8,9-hexahydrothieno[3,2-*b*]quinoline-4(2*H*)-carboxylate 1,1-Dioxide. A solution of compound **14** (1.0 g, 2.4 mmol), Boc_2O (1.0 g, 24 mmol), and DMAP (29 mg, 0.1 mmol) in MeCN was heated to reflux for 1 h, cooled to room temperature, and concentrated, and the residue was purified by flash chromatography on silica gel eluting (EtOAc/hexane 1:1) to provide 900 mg of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.56 (s, 9H), 1.90−2.02 (m, 2H), 2.3−2.5 (m, 2H), 3.00 (m, 2H), 3.45 (m, 2H), 3.50 (m, 2H), 4.83 (s, 1H), 7.20 (m, 1H), 7.32 (t, 1H), 7.37 (dd, 1H).

Method D. A solution of the above intermediate (150 mg, 0.29 mmol) and $Pd(PPh_3)_4$ (10 mol %) in DMF (0.1 M) was treated with vinyl tributylstannane (0.45 mL, 1.4 mmol), heated to 110 °C for 24 h, cooled to room temperature, treated with saturated KF, and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography on silica gel (MeOH:CH_2Cl_2 5:95). Recrystallization from EtOH provided 82 mg of compound **59** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.99−1.82 (m, 2H), 2.25−2.20 (m, 2H), 2.5 (m, 2H), 2.79−2.73 (m, 1H), 3.32−3.30 (m, 4H), 3.25−2.81 (m, 1H), 4.86 (s, 1H), 5.40 (dd, 1H, J = 11.53, 1.35 Hz), 5.80 (dd, 1H, J = 18.0, 1.35 Hz), 6.77 (dd, 1H, J = 17.63, 11.20 Hz), 7.08−7.01 (m, 2H), 7.35 (dd, 1H, J = 7.46, 2.04 Hz), 9.74 (S, 1H); MS (ESI$^-$) *m/z* 358 (M − H)$^-$. Anal. ($C_{19}H_{18}FNO_3S\cdot 0.3H_2O$) C, H, N.

(+)-(8*R*)-8-(3-Bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydro-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (11) and (−)-(8*S*)-8-(3-Bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydro-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (12). A solution of dihydrothiophen-3(2*H*)-one 1,1-dioxide (166 mg, 1.24 mmol), 3-bromo-4-fluorobenzaldehyde (250 mg, 1.23 mmol), and 3-aminocyclopent-2-en-1-one (120 mg, 1.24 mmol) in EtOH (4 mL) was heated to reflux for 72 h and cooled. The precipitate was collected, washed with ethanol, and dried to provide 241 mg of the racemic title compound: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 2.30 (t, 2H), 2.63 (m, 2H), 2.85 (dt, 1H), 3.06 (dt, 1H), 3.40 (t, 2H), 4.72 (s, 1H), 7.27 (m, 2H), 7.47 (d, 1H), 10.33 (br s, 1H); MS (APCI$^-$) *m/z* 396 (M − H)$^-$. The racemic product above (0.80 g) was chromatographed on a 5 × 25 cm Regis WhelkO 2 chiral column with 280 g of packing, eluting with hexane: MeOH:CH_2Cl_2 (70/15/15) as the mobile phase at a flow rate of 117 mL/min to provide 264 mg of compound **11** as the more polar enantiomer (see Supporting Information for X-ray crystal analysis): $[\alpha]^{23}_D$ +4.8° (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 2.3 (m, 2H), 2.62 (m, 2H), 2.85 (m, 1H), 3.05 (m, 1H), 3.4 (m, 2H), 4.72 (s, 1H), 7.25 (m, 2H), 7.48 (d, 1H), 10.35 (s, 1H); MS (ESI$^+$) *m/z* 400 (M + H)$^+$. Anal. ($C_{16}H_{13}BrFNO_3S$) C, H, N. From the above chiral chromatography was obtained 250 mg of compound 12 as the less polar enantiomer: $[\alpha]^{23}_D$ −4.5° (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 2.3 (t, 2H), 2.63 (m, 2H), 2.85 (m, 1H), 3.06 (m, 1H), 3.4 (m, 2H), 4.71 (s, 1H), 7.25 (d, 2H), 7.47 (d, 1H) 10.35 (s, 1H); MS (ESI$^+$) *m/z* 400 (M + H)$^+$. Anal. ($C_{16}H_{13}BrFNO_3S$) C, H, N.

(−)-10-(3-Bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-2*H*-thiopyrano[3,2-*b*]quinolin-9(5*H*)-one 1,1-Dioxide (17) and (+)-10-(3-Bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-2*H*-thiopyrano[3,2-*b*]quinolin-9(5*H*)-one 1,1-Dioxide (18). A solution of dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide (888 mg, 6.00 mmol), 3-bromo-4-fluorobenzaldehyde (1.22 g, 6.00 mmol), Et_3N (0.42 mL, 3 mmol), and 3-aminocyclohex-2-en-1-one (666 mg, 6 mmol) in EtOH (10 mL) was heated to reflux for 72 h and cooled. The solid that precipitated was collected, washed with EtOH, and dried to provide 1.098 g of the racemic title compound as a white solid. The filtrate was evaporated to dryness, redissolved in EtOH, treated with 1.0 M HCl/Et_2O (1.5 mL), heated to reflux for 2 h, and cooled. The solid precipitate was collected, washed with EtOH, and dried to provide an additional 548 mg of the racemic title compound: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 1.75 (m, 1H), 1.90 (m, 1H), 2.20 (m, 4H), 2.55 (m, 4H), 3.20 (m, 2H), 5.01 (s, 1H), 7.20 (m, 2H), 7.40 (dd, 1H), 9.35 (br s, 1H); MS (APCI) *m/e* 426 (M + H)$^+$, 428 (M + H)$^+$. The racemic product from above (1.646 g, 3.86 mmol) was processed by method B to provide 223 mg of compound **18** as a white solid: $[\alpha]^{23}_D$ +7.3 (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.75 (m, 1H), 1.88 (m, 1H), 2.20 (m, 4H), 2.50 (m, 4H), 3.20 (m, 2H), 5.01 (s, 1H), 7.15−7.28 (m, 2H), 7.88 (dd, 1H), 9.39 (br s, 1H); MS (APCI$^-$) *m/z* 424 (M − H)$^-$. Anal. ($C_{18}H_{17}BrFNO_3S$) C, H, N. Also obtained was 148 mg of compound **17** as a white solid: $[\alpha]^{23}_D$ −5.2 (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.73 (m, 1H), 1.88 (m, 1H), 2.20 (m, 4H), 2.50 (m, 4H), 3.20 (m, 2H), 5.01 (s, 1H), 7.15−7.27 (m, 2H), 7.38 (dd, 1H), 9.40 (br s, 1H); MS (APCI$^-$) *m/z* 424 (M − H)$^-$. Anal. ($C_{18}H_{17}BrFNO_3S$) C, H, N.

10-(3-Bromo-4-fluorophenyl)-2,3,4,5,6,7,8,10-octahydro-9*H*-cyclopenta[*b*]thiepino[2,3-*e*]pyridin-9-one (19). A solution of 3-bromo-4-fluorobenzaldehyde (639 mg, 3.14 mmol), 3-aminocyclopent-2-en-1-one (305 mg, 3.14 mmol), and thiacycloheptan-3-one 1,1-dioxide (510 mg, 3.14 mmol) in EtOH (10 mL) was heated to 80 °C in a sealed tube for 3 d and cooled. The solid precipitate was collected, washed with EtOH, and dried to provide 700 mg of compound **19** as a white solid: mp 210 °C;^{1}H NMR (DMSO-d_6) δ 1.60 (m, 1H), 1.82 (m, 1H), 2.05 (m, 2H), 2.32 (m, 2H), 2.62 (m, 3H), 2.92 (m, 2H), 3.20 (m, 1H), 4.75 (s, 1H), 7.25 (dd, 1H, J = 3 Hz), 7.32 (m, 1H), 7.45 (dd, 1H, J = 3 Hz), 10.02 (s, 1H);MS (ESI$^+$) *m/z* 427 (M + H)$^+$. Anal. ($C_{18}H_{17}BrFNO_3S$) C, H, N.

11-(3-Bromo-4-fluorophenyl)-2,3,4,5,7,8,9,11-octahydrothiepino[3,2-*b*]quinolin-10(6*H*)-one 1,1-Dioxide (20). A solution of 3-bromo-4-fluorobenzaldehyde (1.22 g, 6.00 mmol), 3-aminocyclohex-2-en-1-one (667 mg, 6.00 mmol), and thiacycloheptan-3-one 1,1-dioxide (973 mg, 6.00 mmol) in EtOH (10 mL) with Et_3N (0.4 mL) was heated to 80 °C in a sealed tube for 3 d and cooled. The solid precipitate was collected, washed with EtOH, and dried to provide 1.8 g of compound **20** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.65 (m, 1H), 1.75 (m, 2H), 1.90 (m, 1H), 2.02 (m, 2H), 2.52 (m, 2H), 2.75 (m, 3H), 3.15 (m, 1H), 4.95 (s, 1H), 7.20 (m, 1H), 7.25 (m, 1H), 7.40 (dd, 1H, J = 3 Hz), 9.44 (s, 1H); MS (ESI$^+$) *m/z* 441 (M + H)$^+$. Anal. ($C_{19}H_{19}BrFNO_3S$) C, H, N.

8-(3-Bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydrodithieno[3,2-*b*:2′,3′-*e*]pyridine 1,1,7,7-Tetraoxide (21). 3-Bromo-4-fluorobenzaldehyde (305 mg, 1.5 mmol), dihydrothiophen-3(2*H*)-one 1,1-dioxide (402 mg, 3.00 mmol), and 2.0 M NH_3 in EtOH (1.1 mL, 2.2 mmol) were heated in EtOH (3 mL) to 80 °C for 3 d in a sealed tube and cooled. The intermediate hemiaminal precipitate was collected and washed with EtOH. The solid was heated to reflux overnight in EtOH with 1.0 M HCl/Et_2O (1 mL) and cooled, and the solid was collected, washed with EtOH, and dried to provide 185 mg of compound **21** as an off-white solid: ^{1}H NMR (DMSO-d_6) δ 2.80 (m, 2H), 3.01 (dt, 2H), 3.35 (m, 4H), 4.97 (s, 1H), 7.30 (m, 2H), 7.53 (dd, 1H), 9.19 (br s, 1H); MS (APCI$^-$) *m/z* 432 (M − H)$^-$. Anal. ($C_{15}H_{13}BrFNO_4S_2$) C, H, N.

10-(3-Bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-2H,5*H*-dithiopyrano[3,2-*b*:2′,3′-*e*]pyridine 1,1,9,9-Tetraoxide (22). 3-Bromo-4-fluorobenzaldehyde (202 mg, 1.0 mmol), dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide (305 mg, 2.06 mmol), and 2.0 M NH_3 in EtOH (0.70 mL, 1.4 mmol) were heated in EtOH (3 mL) to 80 °C for 5 d in a sealed tube and cooled. The solid precipitate was collected and washed with ethanol. The solid in toluene (10 mL) was then heated to reflux overnight and cooled, and the solid was collected, washed with ethanol, and dried to provide 129 mg of compound **22** as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.17 (m, 4H), 2.50 (m, 4H), 3.18 (m, 4H), 5.09 (s, 1H), 7.24 (m, 2H), 7.38 (dd, 1H), 9.11 (s, 1H); MS (APCI$^-$) *m/z* 460 (M − H)$^-$. Anal. ($C_{17}H_{17}BrFNO_4S_2$) C, H, N.

(+)-(9*R*)-(3-Bromo-4-fluorophenyl)-5,5-dimethyl-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (23) and (−)-(9*S*)-(3-bromo-4-fluorophenyl)-5,5-dimethyl-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (24). 3-Methoxy-4,4-dimethyl-2-cyclohexen-1-one. A stirred solution of 4,4-dimethyl-1,3-cyclohexanedione (3.04 g, 21.7 mmol) and *p*-TsOH·H_2O (413 mg, 2.17 mmol) in MeOH (40 mL) was heated at reflux for 2 h. The reaction mixture was cooled and concentrated to give an oily residue. The residue was purified by flash chromatography (elution with 3% MeOH/EtOAc) to provide 805 mg of 3-methoxy-4,4-dimethyl-2-cyclohexen-1-one as a colorless liquid: ^{1}H NMR (DMSO-d_6) δ 1.12 (s, 6H), 1.83 (t, 3H, J = 7.1 Hz), 2.42 (t, 3H, J = 7.1 Hz), 3.68 (s, 3H), 5.26 (s, 1H); MS (DCI/NH_3) m/z 155 $(M + H)^+$.

3-Amino-4,4-dimethyl-2-cyclohexen-1-one. 3-Methoxy-4,4-dimethyl-2-cyclohexen-1-one in condensed anhydrous NH_3 (50 mL) was heated at 100 °C (850 psi) for 34 h. Ammonia was removed by evaporation, and the residue was dissolved in EtOAc (5 mL) and filtered through Florisil to provide 1.14 g of 3-amino-4,4-dimethyl-2-cyclohexen-1-one as a pale tan oil: ^{1}H NMR (DMSO-d_6) δ 1.11 (s, 3H), 1.18 (s, 3H), 1.67 (t, 3H, J = 7.1 Hz), 2.15 (t, 3H, J = 7.1 Hz), 4.83 (s, 1H), 6.59 (br s, 2H); MS (DCI/NH_3) m/z 139 $(M + H)^+$.

9-(3-bromo-4-fluorophenyl)-5,5-dimethyl-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide. A stirred solution of 3-bromo-4-fluorobenzaldehyde (725 mg, 3.57 mmol), 3-amino-4,4-dimethyl-2-cyclohexen-1-one (496 mg, 3.57 mmol), and tetrahydrothiophene-3-oxo-1,1-dioxide (473 mg, 3.57 mmol) in EtOH (30 mL) was heated at reflux for 96 h. The reaction mixture was cooled and concentrated to give a yellow residue which was redissolved in EtOH (30 mL) and treated with 2 M HCl in Et_2O (2.0 mL). The solution was heated at reflux for 9 h and then cooled to ambient temperature, and the white solid that precipitated was triturated with EtOAc. The solid was purified by flash chromatography (elution with 8% MeOH/CH_2Cl_2) to provide 267 mg of the title compound as an off-yellow solid: mp >270 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 3H), 1.34 (s, 3H), 1.83−1.92 (m, 2H), 2.14−2.21 (m, 1H), 2.36−2.45 (m 1H), 2.89−2.97 (m, 1H), 3.03−3.11 (m, 1H), 3.29−3.44 (m, 2H), 4.85 (s, 1H), 7.13−7.26 (m, 2H), 7.35−7.39 (m, 1H), 9.40 (br s, 1H); MS (DCI/NH_3) m/z 457 $(M + NH_4)^+$. The racemic product from above was chromatographed on an (*R*,*R*)-Whelk-O1 column (2.1 cm × 25 cm), with gradient elution with 3% MeOH−CH_2Cl_2 (2:1)/hexanes to 25% MeOH−CH_2Cl_2 (2:1)/hexanes, to provide compound **23**: t_R = 53 min; $[\alpha]^{23}_D$ +17.6° (c 0.4, DMSO); mp > 270 °C; ^{1}H NMR (DMSO-d_6) δ 0.89 (s, 3H), 0.98 (s, 3H), 1.75 (t, 2H, J = 6.1 Hz), 2.50−2.64 (m, 2H), 2.68−3.07 (m, 3H), 3.29−3.41 (m, 1H), 4.80 (s, 1H), 7.13−7.32 (m, 2H), 7.38 (dd, 1H, J = 6.7, 2.0 Hz), 9.69 (br s, 1H); MS (DCI/NH_3) m/z 457 $(M + NH_4)^+$. Anal. ($C_{19}H_{19}BrFNO_3S$) C, H, N. Also obtained was compound **24**: t_R = 49 min; $[\alpha]^{23}_D$ −19.9° (c = 0.6, DMSO); mp >270 °C; ^{1}H NMR (DMSO-d_6) δ 0.89 (s, 3H), 0.98 (s, 3H), 1.75 (t, 2H, J = 6.1 Hz), 2.50−2.64 (m, 2H), 2.68−3.07 (m, 3H), 3.29−3.41 (m, 1H), 4.80 (s, 1H), 7.13−7.32 (m, 2H), 7.38 (dd, 1H, J = 6.7, 2.0 Hz), 9.69 (br s, 1H); MS (DCI/NH_3) m/z 457 $(M + NH_4)^+$. Anal. ($C_{19}H_{19}BrFNO_3S$) C, H, N.

(+)-(9*R*)-(3-Bromo-4-fluorophenyl)-6,6-dimethyl-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (25) and (−)-(9*S*)-(3-Bromo-4-fluorophenyl)-6,6-dimethyl-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (26). A stirred solution of 3-bromo-4-fluorobenzaldehyde (725 mg, 3.57 mmol), 5,5-dimethyl-1,3-cyclohexanedione (501 mg, 3.57 mmol), and dihydrothiophen-3(2*H*)-one 1,1-dioxide (473 mg, 3.57 mmol) in EtOH (30 mL) was heated at reflux for 48 h. The reaction mixture was cooled and concentrated. The resulting yellow residue was redissolved in ethanol (30 mL) and treated with 2 M HCl in Et_2O (2.0 mL). The solution was then heated at reflux for 9 h and cooled to ambient temperature, and the white solid that precipitated was triturated with EtOAc. The solid was purified by flash chromatography (elution with 8% MeOH/CH_2Cl_2) to provide 9-(3-bromo-4-fluorophenyl)-6,6-dimethyl-2,3,5,6,7,9-hexahydrothieno[3,2-b]quinolin-8(*4H*)-one 1,1-dioxide (534 mg, 34%) as an off-yellow solid. The racemic material was resolved by chiral HPLC using an (*R*,*R*)-Whelk-O 1 column (2.1 cm × 25 cm), with gradient elution with 3% MeOH−CH_2Cl_2 (2:1)/hexanes to 25% MeOH−CH_2Cl_2 (2:1)/hexanes to provide **26** as the less polar enantiomer (149 mg, t_R = 44 min): $[\alpha]^{23}_D$ = −42.2° (c = 0.1, DMSO); mp 251−252 °C; ^{1}H NMR (DMSO-d_6) δ 9.74 (br s, 1H), 7.39 (dd, 1H, J = 6.7, 2.0 Hz), 7.26−7.17 (m, 2H), 4.80 (s, 1H), 3.12−2.99 (m, 2H), 2.90−2.88 (m, 2H), 2.50 (br s, 2 H), 2.14 (br s, 2 H), 2.13 (AB q, 2H, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 28.9 Hz), 1.03 (s, 3H), 0.92 (s, 3H); MS (DCI/NH_3) m/z 440 $(M + H)^+$. Anal. ($C_{19}H_{19}BrFNO_3S$) C, H, N. Also obtained was 25 as the more polar enantiomer (163 mg, t_R = 56 min): $[\alpha]^{23}_D$ = +39.9° (c = 0.2, DMSO); mp 250−252 °C; ^{1}H NMR (DMSO-d_6) δ 9.74 (br s, 1H), 7.39 (dd, 1H, J = 6.7, 2.0 Hz), 7.26−7.17 (m, 2H), 4.80 (s, 1H), 3.12−2.99 (m, 2H), 2.90−2.88 (m, 2H), 2.50 (br s, 2 H), 2.14 (br s, 2 H), 2.13 (AB q, 2H, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 28.9 Hz), 1.03 (s, 3H), 0.92 (s, 3H); MS (DCI/NH_3) m/z 440 $(M + H)^+$. Anal. ($C_{19}H_{19}BrFNO_3S$) C, H, N.

(+)-(9*R*)-(3-Bromo-4-fluorophenyl)-7,7-dimethyl-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (27) and (−)-(9*S*)-(3-Bromo-4-fluorophenyl)-7,7-dimethyl-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (28). A stirred solution of 3-bromo-4-fluorobenzaldehyde (725 mg, 3.57 mmol), 4,4-dimethyl-1,3-cyclohexanedione (500 mg, 3.57 mmol), and dihydrothiophen-3(2*H*)-one 1,1-dioxide (479 mg, 3.57 mmol) in EtOH (40 mL) was treated with anhydrous NH_4OAc (330 mg, 4.29 mmol), and the mixture was heated at reflux for 60 h. The reaction mixture was cooled to room temperature, and the white solid that precipitated was isolated by filtration. The solid was triturated sequentially with 10% EtOAc/EtOH, Et_2O, and then 25% Et_2O/EtOH to provide 543 mg of the racemic title compound as a white solid: mp >270 °C; ^{1}H NMR (DMSO-d_6) δ 0.89 (s, 3H), 0.98 (s, 3H), 1.75 (t, 2H, J = 6.1 Hz), 2.50−2.640 (m, 2H), 2.68−3.07 (m, 3H), 3.29−3.41 (m, 1H), 4.80 (s, 1H), 7.13−7.32 (m, 2H), 7.38 (dd, 1H, J = 6.7, 2.0 Hz), 9.69 (br s, 1H); MS (DCI/NH_3) m/z 457 $(M + NH_4)^+$. The racemic product from above was chromatographed on an (*R*,*R*)-Whelk-O1 column (2.1 cm × 25 cm), with gradient elution with 3% MeOH−CH_2Cl_2 (2:1)/hexanes to 25% MeOH−CH_2Cl_2 (2:1)/hexanes to provide compound **27**: t_R = 47 min. $[\alpha]^{23}_D$ +30.5° (c = 0.6, DMSO); mp >270 C; ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 3H), 1.34 (s, 3H), 1.83−1.92 (m, 2H), 2.14−2.21 (m, 1H), 2.36−2.45 (m 1H), 2.89−2.97 (m, 1 H), 3.03−3.11 (m, 1 H), 3.29−3.44 (m, 2H), 4.85 (s, 1H), 7.13−7.26 (m, 2H), 7.35−7.39 (m, 1H), 9.40 (br s, 1H); MS (DCI/NH_3) m/z 457 $(M + NH_4)^+$. Anal. ($C_{19}H_{19}BrFNO_3S$) C, H, N. Also obtained was compound **28**: t_R = 41 min; $[\alpha]^{23}_D$ −21.6° (c 0.5, DMSO); mp >270 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 3H), 1.34 (s, 3H), 1.83−1.92 (m, 2H), 2.14−2.21 (m, 1H), 2.36−2.45 (m 1H), 2.89−2.97 (m, 1 H), 3.03−3.11 (m, 1 H), 3.29−3.44 (m, 2H), 4.85 (s, 1H), 7.13−7.26 (m, 2H), 7.35−7.39 (m, 1H), 9.40 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 199.2, 157.9, 155.5, 151.4, 144.4, 143.3, 142.2, 132.6, 128.7, 116.2, 113.0, 107.1, 48.8, 33.9, 33.4, 24.7, 24.1, 23.4, 22.8; MS (DCI/NH_3) m/z 457 $(M + NH_4)^+$. Anal. ($C_{19}H_{19}BrFNO_3S$) C, H, N.

7-(3-Bromo-4-fluorophenyl)-5-methyl-2,3,4,7-tetrahydrothieno[3,2-*b*]pyridine-6-carbonitrile 1,1-Dioxide (29). 3-Bromo-4-fluorobenzaldehyde (1.02 g, 5.00 mmol), dihydrothiophen-3(2*H*)-one 1,1-dioxide (0.67 g, 5.0 mmol), and 3-aminocrotononitrile (0.41 g, 5.0 mmol) in MeOH (10 mL) were heated at 65 °C for 2 d and cooled. The solvent was evaporated and the crude product purified by flash chromatography over silica gel eluting with MeOH:CH_2Cl_2 (5:95) to provide 520 mg of compound **29** as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H), 2.72−3.04 (m, 2H), 3.31−3.40 (m, 2H), 4.78 (s, 1H), 7.34 (m, 2H), 7.59 (d, 1H), 9.84 (s, 1H); MS (ESI^-) m/z 383 $(M - H)^-$. Anal. ($C_{15}H_{12}BrFN_2O_2S$) C, H, N.

Methyl 7-(3-Bromo-4-fluorophenyl)-5-methyl-2,3,4,7-tetrahydrothieno[3,2-*b*]pyridine-6-carboxylate 1,1-Dioxide (30). 3-Bromo-4-fluorobenzaldehyde (2.03 g, 10.0 mmol), methyl 3-aminocrotonate (1.15 g, 10.0 mmol), and dihy-

drothiophen-3(2*H*)-one 1,1-dioxide (1.29 g, 9.60 mmol) in MeOH (30 mL) were heated at 65 °C overnight. The white precipitate was collected, washed with acetone, dried, and then heated to reflux in MeOH (30 mL) with 1.0 M HCl in Et_2O (10 mL) for 2 h. The reaction was cooled and solvent evaporated. The solid was triturated with Et_2O, collected, washed with Et_2O, and dried to provide 2.88 g of compound **30** as a white solid: mp 232−234 °C; ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 2.75−3.05 (m, 2H), 3.28−3.35 (m, 2H), 3.52 (s, 3H), 4.87 (s, 1H), 7.19 (m, 1H), 7.26 (t, 1H), 7.48 (d, 1H), 9.50 (s, 1H); MS (ESI$^-$) *m*/*z* 416 (M − H)$^-$. Anal. ($C_{16}H_{15}BrFNO_4S$) C, H, N.

Ethyl 7-(3-Bromo-4-fluorophenyl)-5-methyl-2,3,4,7-tetrahydrothieno[3,2-*b*]pyridine-6-carboxylate 1,1-Dioxide (31). Ethyl 3-aminocrotonate was treated according to the procedure of compound **30** to provide compound **31**: ^{1}H NMR (DMSO-d_6) δ 1.07 (t, 3H), 2.28 (s, 3H), 2.80 (m, 1H), 2.96 (m, 1H), 3.35 (m, 2H), 3.95 (m, 2H), 4.87 (s, 1H), 7.20 (ddd, 1H), 7.28 (t, 1H), 7.39 (dd, 1H), 9.49 (s, 1H); MS (ESI$^-$) *m*/*z* 428 (M − H)$^-$. Anal. ($C_{17}H_{17}BrFNO_4S$) C, H, N.

Ethyl 7-(3-Bromo-4-fluorophenyl)-5-(trifluoromethyl)-2,3,4,7-tetrahydrothieno[3,2-*b*]pyridine-6-carboxylate 1,1-Dioxide (32). Ethyl 4,4,4-trifluoroacetoacetate (368 mg, 2.0 mmol), 3-bromo-4-fluorobenzaldehyde (406 mg, 2 mmol), dihydrothiophen-3(2*H*)-one 1,1-dioxide (268 mg, 2.0 mmol), and 2 M NH_3/EtOH (2 mL) were heated in EtOH to 80 °C overnight in a sealed tube and cooled, and an intermediate hemiaminal was collected as a solid precipitate (370 mg). The intermediate was heated to reflux in toluene with catalytic *p*-TsOH for 6 h and cooled, and the solvent was evaporated and the crude flash chromatographed (5% MeOH/CH_2Cl_2) to provide 125 mg of compound **32**: mp 200−202 °C; ^{1}H NMR (DMSO) δ 1.05 (t, 3H), 2.88−3.08 (m, 2H), 3.37 (t, 2H), 4.01 (q, 2H), 4.96 (s, 1H), 7.28 (m, 1H), 7.34 (t, 1H), 7.50 (d, 1H), 9.98 (s, 1H); MS (ESI$^+$) *m*/*z* 482 (M + H)$^+$ Anal. ($C_{17}H_{14}BrF_4NO_4S$) C, H, N.

7-(3-Bromo-4-fluorophenyl)-5-methyl-2,3,4,7-tetrahydrothieno[3,2-*b*]pyridine-6-carboxylic Acid 1,1-Dioxide (33). Compound **30** (416 mg, 1.00 mmol) in CH_2Cl_2 (4 mL) at 0 °C was treated with 1.0 M BCl_3 in CH_2Cl_2 (6 mL), allowed to warm to room temperature, stirred 4 h, diluted with ice−water (50 mL), and extracted with EtOAc (4×). The organic extracts were dried ($MgSO_4$) and filtered, and solvent was evaporated. The crude material was triturated with EtOAc, and the solid precipitate collected, washed with EtOAc, and dried to provide 271 mg of compound **33** as a yellow solid: mp 220−223 °C; ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 2.23−3.02 (m, 2H), 3.30−3.40 (m, 2H), 4.84 (s, 1H), 7.18 (m, 1H), 7.28 (t, 1H), 7.37 (d, 1H), 9.39 (s, 1H), 11.97 (s, 1H); MS (ESI$^-$) *m*/*z* 400 (M − H)$^-$. Anal. ($C_{15}H_{13}BrFNO_4S$) C, H, N.

1-[8-(3-Bromo-4-fluorophenyl)-3,4,5,8-tetrahydro-6-methyl-1,1-dioxido-2*H*-thiopyrano[3,2-*b*]pyridin-7-yl)]-ethan-1-one (34). A solution of dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide (179 mg, 1.21 mmol), 3-bromo-4-fluorobenzaldehyde (246 mg, 1.21 mmol), and 4-amino-3-penten-2-one (120 mg, 1.21 mmol) in EtOH (4 mL) was heated to reflux for 24 h and cooled. The solid that precipitated was collected, washed with ethanol, and dried to provide 325 mg of compound **34** as a white solid: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 2.17 (m, 2H), 2.20 (s, 3H), 2.30 (s, 3H), 2.50 (m, 2H), 3.20 (m, 2H), 5.06 (s, 1H), 7.20 (m, 2H), 7.40 (dd, 1H), 9.11 (s, 1H); MS (APCI$^-$) *m*/*z* 412 (M − H)$^-$. Anal. ($C_{17}H_{17}BrFNO_3S$) C, H, N.

7-(3-Bromo-4-fluorophenyl)-5-(trifluoromethyl)-2,3,4,7-tetrahydrothieno[3,2-*b*]pyridine 1,1-Dioxide (38). 4-(3-Bromo-4-fluorophenyl)-1,1,1-trifluoro-3-buten-2-one (35). To 3-bromo-4-fluorobenzaldehyde (406 mg, 2.0 mmol) in benzene (10 mL) with piperidine (0.08 mL), and AcOH (0.01 mL) was added 1,1,1-trifluoroacetone (1.8 mL, 20 mmol) to the bottom of the vessel by syringe. The reaction vessel was sealed and heated to 50 °C overnight. The solvents were evaporated, and the residue was flash chromatographed over silica gel eluting with hexane:EtOAc (4:1) to provide 226 mg of the title compound: ^{1}H NMR ($CDCl_3$) δ 6.95 (d, 1H), 7.21 (t, 1H), 7.58 (m, 1H), 7.85 (d, 1H), 7.87 (dd, 1H). Compound **35** (800 mg, 2.69 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide (361 mg, 2.69 mmol), and 2.0 M NH_3/EtOH (2.1 mL) in EtOH (5 mL) were heated to reflux overnight. The solvent was evaporated, and the residue was dissolved in toluene, treated with *p*-TsOH (cat.), and heated to reflux for 1 h. The solvent was evaporated and the crude product flash chromatographed over silica gel eluting with MeOH:CH_2Cl_2 (5:95) to provide 630 mg of **38** as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.84 (m, 1H), 2.98 (m, 1H), 3.3 (m, 2H), 4.81 (s, 1H), 5.42 (s, 1H), 7.33 (m, 2H), 7.56 (d, 1H), 9.57 (br s, 1H); MS (APCI+) *m*/*z* 429 (M + NH_4)$^+$. Anal. ($C_{14}H_{10}BrF_4NO_2S$) C, H, N.

(9*S*)-(4-Fluoro-3-iodophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (41). 3-Amino-4-fluorobenzoic acid (15 g, 97 mmol) in THF at 0 °C was treated with 1.0 M BH_3·THF (50 mL), stirred overnight at room temperature, treated with an additional 130 mL of 1.0 M BH_3·THF, stirred 10 h, quenched by the addition of MeOH, and stirred for 3 h at room temperature. The solvent was evaporated, the product was partitioned between aqueous $NaHCO_3$/CH_2Cl_2, and the organic layer was dried (Na_2SO_4) and filtered. The solvent was evaporated and the product was purified by flash chromatography over silica gel (EtOAc/hexane 1:1) to provide 7.0 g of 3-amino-4-fluorobenzyl alcohol. ^{1}H NMR ($CDCl_3$) δ 4.58 (s, 2H), 6.67 (br m, 1H), 6.81 (d, 1H), 6.95 (t, 1H). 3-Amino-4-fluorobenzyl alcohol (7.0 g, 50 mmol) in water (100 mL) at 0 °C was treated slowly with concentrated H_2SO_4 (30 mL) at a rate to maintain the temperature below 10 °C and then treated dropwise with an aqueous solution of $NaNO_2$ (3.45 g, 50 mmol). This solution was then added to a solution of KI (8.13 g, 50 mmol) in water (15 mL). The reaction was heated to 60 °C for 2 h, cooled, and extracted with CH_2Cl_2. The organics were washed with 10% NaOH, 1 M $Na_2S_2O_3$, 10% HCl, and aqueous $NaHCO_3$, dried (Na_2SO_4), and filtered, and solvent was evaporated. The material was purified by flash chromatography over silica gel (EtOAc/hexane 7:3) to provide 6.4 g of 4-fluoro-3-iodobenzyl alcohol: ^{1}H NMR ($CDCl_3$) δ 1.69 (t, 1H), 4.66 (d, 2H), 7.05 (t, 1H), 7.60 (d, 1H), 7.78 (dd, 1H). 4-Fluoro-3-iodobenzyl alcohol (6.4 g, 26 mmol) in $CHCl_3$ (300 mL) was treated with MnO_2 (4.5 g, 50 mmol), stirred overnight, treated with an additional portion of MnO_2 (2.25 g), stirred overnight, and filtered, and the solvent was evaporated. The material was purified by flash chromatography over silica gel (EtOAc/hexane 1:4) to provide 1.9 g of 4-fluoro-3-iodobenzaldehyde: ^{1}H NMR ($CDCl_3$) δ 7.23 (t, 1H), 7.89 (m, 1H), 8.32 (dd, 1H), 9.91 (s, 1H). 4-Fluoro-3-iodobenzaldehyde (0.25 g, 1.0 mmol) was processed according to method A to provide 0.20 g of the title compound as the racemate: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.88 (m, 2H), 2.22 (m, 2H), 2.62 (m, 2H), 2.7 (m, 1H), 3.02 (m, 1H), 3.45 (m, 2H),4.81 (s, 1H), 7.12 (m, 1H), 7.18 (m, 1H), 7.55 (dd, 1H), 9.81 (s, 1H); MS (ESI$^+$) *m*/*z* 460 (M + H)$^+$. Anal. Calcd for $C_{17}H_{15}FINO_3S$: C, 44.45; H, 3.29; N, 3.04. Found: C, 44.51; H, 3.31; N, 2.97. (312678) The racemic compound (110 mg) was chromatographed over a Regis WhelkO-1 2 × 25 cm chiral column eluting with hexane: MeOH:CH_2Cl_2 (60:27:13) at a flow rate of 10 mL/min to provide 45 mg of the less polar enantiomer, compound **41**, as an off-white solid: $[\alpha]^{20}_D$ −47.3° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.80−1.95 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 2.75−3.08 (m, 2H), 3.30−3.35 (m, 2H), 4.81 (s, 1H), 7.12 (t, 1H), 7.18 (m, 1H), 7.54 (d, 1H), 9.79 (s, 1H); MS (ESI$^+$) *m*/*z* 460 (M + H)$^+$; MS (ESI$^-$) *m*/*z* 458 (M − H)$^-$. Anal. ($C_{17}H_{15}FINO_3S$ 0.1C_6H_{14}) C, H, N.

(−)-(9*S*)-(3-Chloro-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (42). 3-Chloro-4-fluorobenzaldehyde (264 mg, 1.66 mmol) was treated according to method A to provide 317 mg of the racemic title compound as a white solid: mp >260 °C ^{1}H NMR (DMSO-d_6) δ 1.73−1.96 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 2.82 (dt, 1H), 3.02 (dt, 1H), 3.46 (m, 2H), 4.85 (s, 1H), 7.17 (m, 1H), 7.28 (m, 2H), 9.75 (br s, 1H); MS (APCI$^-$) *m*/*z* 366 (M − H)$^-$. Anal. Calcd for $C_{17}H_{15}ClFNO_3S$: C, 55.51; H, 4.11; N, 3.80. Found: C, 55.24; H, 3.97; N, 3.85. The racemic compound was processed according to method C to provide compound **42**: mp >250 °C; $[\alpha]^{23}_D$ −49.57 (*c* = 0.56, DMSO); ^{1}H NMR (DMSO-d_6) δ 1.86 (m, 2H), 2.22 (m, 2H), 2.56 (m, 2H), 2.85 (m, 1H), 3.05 (m, 1H), 3.35 (m, 2H), 4.85 (s, 1H), 7.18 (m, 1H), 7.28 (m, 2H),

9.88 (s, 1H); MS (ESI$^+$) *m/z* 368 (M + H)$^+$. Anal. ($C_{17}H_{15}ClFNO_3S$) C, H, N.

(−)-(9*S*)-(3,4-Difluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (43). 3,4-Difluorobenzaldehyde (110 μL, 1.00 mmol) was treated according to method A to provide 151 mg of the racemic title compound as an off-white solid: ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 2.82 (dt, 1H), 3.02 (dt, 1H), 3.35 (m, 2H), 4.86 (s, 1H), 7.02 (m, 1H), 7.15 (ddd, 1H), 7.29 (dt, 1H), 9.79 (br s, 1H); MS (APCI) *m/e* 352 (M + H)$^+$. Anal. Calcd for $C_{17}H_{15}F_2NO_3S$: C, 58.11; H, 4.30; N, 3.99. Found: C, 57.90; H, 3.96; N, 3.88. The racemic compound (1.2 g, 3.4 mmol) was processed according to method C to provide 200 mg of compound **43**. mp >250; $[\alpha]^{23}_D$ −34.0 (*c* = 0.70, DMSO); ^{1}H NMR (DMSO-d_6) δ 1.88 (m, 2H), 2.25 (m, 2H), 2.55 (m, 2H), 2.82 (m, 1H), 3.02 (m, 1H), 3.35 (m, 2H), 4.85 (s, 1H), 7.03 (m, 1H), 7.15 (m, 1H), 7.28 (m, 1H), 9.82 (s, 1H); MS (ESI$^+$) *m/z* 352 (M + H)$^+$. Anal. ($C_{17}H_{15}F_2NO_3S$) C, H, N.

(−)-(9*S*)-(3-Iodo-4-methylphenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-dioxide (44). To a slurry of 3-iodo-4-methylbenzoic acid (1.0 g, 3.96 mmol) in 1:1 CH_2Cl_2–THF (200 mL) was added oxalyl chloride (1 mL, 11.9 mmol) and several drops of DMF. The reaction was heated to 65 °C for 30 min, cooled to room temperature, and concentrated to form a light yellow solid that was dissolved in THF (200 mL), treated with a solution of LiAlH(O^{t}Bu) (4.1 mL, 4.1 mmol) at −78 °C, stirred 30 min, and treated with a solution of saturated Rochelle's salt to quench the reaction at −78 °C. The mixture was warmed to room temperature, the layers were separated, the organic layer was washed with 1 N HCl, sat. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated, and the resulting residue was purified by flash chromatography (hexane/EtOAc 4:1) to yield 3-iodo-4-methylbenzaldehyde as a white solid (300 mg, 18%). 3-Iodo-4-methylbenzaldehyde (300 mg, 1.63 mmol) was treated according to method A to provide 314 mg of the racemic title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.75−1.94 (m, 4H), 2.20−2.24 (m, 2H), 2.28 (s, 3H), 2.83−2.86 (m, 1H), 2.96−3.06 (m, 1H), 3.2−3.5 (m, 2H), 4.76 (s, 1H), 7.08 (dd, 1H, *J* = 7.67,1.47 Hz), 7.17 (d, 7.67H), 7.56 (d, 1.47H), 9.76 (s, 1H); MS (ESI$^-$) *m/z* 454 (M − H)$^-$. The racemate was chromatographed on a Regis Whelk-O1 chiral column eluting with hexane:MeOH:CH_2Cl_2 (50:34:16) to provide compound **44** as the less polar enantiomer: $[\alpha]^{20}_D$ −53.6° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.75−1.94 (m, 4H), 2.20−2.24 (m, 2H), 2.28 (s, 3H), 2.83−2.86 (m, 1H), 2.96−3.06 (m, 1H), 3.2−3.5 (m, 2H), 4.76 (s, 1H), 7.08 (dd, 1H, *J* = 7.67,1.47 Hz), 7.17 (d, 7.67H), 7.56 (d, 1.47H), 9.76 (s, 1H); MS (ESI$^-$) *m/z* 454 (M − H)$^-$. Anal. ($C_{18}H_{18}INO_3S$ 0.5H_2O) C, H, N.

(−)-(9*S*)-(3-Bromo-4-methylphenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (45). 3-Bromo-4-methylbenzaldehyde (0.70 g, 3.5 mmol) was treated according to method A to provide 0.87 g of the racemic title compound: ^{1}H NMR (DMSO-d_6) δ 1.76−1.94 (m, 2H), 2.17−2.24 (m, 2H), 2.26 (s, 3H), 2.49−2.57 (m, 2H), 2.78−2.85 (m, 1H), 2.98−3.04 (m, 1H), 3.25−3.35 (m, 2H), 4.80 (s, 1H), 7.07 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.19 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 1.5 Hz); MS (ESI$^+$) *m/z* 410, 408 (M + H)$^+$. The racemate (600 mg) was chromatographed on a 2 × 25 cm Regis Whelk-O1 column, eluting with hexane:MeOH:CH_2Cl_2 (65:24:11) as the mobile phase at a flow rate of 10 mL/min to provide 250 mg of compound **45**, the less polar enantiomer, as a white solid: $[\alpha]^{20}_D$ −73.66° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.76−1.94 (m, 2H), 2.17−2.24 (m, 2H), 2.26 (s, 3H), 2.49−2.57 (m, 2H), 2.78−2.85 (m, 1H), 2.98−3.04 (m, 1H), 3.25−3.35 (m, 2H), 4.80 (s, 1H), 7.07 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.19 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 1.5 Hz); MS (ESI$^+$) *m/z* 410, 408 (M + H)$^+$. Anal. ($C_{18}H_{18}BrNO_3S$·0.75H_2O) C, H, N.

(−)-(9*S*)-(3-Bromo-4-chlorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (46). 3-Amino-4-chlorobenzaldehyde. 4-Chloro-3-nitrobenzaldehyde (4.00 mg, 21.6 mmol) in CH_2Cl_2 (150 mL) at 23 °C was treated with water (50 mL) and *N*,*N*′-diheptyl-4,4′-bipyridinium dibromide (220 mg, 10 mg/mmol of substrate). The biphasic mixture was cooled to 5 °C and treated with a solution of sodium dithionite (15.0 g, 86.0 mmol) and K_2CO_3 (13.4 g, 87.0 mmol) in water (45 mL). The cooling bath was removed and the biphasic mixture stirred vigorously at 23 °C for 4 h. The mixture was partitioned between additional CH_2Cl_2 (75 mL) and water (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (75 mL). The organic portions were washed with brine (75 mL) and dried (Na_2SO_4). The residue was treated with EtOAc (25 mL) and silica gel (75 g) and the suspension was filtered through a small pad of Celite, rinsing with 10% EtOAc/CH_2Cl_2 (15 mL). The filtrate was concentrated to provide 3-amino-4-chlorobenzaldehyde as an off-yellow powder (3.44 g, 22%): MS (DCI/NH_3) *m/e* 218 (M + NH_4)$^+$.

3-Bromo-4-chlorobenzaldehyde. The product from above (3.4 g, 22 mmol) in concentrated 48% aqueous HBr (20 mL) at 0 °C was treated with a 0 °C solution of $NaNO_2$ (1.5 g, 22 mmol) in water (30 mL). The reaction mixture was stirred for 30 min and then transferred cold to a stirred solution of CuBr (4.44 g, 31 mmol) in 48% aqueous HBr (20 mL) at 23 °C (significant frothing!). Water (40 mL) was added, the solution was heated at 60 °C for 45 min, cooled, diluted with EtOAc (200 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2×, 50 mL). The organic layers were combined, washed with 1 M HCl (2×, 100 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to provide 3-bromo-4-chlorobenzaldehyde as a pale yellow powder (3.9 g, 82%). 3-Bromo-4-chlorobenzaldehyde (650 mg, 2.96 mmol) was treated according to method A to provide 842 mg of the title compound as a racemate. Resolution of this material by chiral HPLC using an (*R*,*R*)-Whelk-O 1 column (2.1 cm × 25 cm), eluting with 40% MeOH−CH_2Cl_2 (2:1)/hexanes (10 mL/min), afforded compound **46**, the less polar enantiomer (*t* = 31 min): mp >270 C; $[\alpha]^{23}_D$ = −26.1° (*c* = 0.3, DMSO); ^{1}H NMR (DMSO-d_6) δ 1.70−1.91 (m, 2H), 2.14−2.23 (m, 2H), 2.43−2.55 (m, 3H), 3.32−3.40 (m, 1H), 2.78 (dt, 1H, *J* = 17.0, 6.6 Hz), 2.98 (dt, 1H, *J* = 17.0, 6.6 Hz), 4.78 (s, 1H), 7.15 (dd, 1H, *J* = 8.1, 2.2 Hz), 7.22 (d, 1H, *J* = 2.4 Hz), 7.24 (d, 1H, *J* = 8.0 Hz), 9.80 (br s, 1H); MS (DCI/NH_3) *m/z* 445 (M + NH_4)$^+$. Anal. ($C_{17}H_{15}BrClNO_3S$) C, H, N.

(−)-(9*S*)-(3,4-Dibromophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (47). 3,4-Dibromobenzaldehyde (1.58 g, 6.00 mmol) was treated according to method A to provide 1.8 g of the racemic title compound. mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.25 (m, 2H), 2.60 (m, 2H), 2.85 (m, 1H), 3.02 (m, 1H), 3.38 (m, 2H), 4.80 (s, 1H), 7.12 (dd, 1H, *J* = 3, 9 Hz), 7.48 (d, 1H, *J* = 3 Hz), 7.62 (d, 1H, *J* = 9 Hz), 9.85 (s, 1H); MS (ESI$^+$) *m/z* 474 (M + H)$^+$. The racemic title compound (180 mg) was separated into the individual enantiomers using the HPLC conditions of compound **53** to provide 44 mg of compound **47**, the less polar enantiomer: mp >250 °C; $[\alpha]^{20}_D$ −50.1° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.25 (m, 2H), 2.60 (m, 2H), 2.86 (m, 1H), 3.02 (m, 1H), 3.38 (m, 2H), 4.80 (s, 1H), 7.12 (dd, 1H, *J* = 3, 9 Hz), 7.48 (d, 1H, *J* = 3 Hz), 7.62 (d, 1H, *J* = 9 Hz), 9.85 (br, s, 1H); MS (ESI$^+$) *m/z* 474 (M + H)$^+$. Anal. ($C_{17}H_{15}Br_2NO_3S$) C, H, N.

(−)-(9*S*)-(3-Bromo-4-trifluoromethylphenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (48). [3-Nitro-4-(trifluoromethyl)phenyl]methanol. α,α,α-Trifluoromethyl-*p*-toluic acid (15 g, 78.9 mmol) in 90 mL of concentrated H_2SO_4 was treated dropwise with a mixture of fuming HNO_3 (2 mL) and H_2SO_4 (24 mL). The reaction mixture was stirred at room temperature for 48 h and quenched into ice−water, and the precipitate (12 g) was collected (mixture of nitration products and unreacted starting material), washed with water, and dried under reduced pressure. The resulting dry solid was dissolved in THF (300 mL), cooled to 0 °C, treated with 1 M BH_3·THF complex (80 mL), and stirred at room temperature overnight. The mixture was treated carefully with MeOH (5 mL) and then concentrated HCl (5 mL), refluxed for 1 h, evaporated to dryness, and partitioned between water and Et_2O. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 30% EtOAc /hexanes to provide

[3-nitro-4-(trifluoromethyl)phenyl]methanol (3.6 g, 20% yield): ^{1}H NMR ($CDCl_3$) δ 4.9 (s, 2H), 7.7 (d, 1H), 7.8 (d, 1H), 7.9 (s, 1H).

[3-Amino-4-(trifluoromethyl)phenyl]methanol. The product from above (3.6 g, 16.28 mmol) in MeOH (100 mL) was hydrogenated in the presence of a catalytic amount of Pd/C for 4 h. The catalyst was filtered off, and the volatiles were evaporated to yield 2.7 g of [3-amino-4-(trifluoromethyl)phenyl]-methanol: ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 2H), 6.75 (m, 2H), 7.5 (d, 1H).

[3-Bromo-4-(trifluoromethyl)phenyl]methanol. [3-Amino-4-(trifluoromethyl)phenyl]methanol (0.76 g, 4 mmol) in water (8 mL) at 0 °C was treated with concentrated H_2SO_4 (3 mL) and then treated dropwise with an aqueous solution of $NaNO_2$ (0.41 g, 6 mmol), and the temperature was kept below 10 °C. After stirring for 1 h, this solution was added to a solution of CuBr (0.85 g, 5 mmol) in 48% HBr (50 mL). The reaction mixture was heated at 60 °C for 3 h, cooled to room temperature, and partitioned between water and EtOAc. The organic layer was washed with aqueous Na_2CO_3, dried ($MgSO_4$), and concentrated to provide [3-bromo-4-(trifluoromethyl)phenyl]-methanol contaminated with approximately 30% of 2-bromo-4-(bromomethyl)-1-(trifluoromethyl)benzene.

3-Bromo-4-(trifluoromethyl)benzaldehyde. The crude product from above in $CHCl_3$ (100 mL) was treated with MnO_2 (1.1 g, 12.6 mmol), stirred overnight, filtered, and concentrated. The residue was chromatographed on silica gel (15% EtOAc/hexanes) to provide 0.28 g of 3-bromo-4-(trifluoromethyl)-benzaldehyde: ^{1}H NMR ($CDCl_3$) δ 7.9 (m, 2H), 8.2 (s, 1H), 10.02 (s, 1H). 3-Bromo-4-trifluoromethyl-benzaldehyde (0.35 g,1.5 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide (0.2 g, 1.5 mmol), and 3-amino-2-cyclohexene-1-one (0.17 g, 1.5 mmol) were heated in EtOH (4 mL) to 80 °C in a sealed tube for 2 d. The reaction mixture was cooled, solvent evaporated, and the residue flash chromatographed on silica gel (10% EtOH/CH_2Cl_2 to give a hemiaminal (0.37 g) that was suspended in EtOH (30 mL) and heated to reflux for 3 h with 1 M HCl/Et_2O (1 mL). The reaction mixture was concentrated and chromatographed on silica gel (10% EtOH/CH_2Cl_2) to yield 0.27 g of the title compound as a racemate. Separation of enantiomers was accomplished on a Welk-O1 column, eluting with CH_2Cl_2:MeOH:hexane (5:10:85) to yield 0.09 g of compound **48** as the less polar enantiomer: $[\alpha]^{20}_D$ −34.0° (DMSO); ^{1}H NMR (DMSO) δ 1.9 (m, 2H), 2.23 (m, 2H), 2.58 (m, 2H), 2.85 (m, 2H), 3.0.5 (m, 2H), 4.9 (s, 1H), 7.49 (d, 1H), 7.6 (s, 1H), 7.72 (d, 1H), 9.89 (s, 1H); MS (ESI$^-$) *m*/*z* 462 $(M - 1)^-$ Anal. ($C_{18}H_{15}NBrF_3O_3S$) C, H, N.

(−)-(9*S*)-(4-Methyl-3-nitrophenyl)-2,3,5,6,7,9-hexahydro-[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (49). 4-Methyl-3-nitrobenzaldehyde (165 mg, 1.00 mmol) was treated according to method A to provide 196 mg of the racemic title compound: ^{1}H NMR (DMSO-d_6) δ 1.88 (m, 2H), 2.23 (m, 2H), 2.45 (s, 3H), 2.56 (m, 2H), 2.85 (dtd, 1H), 3.03 (dt, 1H), 3.35 (m, 2H), 4.93 (s, 1H), 7.36 (d, 1H), 7.45 (dd, 1H), 7.72 (d, 1H), 9.83 (br s, 1H); MS (APCI) *m/e* 375 $(M + H)^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5S \cdot 0.25H_2O$: C, 57.06; H, 4.92; N, 7.39. Found: C, 57.24; H, 4.77; N, 7.23. The racemic title compound (1.24 g, 3.32 mmol) was separated into the individual enantiomers using the HPLC conditions for compound **14** to provide 63 mg of compound **49**, the less polar enantiomer, as a white solid: $[\alpha]^{20}_D$ −39.3° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.82 (m, 1H), 1.90 (m, 1H), 2.23 (m, 2H), 2.45 (s, 3H), 2.54 (m, 2H), 2.84 (dt, 1H), 3.03 (dt, 1H), 3.35 (m, 2H), 4.91 (s, 1H), 7.37 (d, 1H), 7.45 (dd, 1H), 7.71 (d, 1H), 9.87 (br s, 1H); MS (APCI-) *m*/*z* 373 $(M - H)^-$. Anal. ($C_{18}H_{18}N_2O_5S$) C, H, N.

9-(4-Ethyl-3-nitrophenyl)-2,3,5,6,7,9-hexahydrothieno-[3,2-*b*]quinolin-8(4*H*) -one 1,1-Dioxide (50). 4-Ethyl-3-nitrobenzaldehyde[33] (0.165 g, 1.00 mmol) was treated according to method A to provide 0.145 g of compound **50**: ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H),1.88 (m, 2H), 2.25 (m, 2H), 2.53 (m, 2H),2.75 (q, 2H),2.85 (m, 1H), 3.0 (m, 1H), 4.91 (s, 1H), 7.39 (d, 1H), 7.47 (dd, 1H), 7.62 (d, 1H), 9.84 (s, 1H); MS (ESI$^-$) *m*/*z* 387 $(M - H)^-$. Anal. ($C_{19}H_{20}N_2O_5S$) C, H, N.

(−)-(9*S*)-(4-Chloro-3-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (52). 4-Chloro-3-fluorobenzaldehyde (0.95 g, 6.0 mmol) was treated according to method A to provide the racemic title compound: mp >250; ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.26 (m, 2H), 2.54 (m, 2H), 2.86 (m, 1H), 3.02 (m, 1H), 3.38 (m, 2H), 4.86 (s, 1H), 7.05 (dd, 1H, J = 1.5,9.0 Hz), 7.14 (dd, 1H, J = 1.5;9.0 Hz), 7.48 (t, 1H, J = 9.0 Hz), 9.85 (s, 1H); MS (ESI$^+$) *m*/*z* 368 $(M + H)^+$. The racemate was chromatographed on a 2 × 25 cm Regis Whelk-O1 column, eluting with hexane:MeOH:CH_2Cl_2 (60:27:13) as the mobile phase at a flow rate of 10 mL/min to provide compound **52**, the less polar enantiomer: mp > 250; $[\alpha]^{20}_D$ −77.1° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.26 (m, 2H), 2.54 (m, 2H), 2.86 (m, 1H), 3.02 (m, 1H), 3.38 (m, 2H), 4.86 (s, 1H), 7.05 (dd, 1H, J = 1.5, 9.0 Hz), 7.14 (dd, 1H, J = 1.5;9.0 Hz), 7.48 (t, 1H, J = 9.0 Hz), 9.85 (s, 1H); MS (ESI$^+$) *m*/*z* 368 $(M + H)^+$. Anal. ($C_{17}H_{15}ClFNO_3S$) C, H, N.

(9*S*)-(3-Cyano-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (53). 1,1-Dimethylethyl9-(3-Bromo-4-fluorophenyl)-8-oxo-3,5,6,7,8,9-hexahydrothieno[3,2-*b*]quinoline-4(2*H*)-carboxylate 1,1-Dioxide (40). A solution of 9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-dioxide (racemic **14**, 1.0 g, 2.4 mmol), Boc_2O (1.0 g, 24 mmol), and DMAP (29 mg, 0.1 mmol) in MeCN was heated to reflux for 1 h, cooled to room temperature, concentrated, and purified by flash chromatography on silica gel (1:1 EtOAc/hexane) to provide 900 mg of compound **40**: ^{1}H NMR (DMSO-d_6) δ 1.57 (s, 9H), 1.90−2.00 (m, 2H), 2.3−2.5 (m, 2H), 3.00 (m, 2H), 3.45 (m, 2H), 3.50 (m, 2H), 4.83 (s, 1H), 7.20 (m, 1H), 7.32 (t, 1H), 7.37 (dd, 1H). Compound **40** (200 mg, 0.390 mmol) and $ZnCN_2$ were reacted according to method D to provide the racemic compound 53 that was chromatographed (60 mg) on a 2 × 25 cm Regis Whelk-O1 column, eluting with hexane:MeOH:CH_2Cl_2 (60:27:13) as the mobile phase at a flow rate of 10 mL/min to provide 18 mg of the less polar enantiomer, compound **53**, as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.8−2.0 (m, 2H), 2.19−2.30 (m, 2H), 2.51 (m, 2H), 2.85 (m, 2H), 2.9−3.1 (m, 2H), 4.91 (s, 1H), 7.40 (t, 1H, J = 8.83 Hz), 7.60−7.76 (m, 2H), 9.98 (s, 1H); MS (ESI$^+$) *m*/*z* 359 $(M + H)^+$. Anal. ($C_{18}H_{15}FN_2O_3S \cdot 0.5H_2O$) C, H, N.

9-(4-Fluoro-3-methylphenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (54). 3-Methyl-4-fluorobenzaldehyde[34] (77 mg, 0.56 mmol), dihydrothiophen-3(2*H*)-one 1,1-dioxide (68 mg, 0.51 mmol), 3-aminocyclohex-2-en-1-one (55 mg, 0.50 mmol), and Et_3N (35 μL) were heated in EtOH (2 mL) to 80 °C in a sealed tube for 48 h and cooled, and the solvent was evaporated. The crude reaction product was flash chromatographed over silica gel (MeOH:CH_2Cl_2 7:93) to provide 92 mg of an intermediate hemiaminal that was heated to reflux in EtOH (6 mL), treated with 1.0 M HCl/Et_2O (0.5 mL), heated for 1 h, and cooled, and the solid precipitate was collected, washed with EtOH, and dried to provide 55 mg of compound **54** as a white solid: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 1.70−1.98 (m, 2H), 2.22 (m, 2H), 2.54 (m, 2H), 2.80 (dt, 1H), 2.99 (dt, 1H), 3.33 (t, 2H), 4.80 (s, 1H), 6.91−7.07 (m, 3H), 9.74 (br s, 1H); MS (APCI$^-$) *m*/*z* 346 $(M - H)^-$. Anal. ($C_{18}H_{18}FNO_3S$) C, H, N.

(−)-(9*S*)-[4-Fluoro-3-(trifluoromethyl)phenyl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (55). 4-Fluoro-3-trifluoromethylbenzaldehyde (1.9 g, 5.4 mmol) was treated according to methods A and C to provide 312 mg of compound **55**: mp >250 °C; $[\alpha]^{23}_D$ −50.26 (c = 0.59, DMSO); ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.23 (m, 2H), 2.56 (m, 2H), 2.88 (m, 1H), 3.05 (m, 1H), 3.35 (t, 2H, J = 9 Hz), 4.92 (s, 1H), 7.38 (m, 1H), 7.51 (m, 2H), 9.95 (s, 1H); MS (ESI$^+$) *m*/*z* 402 $(M + H)^+$. Anal. ($C_{18}H_{15}F_4NO_3S$) C, H, N.

9-[4-Methyl-3-(methylsulfanyl)phenyl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (56). 2-(3-Bromo-4-methylphenyl)-1,3-dioxolane. To a solution of 3-bromo-4-methylbenzaldehyde (10.0 g, 50.5 mmol) in benzene (100 mL) was added ethylene glycol (10 mL) and *p*-TsOH (0.05 g). The reaction was heated at reflux for 4 h and water was removed as an azeotrope with benzene using a

Dean−Stark apparatus. The reaction was cooled to room temperature, diluted with EtOAc (100 mL), and quenched with aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated to provide 11.5 g of 2-(3-bromo-4-methylphenyl)-1,3-dioxolane as an oil: ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3H), 3.91−4.07 (m, 4H), 5.71 (s, 1H), 7.32−7.39 (m, 2H), 7.60 (d, J = 1.5 Hz, 1H).

2-[4-Methyl-3-(methylsulfanyl)phenyl]-1,3-dioxolane. To a solution of the dioxolane product from above (6.95 g, 28.7 mmol) in dry THF (100 mL) at −78 °C was added *n*-BuLi (19.7 mL of 1.6 M, 31.5 mmol), and the reaction stirred for 30 min at −78 °C, at which point a solution of Me_2S_2 (4.05 g, 43.0 mmol) in THF (10 mL) was added dropwise over 10 min. The reaction was allowed to stir at −78 °C for 30 min and then warmed to room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with EtOAc (2 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to provide 5.0 g of 2-[4-methyl-3-(methylsulfanyl)phenyl]-1,3-dioxolane: ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3H), 2.46 (s, 3H), 3.91−4.07 (m, 4H), 5.70 (s, 1H), 7.12 (dd, J = 7.8, 1.5 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 1.5 Hz, 1H).

4-Methyl-3-(methylsulfanyl)benzaldehyde. To a solution of the above product (1.4 g, 6.7 mmol) in MeCN (50 mL) was added 2.0 M HCl (50 mL) and the reaction mixture was allowed to stir for 2 h at room temperature. The reaction mixture was poured onto a mixture of ice and saturated aqueous $NaHCO_3$ and diluted with EtOAc, and the layers were separated. The organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (hexanes/EtOAc 5:1) to provide 1.1 g of 4-methyl-3-(methylsulfanyl)benzaldehyde: ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H), 2.55 (s, 3H), 7.42 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 7.8, 1.5 Hz, 1H), 7.70 (d, J = 1.5 Hz, 1H), 9.98 (s, 1H). The aldehyde product from above (0.77 g, 4.64 mmol) was treated according to method A to provide 0.725 g compound **56**: ^{1}H NMR (DMSO-d_6) δ 1.78−1.96 (m, 2H), 2.13 (s, 3H), 2.19−2.25 (m, 2H), 2.39 (s, 3H), 2.48−2.55 (m, 2H), 2.75−2.85 (m, 1H), 2.94−3.04 (m, 1H), 3.25−3.38 (m, 2H), 4.84 (s, 1H), 6.82 (dd, 1H, J = 7.5,2.0 Hz), 7.00 (d, 1H, J = 2.0 Hz), 7.01 (d, 1H, J = 7.5 Hz), 9.71 (s, 1H); MS (ESI$^+$) m/z 376 (M + H)$^+$. Anal. ($C_{19}H_{21}NO_3S_2 \cdot 0.2H_2O$) C, H, N.

9-[4-Methyl-3-(methylsulfonyl)phenyl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (57). 4-Methyl-3-(methylsulfonyl)benzaldehyde. To a solution 2-[4-methyl-3-(methylsulfanyl)phenyl]-1,3-dioxolane (see previous text) (3.6 g, 17.1 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added mCPBA (11.81 g, 68.4 mmol) and the reaction stirred for 30 min at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, and the organic layer was dried (Na_2SO_4), filtered, and concentrated to provide 3.8 g of an intermediate sulfone (3.8 g, 15.7 mmol) that was dissolved in MeCN (50 mL) and treated with 2.0 M HCl (50 mL). The reaction mixture was stirred for 2 h at room temperature, quenched in cold, saturated aqueous $NaHCO_3$, extracted with EtOAc, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes/EtOAc 2:1) to provide 2.2 g of 4-methyl-3-(methylsulfonyl)benzaldehyde: ^{1}H NMR (DMSO-d_6) δ 2.75 (s, 3H), 3.30 (s, 3H), 7.72 (d, J = 7.8 Hz, 1H), 8.13 (dd, J = 7.8, 1.7 Hz, 1H), 8.41 (d, J = 1.7 Hz, 1H), 10.07 (s, 1H). The aldehyde product from above (0.80 g, 4.04 mmol) was treated according to method A to provide 0.425 g of the title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.83−1.99 (m, 2H), 2.16−2.26 (m, 2H), 2.50−2.60 (m, 2H), 2.56 (s, 3H), 2.78−2.88 (m, 1H), 2.94−3.04 (m, 1H), 3.13 (s, 3H), 3.29−3.39 (m, 2H), 4.90 (s, 1H), 7.32 (d, 1H, J = 7.8 Hz), 7.39 (dd, 1H, J = 7.8, 2.0 Hz), 7.73 (d, 1H, J = 2.0 Hz), 9.81 (s, 1H); MS (ESI$^+$) m/z 408 (M + H)$^+$. Anal. ($C_{19}H_{21}NO_5S_2 \cdot H_2O$) C, H, N.

9-(3-Acetyl-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno-[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (58). 9-[3-(1-Ethoxyvinyl)-4-fluorophenyl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]-quinolin-8(4*H*)-one 1,1-Dioxide. Compound **40** (100 mg, 0.195 mmol) and tributyl(1-ethoxyvinyl)tin were processed by method D to provide 54.2 mg of the title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.10 (m, 2H), 1.32 (t, 3H, J = 7.01 Hz), 1.60 (m, 2H), 1.80−1.99 (m, 2H), 2.2 (m, 2H), 2.80 (m, 1H), 3.00 (m, 1H), 3.86 (q, 2H, J = 7.01 Hz), 4.48 (d, 1H, J = 2.5 Hz), 4.55 (d, 1H, J = 2.5 Hz), 4.83 (s, 1H), 7.03−7.20 (m, 2H), 7.41 (dd, 1H, J = 7.31, 1.90 Hz), 9.78 (s, 1H); MS (ESI$^+$) m/z 404 (M + H)$^+$. Anal. Calcd for $C_{21}H_{22}FNO_4S$: C, 62.51; H, 5.50; N, 3.47. Found: C, 59.95; H, 5.28; N, 3.13. The intermediate enol ether from above (108 mg, 0.27 mmol) in Et_2O at 0 °C was treated with 1.0 M HCl/Et_2O (1 mL, 1 mmol), stirred for 2 h, treated with saturated $NaHCO_3$, and extracted with EtOAc. The residue was purified by flash chromatography on silica gel eluting with 5% MeOH/CH_2Cl_2, followed by recrystallization from EtOH, to provide 93 mg of compound **58**. ^{1}H NMR (DMSO-d_6) δ 1.8 (m, 2H), 2.2 (m, 2H), 2.5 (m, 2H), 2.55 (s, 3H), 2.8 (m, 2H), 3.0 (m, 2H), 4.89 (s, 1H), 7.21 (dd, 1H, J = 8.5, 2.94 Hz), 7.48 (m, 1H), 7.60 (m, 1H), 9.82 (s, 1H); MS (ESI$^+$) m/z 376 (M + H)$^+$. Anal. ($C_{19}H_{18}FNO_4S \cdot 0.25H_2O$) C, H, N.

(−)-(9*S*)-[4-Fluoro-3-(2-furyl)phenyl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (60). Compound **40** (200 mg, 0.39 mmol) and 2-(tributylstannyl)furan were processed by method D to provide 64 mg of the racemic title compound: ^{1}H NMR (DMSO-d_6) δ 1.96 (m, 2H), 2.2 (m, 2H), 2.5 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 4.88 (s, 1H), 6.6 (dd, 1H, J = 3.31, 1.47 Hz), 6.81 (t, 1H, J = 3.68 Hz), 7.15 (m, 2H), 7.58 (dd, 1H, J = 7.19, 2.21 Hz), 7.85 (d, 1H, J = 1.8 Hz), 9.80 (s, 1H); MS (ESI$^+$) m/z 400 (M + H)$^+$. The racemic compound was chromatographed on a 2 × 25 cm Regis Whelk-O1 column, eluting with hexane:MeOH:CH_2Cl_2 (78:14:8) as the mobile phase at a flow rate of 10 mL/min to provide 40 mg of compound **60**, the less polar enantiomer, as a white solid: $[\alpha]^{20}_D$ −54.95° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.96 (m, 2H), 2.2 (m, 2H), 2.51 (m, 2H), 2.82 (m, 2H), 3.03 (m, 2H), 4.88 (s, 1H), 6.6 (dd, 1H, J = 3.31, 1.47 Hz), 6.81 (t, 1H, J = 3.68 Hz), 7.15 (m, 2H), 7.58 (dd, 1H, J = 7.19, 2.21 Hz), 7.85 (d, 1H, J = 1.8 Hz), 9.80 (s, 1H); MS (ESI$^+$) m/z 400 (M + H)$^+$. Anal. ($C_{21}H_{18}FNO_4S \cdot 0.5H_2O$) C, H, N.

9-[4-Fluoro-3-(2-thienyl)phenyl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (61). Compound **40** (200 mg, 0.39 mmol) and 2-(tributylstannyl)-thiophene were processed by method D to provide 119 mg of compound **61** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.9 (m, 2H), 2.22 (m, 2H), 2.52 (m, 2H), 2.86 (m, 2H), 3.00 (m, 2H), 4.90 (s, 1H), 7.08−7.21 (m, 4H), 7.48−7.51 (m, 2H), 7.66 (d, 1H, J = 5.15 Hz), 9.81 (s, 1H); MS (ESI$^+$) m/z 333 (M + H)$^+$. Anal. ($C_{21}H_{18}FNO_3S_2$) C, H, N.

9-[4-Fluoro-3-(3-pyridinyl)phenyl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (62). Compound **40** (200 mg, 0.390 mmol) and 3-(tributylstannyl)pyridine were processed by method D to provide 89 mg of compound **62** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.8−1.95 (m, 2H), 2.20−2.30 (m, 2H), 2.8 (m, 1H), 3.0 (m, 1H), 4.95 (s, 1H), 7.20−7.30 (m, 2H), 7.34 (d, 1H, J = 7.5 Hz), 7.52 (d, 1H, J = 7.5 Hz), 7.92 (m, 1H), 8.61 (m, 1H), 8.68 (s, 1H), 9.79 (s, 1H); MS (ESI$^+$) m/z 411 (M + H)$^+$. Anal. ($C_{22}H_{19}FN_2O_3S$ $0.75H_2O$) C, H, N.

9-[6-Fluoro-(1,1′-biphenyl)-3-yl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (63). Compound **40** (200 mg, 0.39 mmol) and tetraphenyltin were processed by method D to provide 95 mg of compound **63**: ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.25 (m, 2H), 2.5 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 4.92 (s, 1H), 7.16 (m, 1H), 7.18 (s, 1H), 7.27 (d, 1H, J = 6.6 Hz), 7.40 (m, 1H), 7.48 (s, 2H), 7.49 (s, 2H), 9.77 (s, 1H); MS (ESI$^+$) m/z 410 (M + H)$^+$. Anal. ($C_{23}H_{20}FNO_3S$ H_2O) C, H, N.

(−)-(9*S*)-(2,1,3-Benzoxadiazol-5-yl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (64). 2,1,3-Benzoxadiazole-5-carboxaldehyde[35] (0.296 g, 2.00 mmol) was treated according to method A to provide 0.42 g of the racemic title compound: ^{1}H NMR (DMSO-d_6) δ 1.9 (m, 2H), 2.25 (m, 2H), 2.55 (m, 2H), 2.88 (m, 1H), 3.05 (m, 1H), 3.4 (m, 2H), 5.0 (s, 1H), 7.51 (d, 1H), 7.7 (s, 1H), 7.95 (d, 1H), 9.96 (s, 1H); MS (ESI$^+$) m/z 358 (M + H)$^+$. The racemate (1.34 g) was processed according to method C to provide 110 mg of compound **64** as a white solid: $[\alpha]^{23}_D$ −41.7° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.9 (m, 2H), 2.25 (m, 2H), 2.57 (m, 2H), 2.9 (m, 1H), 3.05 (m,

1H), 3.4 (m, 2H), 5.0 (s, 1H), 7.51 (d, 1H), 7.7 (s, 1H), 7.95 (d, 1H), 9.95 (s, 1H); MS (ESI$^-$) *m/z* 356 (M − H)$^-$. Anal. ($C_{17}H_{15}N_3O_4S$) C, H, N.

(9*S*)-(2,1,3-Benzothiadiazol-5-yl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-dioxide (65). 5-Bromomethylbenzo-2,1,3-thiadiazole. 5-Methylbenzo-2,1,3-thiadiazole (5.0 g, 33 mmol), NBS (5.92 g, 33.3 mmol), and catalytic AIBN were heated at reflux for 16 h in $CHCl_3$ (75 mL). The reaction mixture was cooled and the resulting precipitate was filtered off and discarded. The filtrate was evaporated and recrystallized from EtOH to provide 4.8 g of 5-bromomethylbenzo-2,1,3-thiadiazole: ^{1}H NMR ($CDCl_3$) 4.65 (s, 2H), 7.65 (dd, 1H), 8.01 (d, 2H).

5-Hydroxymethylbenzo-2,1,3-thiadiazole. 5-Bromomethylbenzo-2,1,3-thiadiazole (4.8 g) and $CaCO_3$ (10 g) were heated at reflux in 1:1 dioxane/water (120 mL) for 3 h. The solvents were evaporated, and the residue was partitioned between 2 N HCl and CH_2Cl_2. The organic layers were dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/hexane) to provide 2.66 g of 5-hydroxymethylbenzo-2,1,3-thiadiazole: ^{1}H NMR ($CDCl_3$) 1.92 (t, 1H), 4.9 (d, 1H), 7.6 (dd, 1H), 8.0 (m, 2H).

2,1,3-benzothiadiazole-5-carboxaldehyde. 5-Hydroxymethylbenzo-2,1,3-thiadiazole (2.6 g, 16 mmol) and MnO_2 (6.0 g, 64 mmol) in $CHCl_3$ (150 mL) were stirred at room temperature overnight. The reaction mixture was filtered and the filtrate evaporated to provide 1.9 g of 2,1,3-benzothiadiazole-5-carboxaldehyde: ^{1}H NMR ($CDCl_3$) 8.12 (s, 2H), 8.51 (m, 1H), 10. 21 (s, 1H). 2,1,3-Benzothiadiazole-5-carboxaldehyde (0.33 g, 2 mmol) was treated according to method A to provide 0.35 g of racemic 9-(2,1,3-benzothiadiazol-5-yl)-2,3,5,6,7,9-hexahydrothieno[3,2-b]quinolin-8(*4H*)-one 1,1-dioxide: ^{1}H NMR (DMSO-d_6) δ 1.87 (m, 2H), 2.22 (m, 2H), 2.56 (m, 2H), 2.87 (m, 1H), 3.05 (m, 1H), 3.32 (m, 2H), 5.06 (s, 1H), 7.61 (dd, 1H), 7.75 (s, 1H), 7.98 (d, 1H), 9.89 (s, 1H); MS (ESI$^-$) *m/z* 372 (M − H)$^-$. The racemate (0.14 g) was chromatographed on a Regis Whelk-O1 chiral column eluting with hexane:MeOH:CH_2Cl_2 (65:24:11) to provide 0.06 g of compound **65** as the less polar enantiomer: $[\alpha]^{20}_D$ −36.4° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.9 (m, 2H), 2.22 (m, 2H), 2.48 (m, 2H), 2.88 (m, 1H), 3.04 (m, 1H), 5.05 (s, 1H), 7.61 (dd, 1H), 7.75 (s, 1H), 7.98 (d, 1H), 9.9 (s, 1H); MS (ESI) *m/z* 372 (M − H)$^-$. Anal. ($C_{17}H_{15}N_3O_3S_2$) C, H, N.

9-(5-Bromo-4-fluoro-2-hydroxyphenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (66). 4-Fluoro-5-bromo-2-hydroxybenzaldehyde. 4-Fluoro-2-hydroxybenzaldehyde[36] (2.00 g, 14.3 mmol) in $CHCl_3$ (10 mL) was treated slowly with a solution of Br_2 (0.70 mL, 13 mmol) in $CHCl_3$ (6 mL) at room temperature. After the free Br_2 had disappeared, the mixture was refluxed with 20% NaOH (20 mL) for 4 h and cooled, the $CHCl_3$ evaporated, and the solid was dissolved in EtOAc and acidified with 1 N HCl (pH = 5). The solvents were evaporated, and the crude product was purified by flash chromatography over silica gel (hexane:EtOAc 6:1) to provide 1.95 g of 4-fluoro-5-bromo-2-hydroxybenzaldehyde: ^{1}H NMR ($CDCl_3$) δ 6.78 (d, 1H, *J* = 9 Hz), 7.75 (d, 1H, *J* = 9 Hz), 9.80 (s, 1H), 11.25 (s, 1H); MS (ESI$^+$) *m/z* 219 (M + H)$^+$. The aldehyde from above (657 mg, 3.00 mmol) was treated according to method A to provide 1.1 g of compound **66**: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.25 (m, 2H), 2.55 (m, 2H), 2.80 (m, 1H), 2.92 (m, 1H), 3.26 (t, 2H, *J* = 7.5 Hz), 5.10 (s, 1H), 6.6 (d, 1H, *J* = 12 Hz), 7.05 (d, 1H, *J* = 9 Hz), 9.70 (s, 1H), 10.25 (s, 1H); MS (ESI$^+$) *m/z* 429 (M + H)$^+$. Anal. ($C_{17}H_{15}BrFNO_4S$) C, H, N.

9-(5-Bromo-2-hydroxyphenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8 (4*H*)-one 1,1-Dioxide (67). 5-Bromosalicylaldehyde (0.201 g, 1.0 mmol) was treated according to method A to provide 0.13 g of compound **67** as an orange-yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.74−2.0 (m, 2H), 2.23 (m, 2H), 2.56 (m, 2H), 2.78 (dt, 1H), 2.95 (dt, 1H), 3.28 (t, 2H), 5.11 (s, 1H), 6.63 (d, 1H), 6.97 (d, 1H), 7.07 (dd, 1H), 9.70 (s, 1H), 9.73 (s, 1H); MS (APCI$^-$) *m/z* 408 (M − H)$^-$. Anal. ($C_{17}H_{16}BrNO_4S$) C, H, N.

9-[4,5-Dichloro-2-(hydroxymethyl)phenyl]-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-Dioxide (68). To 5,6-dichloro-3*H*-isobenzofuran-1-one[37] (6.0 g, 29.5 mmol) in toluene (500 mL) at −78 °C was added DIBAL (42.4 mL, 1.0 M in toluene) dropwise over 30 min. The reaction was stirred for 4 h and quenched with sat. Rochelle's salt (150 mL). After warming to room temperature, the solution was filtered, the solvent was removed in vacuo, and the residue partitioned between CH_2Cl_2 (200 mL) and water (200 mL). The organic layer was washed twice with water and brine and dried ($MgSO_4$) before filtration and concentration to give the crude aldehyde as a white solid (3.75 g, 62%). The lactol:hydroxyaldehyde ratio determined by proton NMR was 2:1. The aldehyde (1.50 g, 7.32 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide (0.98 g, 7.32 mmol), 3-amino-2-cyclohexene-1-one (0.81 g, 7.32 mmol), and Et_3N (1 mL) in EtOH (40 mL) were heated to reflux for 13 h. The red solution was concentrated in vacuo and the residue partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was dried (Na_2SO_4) before filtration and concentration to give a yellow-white solid that was dissolved in EtOH (30 mL), treated with 1.0 M HCl/Et_2O (1 mL), and stirred for 2 h. The solvent was evaporated to give a white solid which was washed with EtOAc and MeOH and dried to give 1.08 g of compound **68**: ^{1}H NMR (DMSO) δ 1.86 (m, 2H), 2.21 (m, 2H), 2.50−2.62 (m, 2H), 2.82 (m, 1H), 3.00 (m, 1H), 3.33 (m, 2H), 3.92 (1H, br s), 4.75 (d, 1H), 4.78 (s, 1H), 5.04 (d, 1H), 7.16 (s, 1H), 7.54 (s, 1H), 9.88 (s, 1H); MS (DCI) *m/z* 431 (30, M + NH_3), 414 (10, M$^+$), 187 (100). Anal. Calcd for $C_{18}H_{17}Cl_2NO_4S$ 0.5H_2O: C, 50.01; H, 4.43. Found: C, 50.46; H, 4.27.

(−)-(9*S*)-(3-Cyanophenyl)-2,3,5,6,7,9-hexahydrothieno-[3,2-*b*]quinolin-8(4*H*) -one 1,1-Dioxide (69). 3-Cyanobenzaldehyde (136 mg, 1.04 mmol) was treated according to the method A to provide 160 mg of the racemic title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.88 (m, 2H), 2.22 (m, 2H), 2.56 (m, 2H), 2.85 (dtd, 1H), 3.03 (dt, 1H), 3.36 (m, 2H), 4.90 (s, 1H), 7.45 (td, 1H), 7.54 (dd, 1H), 7.56 (d, 1H), 7.61 (dd, 1H), 9.81 (br s, 1H); MS (APCI) *m/e* 341 (M + H)$^+$. Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.73; N, 8.22. Found: C, 63.31; H, 4.61; N, 8.19. Racemate (1.27 g) was processed according to method C to provide 280 mg of compound **69**: mp >250 °C; $[\alpha]^{23}_D$ −33.77, (*c* = 0.53, DMSO); ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 2H), 2.20 (m, mH, *J* = 2 Hz), 2.55 (m, 2H), 2.85 (m, 1H), 3.05 (m, 1H), 3.32 (m, 2H), 4.90 (s, 1H), 7.45 (t, 1H, *J* = 7.5 Hz), 7.55 (d, 2H, *J* = 9 Hz), 7.62 (d, 1H, *J* = 7.5 Hz), 10.45 (s, 1H); MS (ESI$^+$) *m/z* 341 (M + H)$^+$. Anal. ($C_{18}H_{16}N_2O_3S$) C, H, N.

9-(3-Bromophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]-quinolin-8(4*H*)-one 1,1-Dioxide (70). 3-Bromobenzaldehyde was treated according to method A to provide compound **70**: ^{1}H NMR (DMSO) δ 1.89 (m, 2H), 2.21 (m, 2H), 2.55 (m, 2H), 2.82 (m, 1H), 3.0 (m, 1H), 3.32 (m, 2H), 4.81 (s, 1H), 7.18 (m, 1H), 7.3 (m, 2H), 9.8 (s, 1H); MS (ESI$^-$) *m/z* 394 (M − H)$^-$. Anal. ($C_{17}H_{16}NBrO_3S$) C, H, N.

9-(4-Bromophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]-quinolin-8(4*H*)-one 1,1-Dioxide (71). 4-Bromobenzaldehyde was treated according to method A to provide compound **71**: ^{1}H NMR (DMSO) δ 1.88 (m, 2H), 2.2 (m, 2H), 2.52 (m, 2H), 2.81 (m, 1H), 2.97 (m, 1H), 3.32 (m, 2H), 4.8 (s, 1H), 7.12 (d, 2H), 7.4 (d, 2H), 9.78 (s, 1H),; MS (ESI$^-$) *m/z* 394 (M − H)$^-$. Anal. ($C_{17}H_{16}NBrSO_3$) C, H, N.

8-(6-Cyano-2-pyridinyl)-2,3,4,5,6,8-hexahydro-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (72). 2-Cyano-6-formylpyridine[38] (140 mg, 1.06 mmol) was treated as in example **75** to provide 40 mg of compound **72** as a gray powder: ^{1}H NMR (DMSO) δ 2.32 (t, 2H), 2.6−3.1 (m, 4H), 3.4 (m, 2H), 5.77 (s, 1H), 7.65 (d, 1H), 7.88 (d, 1H), 7.95 (t, 1H), 10.37 (s, 1H); MS (APCI) *m/z* 328 (M + H)$^+$ Anal. ($C_{16}H_{13}N_3O_3S$·0.25H_2O·0.05HCl) C, H, N.

8-(4-Cyano-2-pyridinyl)-2,3,4,5,6,8-hexahydro-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (73). 4-Cyano-2-pyridinecarboxaldehyde[37] (40 mg, 0.30 mmol) was treated as in Example **75** with the solvent for the second step being 15% MeOH/CH_2Cl_2 to provide 11 mg of compound **73** as

a brown solid: mp 160 °C (dec); ^{1}H NMR (DMSO) δ 2.31 (m, 2H), 2.65 (m, 2H), 2.95 (m, 2H), 3.35 (m, 2H), 4.93 (s, 1H), 7.68 (d, 1H), 7.81 (s, 1H), 8.70 (d, 1H), 10.35 (s, 1H); MS (APCI$^+$) *m*/ *z* 328 (M + H)$^+$; MS (APCI$^-$) *m*/*z* 326 (M − H)$^-$. Anal. ($C_{16}H_{13}N_3O_3S\cdot0.15CH_2Cl_2\cdot1.5CH_4O$) C, H, N.

8-(5-Nitro-3-pyridinyl)-2,3,4,5,6,8-hexahydro-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (74). 5-Nitronicotinaldehyde[38] (120 mg, 0.80 mmol) was treated as in example **75** to provide 88 mg of compound **74** as a white solid: mp >260 °C; ^{1}H NMR (DMSO) δ 2.32 (m, 2H), 2.65 (m, 2H), 3.0 (m, 2H), 3.43 (m, 2H), 5.03 (s, 1H), 8.39 (s, 1H), 8.90 (s, 1H), 9.20 (s, 1H), 10.45 (s, 1H); MS (APCI$^+$) *m*/*z* 348 (M + H)$^+$; MS (APCI$^-$) *m*/*z* 346 (M − H)$^-$. Anal. ($C_{15}H_{13}N_3O_5S$) C, H, N.

8-(2-Cyano-4-pyridinyl)-2,3,4,5,6,8-hexahydro-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (75). Dihydrothiophen-3(2*H*)-one 1,1-dioxide (241 mg, 1.8 mmol), 3-aminocyclopent-2-en-1-one (146 mg, 1.5 mmol), and 2-cyano-4-pyridinecarboxaldehyde[38] (200 mg, 1.5 mmol) were heated to 40−50 °C in IPA for 3 days. Solvent was evaporated and the crude material flash chromatographed on silica gel (10% MeOH/CH_2Cl_2) to give an intermediate hemiaminal that was redissolved in IPA, treated with 1.5 mL of 1.0 M HCl/Et_2O, and heated to 50 °C for 10 min. The solvent was evaporated and the material triturated with Et_2O to provide 63 mg of compound **75** as a light yellow solid: mp 160 °C (dec); ^{1}H NMR (DMSO) δ 2.30 (t, 2H), 2.65 (m, 2H), 3.02 (m, 2H), 3.45 (t, 2H), 4.85 (s, 1H), 7.64 (d, 1H), 7.94 (s, 1H), 8.65 (d, 1H), 10.48 (s, 1H); MS (APCI); *m*/ *z* 326 (M − H)$^+$ Anal. ($C_{16}H_{13}N_3O_3S\cdot0.42C_4H_{10}O\cdot0.14HCl$) C, H, N.

2,3,4,5,6,8-Hexahydro-8-(5-nitro-3-thienyl)-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (76). 2-Nitrothiophene-4-carboxaldehyde (0.41 g, 2.6 mmol) was treated according to the procedure described in example **79** to provide 0.423 g of compound **76** as a brown powder: ^{1}H NMR (DMSO-d_6) δ 2.34 (t, 2H), 2.52−2.74 (m, 2H), 2.80−2.92 (m, 1H), 2.98−3.11 (m, 1H), 3.43 (t, 2H), 4.84 (s, 1H), 7.78 (d, 1H), 7.94 (d, 1H), 10.39 (s, 1H); MS (APCI$^+$) *m*/*z* 353 (M + H)$^+$, 370 (M + NH_4)$^+$; MS (APCI$^-$) *m*/*z* 351 (M − H)$^-$. Anal. ($C_{14}H_{12}N_2O_5S_2$) C, H, N.

8-(5-Bromo-2-thienyl)-2,3,4,5,6,8-hexahydro-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (77). 5-Bromothiophene-2-carboxaldehyde (500 mg, 2.6 mmol) was treated according to the procedure described for compound **79** to provide 0.297 g of compound **77** as a brown solid: mp 246−247 °C; ^{1}H NMR (DMSO-d_6) δ 2.35 (t, 2H), 2.52−2.73 (m, 2H), 2.78−2.90 (m, 1H), 2.95−3.08 (m, 1H), 3.41 (t, 2H), 4.92 (s, 1H), 6.73 (d, 1H), 6.97 (d, 1H), 10.39 (s, 1H); MS (APCI$^-$) *m*/*z* 384 (M − H)$^-$. Anal. ($C_{14}H_{12}NO_3S_2Br$) C, H, N.

2,3,4,5,6,8-Hexahydro-8-(5-nitro-2-thienyl)-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (78). 5-Nitrothiophene-2-carboxaldehyde (205 mg, 1.30 mmol) was treated according to the procedure described for compound **79** to provide 238 mg of compound **78** as a brown solid: mp 251−254 °C; ^{1}H NMR (DMSO-d_6) δ 2.37 (t, 2H), 2.56−2.78 (m, 2H), 2.83−2.96 (m, 1H), 3.01−3.14 (m, 1H), 3.46 (t, 2H), 5.07 (s, 1H), 7.10 (d, 1H), 7.97 (d, 1H), 10.59 (s, 1H); MS (APCI$^+$) *m*/*z* 353 (M + H)$^+$, 370 (M + NH_4)$^+$; MS (APCI$^-$) *m*/*z* 351 (M − H)$^-$. Anal. ($C_{14}H_{12}N_2O_5S_2$) C, H, N.

8-(4-Bromo-2-thienyl)-2,3,4,5,6,8-hexahydro-7*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridin-7-one 1,1-Dioxide (79). 4-Bromothiophene-2-carboxaldehyde (500 mg, 2.6 mmol), dihydrothiophen-3(2*H*)-one 1,1-dioxide (295 mg, 2.2 mmol), and 3-amino-2-cyclopenten-1-one (215 mg, 2.2 mmol) were heated in EtOH (5 mL) to 80 °C in a sealed tube for 2 d and cooled, and the solid precipitate was collected, washed with EtOH, dissolved in a solution of MeOH/CH_2Cl_2 1:3, filtered through cotton, concentrated on a steam bath, and allowed to crystallize to provide 0.34 g of compound **79** as a light brown solid: mp 254−255 °C; ^{1}H NMR (DMSO-d_6) δ 2.35 (t, 2H), 2.53−2.75 (m, 2H), 2.78−2.91 (m, 1H), 2.97−3.10 (m, 1H), 3.42 (t, 2H), 4.95 (s, 1H), 6.88 (d, 1H), 7.46 (d, 1H), 10.43 (bs, 1H); MS (APCI$^+$) *m*/*z* 386 (M + H)$^+$, 403 (M + NH_4)$^+$; MS (APCI$^-$) *m*/*z* 384 (M − H)$^-$. Anal. ($C_{14}H_{12}NO_3S_2Br$) C, H, N.

Supporting Information Available: X-ray crystal structure analysis of compounds **11**, **13**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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