Synthesis and Structure−Activity Relationships of a Novel Series of Tricyclic Dihydropyridine-Based K_{ATP} Openers That Potently Inhibit Bladder Contractions in Vitro

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Structure−activity relationships were investigated on a novel series of tricyclic dihydropyridine-containing K_{ATP} openers. This diverse group of analogues, comprising a variety of heterocyclic rings fused to the dihydropyridine nucleus, was designed to determine the influence on activity of hydrogen-bond-donating and -accepting groups and their stereochemical disposition. Compounds 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 subset of compounds. All compounds studied showed greater potency to inhibit spontaneous bladder contractions relative to their potencies to inhibit contractions elicited by electrical stimulation.

Introduction

ATP-sensitive potassium (K_{ATP}) channels play a critical role in linking cellular energy metabolism to membrane potential and cellular excitability.[1,2] Opening of K_{ATP} channels results in an efflux of potassium ions from the cell and an accompanying reduction in membrane potential (hyperpolarization) that restricts calcium entry through L-type calcium channels and dampens cellular excitability. K_{ATP} channels are heterooctameric complexes composed of four inwardly rectifying potassium channel (Kir) subunits that form the pore and four regulatory sulfonylurea receptor (SUR) subunits.[3,4] K_{ATP} channels are located in the pancreas, central nervous system, heart, skeletal muscle, and diverse smooth muscle tissues such as the bladder and peripheral vasculature. Recent molecular biological advances have resulted in the subclassification of the Kir and SUR subunits, with distinct combinations found in different tissues. For example, the pancreatic β-cell K_{ATP} that regulates insulin release is composed of the combination of SUR1 with Kir6.2. The SUR2A/Kir6.2 combination has been identified as the cardiac K_{ATP}, whereas the smooth muscle K_{ATP} consists of SUR2B with either Kir6.1 or Kir6.2. Additional splice variants of SUR1 and SUR2[5] have also been described.

There has been considerable interest in exploring K_{ATP} openers as therapeutic agents in the treatment of bladder overactivity, a condition that may be associated, in part, with the hyperexcitability of diseased bladder smooth muscle cells.[6,7] Although the K_{ATP} openers cromakalim (**1**, Figure 1) and ZD6169 (**2**) have both been studied in clinical trials for overactive bladder (OAB), definitive proof of efficacy in a placebo-controlled trial has not been demonstrated for either agent.[8] Cromakalim was dropped from further study due to unspecified animal toxicity, and **2** was also reportedly discontinued from development in favor of another K_{ATP} opener, ZD0947.[9] Thus, it remains to be established whether the K_{ATP}-opening mechanism can ameliorate the symptoms of OAB. Also, given the initial interest in K_{ATP} openers as antihypertensives, it is expected that hypotensive effects may limit dosing.

Preclinically, the focus continues to be directed toward identifying agents with selective actions on the bladder and minimal cardiovascular effects. The arylsquarate K_{ATP} openers WAY-133537 (**3**)[10] and WAY-151616 (**4**)[11] have been reported to inhibit spontaneous, diseased bladder contractions in rats and to have improved therapeutic indexes (TIs) with respect to hypotensive effects compared to **2**. The acridinedione ZM244085 (**5**) has also been reported to inhibit bladder function in rats without effects on blood pressure.[12]

The reported bladder selective actions of **5** make it an attractive lead from which to design novel K_{ATP} openers. In our accompanying paper we describe initial SAR studies in this area that led to the discovery of **6** (A-278637). Those efforts focused on extensive modifications of the aromatic ring substitution as well as an examination of ring sizes and stereochemistry. The present studies greatly extend the SAR of the tricyclic dihydropyridine (DHP) core structure in the form of diverse heterocyclic ring combinations. The SAR studies described herein were conducted exclusively with the 3-bromo-4-fluoro substitution pattern on the aromatic ring as this had previously been found to impart high potency. The primary focus of these investigations was to examine the effect of insertion of hydrogen-bond-donating or -accepting groups in the rings flanking the

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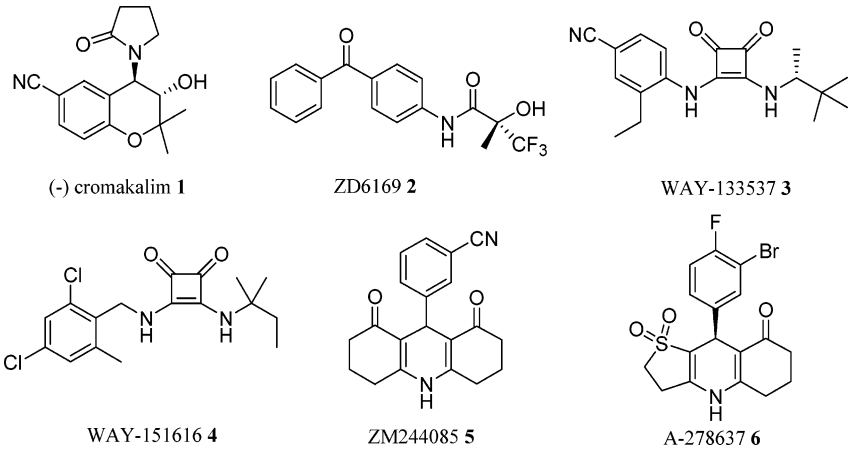


Figure 1.

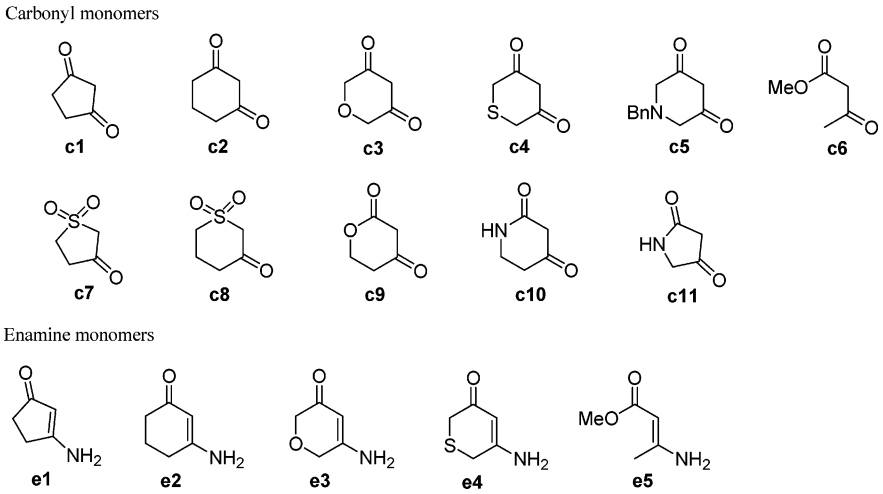


Figure 2.

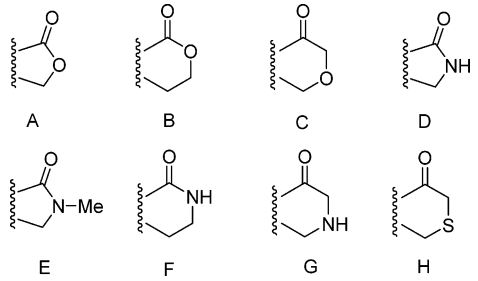


Figure 3.

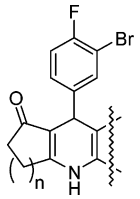
dihydropyridine but in positions other than the 2-, 3-, 5-, or 6-position of the dihydropyridine. A variety of unique combinations of heteroatoms either on one or both sides of the dihydropyridine core (see Figures 2 and 3 and the structures accompanying Tables 1−3 for the types of ring systems to be discussed) were prepared and evaluated for K_{ATP} activity in both cell- and tissue-based assays.

Chemistry

Final compounds and intermediates containing a dihydropyridine ring were prepared using the Hantzsch dihydropyridine synthesis (Scheme 1, method A). An array of carbonyl (**c1**−**c11**) and enamine (**e1**−**e5**) monomers (Figure 2) were reacted to create diverse combinations of the core structure, with the final compounds obtained by this method indicated in Scheme 1. Several piperidine-containing compounds (**37**, **38**, **48**, **51**, **56**) encountered in this discussion were prepared via the intermediacy of an *N*-benzyl derivative that was debenzylated via the respective vinylchloroformates (see the Experimental Section for details). In the preparation of **32** and **33**, the initial Hantzsch reaction provided an intermediate that necessitated treatment with HCl to effect conversion to the racemic dihydropyridine (method B). Certain symmetrical target compounds (**40**, **47**, **48**) were prepared directly through reaction of 2 equiv of the cyclic dione with an aldehyde and ammonia source (see method C in the Experimental Section).

Final compounds containing a γ-lactone were prepared by bromination and cyclization of an intermediate bicyclic dihydropyridine (Scheme 2, method D). Similarly, γ-lactams were prepared from the same intermediates by reacting the bromo intermediate with a primary amine or ammonia (method E). Final compounds prepared by these methods are shown in Scheme 2. For the preparation of single enantiomers containing either a γ-lactone or γ-lactam, a bicyclic intermediate was derivatized as the ester with mandelic acid to produce a mixture of diastereomers that were separable through silica gel chromatography (Scheme 3, method F). Transesterification led to the enantiomerically pure methyl ester intermediate that was transformed to the γ-lactones and γ-lactams using methods D and E, respectively, from Scheme 2. The combination of methods F and E was utilized in parallel fashion to explore

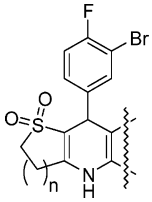
Table 1



compd	n	ring fusion	stereochem	pEC50 GPB[a,e]	pEC50 FSLPD[b,f]
7	1	A	R	6.94(0.11)[d]	6.67 ± 0.04
8	1	A	S	7.65(0.18)[d]	6.57 ± 0.19
9	2	A	R	6.40(0.39)[d]	5.96 ± 0.09
10	2	A	S	8.20(0.16)[d]	6.87 ± 0.24
11	1	B	rac	7.17(0.03)[c]	NT
12	2	B	rac	7.10(0.01)[c]	7.03 ± 0.04
13	1	C	rac	7.50(0.21)[d]	NT
14	2	C	rac	7.45(0.03)[d]	NT
15	2	D	R	6.68(0.27)[d]	5.85 ± 0.14
16	2	D	S	5.96(0.38)[c]	5.16 ± 0.26
17	1	E	R	6.94(0.25)[d]	6.69 ± 0.22
18	1	E	S	5.58(0.41)[d]	NT
19	2	E	R	6.85(0.17)[d]	5.94 ± 0.13
20	2	E	S	6.50(0.18)[c]	6.29 ± 0.07
21	1	F	rac	6.75(0.41)[c]	4.78 ± 0.31
22	2	F	rac	6.16(0.14)[d]	NT
23	1	G	(-)	6.73(0.17)[d]	6.35 ± 0.15
24	1	G	(+)	5.99(0.25)[d]	5.35 ± 0.18
25	2	G	(-)	6.24(0.03)[d]	5.41 ± 0.24
26	2	G	(+)	5.30(0.12)[c]	5.16 ± 0.18
27	1	H	rac	6.93(0.18)[d]	NT
28	2	H	rac	6.97(0.21)[d]	6.18 ± 0.22
1	–	–		6.37(0.25)[d]	6.59 ± 0.16

[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 2



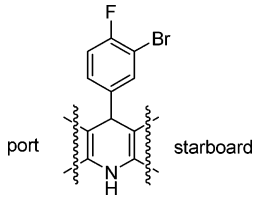
compd	n	ring fusion	stereochem	pEC50 GPB[a,e]	pEC50 FSLPD[b,f]
29	1	A	rac	7.14(0.13)[d]	6.26 ± 0.06
30	2	A	(−)	8.06(0.17)[d]	6.61 ± 0.06
31	2	A	(+)	<5[c]	NT
32	1	C	R	8.31(0.40)[d]	7.17 ± 0.09
33	1	C	S	6.38(0.36)[c]	5.95 ± 0.12
34	2	C	rac	7.27(0.28)[d]	NT
35	1	E	rac	6.36(0.46)[d]	NT
36	2	E	rac	5.91(0.00)[c]	NT
37	1	G	rac	5.86(0.07)[c]	4.30 ± 0.11
38	2	G	rac	5.59(0.08)[c]	3.88 ± 0.04

[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.

a variety of R_1 substitutions appended to the γ-lactam nitrogen (Scheme 3).

The preparation of single enantiomers **23**−**26**, containing a piperidine ring, was accomplished via chromatographic separation of diastereomeric 8-phenylmenthyl carbamates followed by cleavage of the chiral auxiliary to provide the unsubstituted piperidine (Scheme 4). The individual enantiomers **30**−**33** were prepared using the 8-phenylmenthylcarbamate method described in our preceding paper (see Experimental Section for details). Single enantiomers of other final products from Schemes 1 and 2 were obtained by chiral HPLC of the racemic mixtures. The reader is referred to the Experimental Section for details of the separation methods.

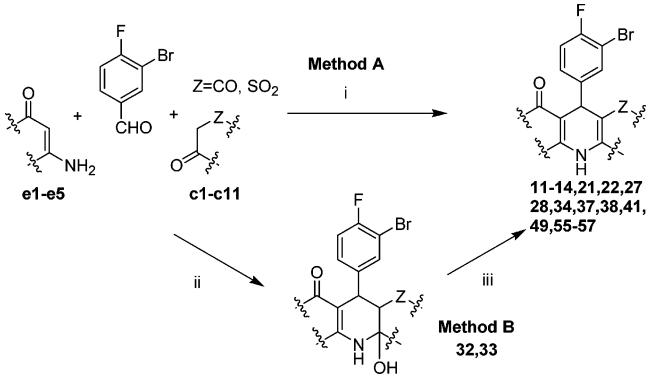
Table 3



compd	port	starboard	stereochem	pEC50 GPB[a,e]	pEC50 FSLPD[b,f]
39	A	A		7.20 (0.30)[d]	6.30 ±0.15
40	B	B		7.09 (0.25)[d]	6.75 ± 0.15
41	C	C		7.57 (0.32)[d]	6.90 ± 0.13
42	A	B	rac	7.85 (0.29)[d]	NT
43	C	A	R	7.59 (0.37)[d]	6.23 ± 0.14
44	A	C	S	7.95 (0.04)[c]	6.58 ± 0.05
45	D	D		5.55 (0.05)[c]	4.43 ± 0.32
46	E	E		6.00 (0.33)[d]	5.69 ± 0.07
47	F	F		<5[c]	NT
48	G	G		5.24 (0.12)[d]	NT
49	H	H		9.27 (0.13)[c]	6.07 ± 0.05
50	A	D	rac	6.63 (0.09)[c]	NT
51	A	G	rac	6.16 (0.05)[c]	5.63 ± 0.15
52	A	H	rac	7.19 (0.26)[c]	5.93 ± 0.17
53	C	D	rac	6.01 (0.07)[c]	NT
54	C	E	rac	7.89 (0.33)[d]	NT
55	C	F	rac	6.55 (0.28)[d]	5.32 ± 0.20
56	C	G	rac	6.25 (0.27)[d]	6.01 ± 0.11
57	C	H	rac	7.20 (0.21)[d]	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.

Scheme 1[a]

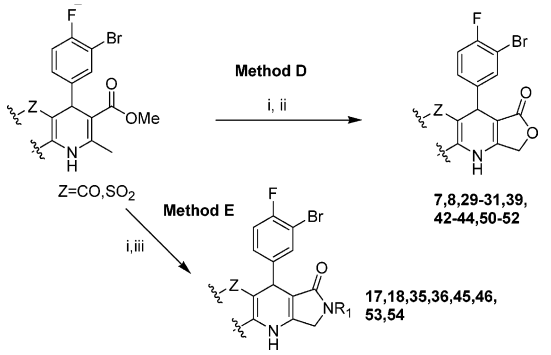


[a] Conditions: (i) EtOH, 80 °C; (ii) EtOH, Et_3N, 80 °C; (iii) HCl, EtOH, 80 °C.

Biological Assays

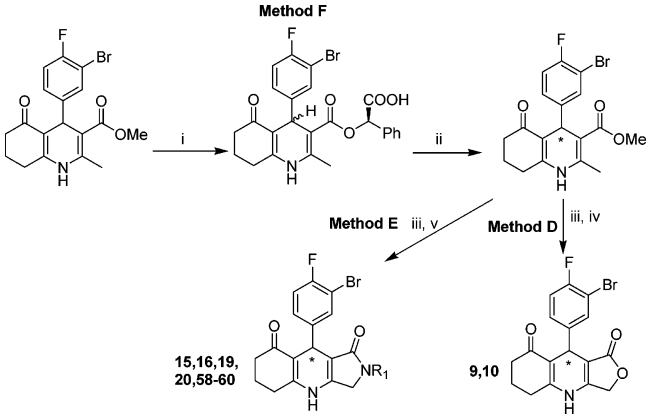
Guinea Pig Bladder (GPB) Assay.[13] Membrane potential changes elicited by test compounds were measured using a fluorometric imaging plate reader (FLIPR). Dose−response curves were generated for changes in fluorescence with the membrane potential sensitive dye $DiBAC_4(3)$. Potencies are expressed as the negative logarithm of the EC_{50} (pEC_{50}), and efficacies were determined relative to the standard P1075.

Scheme 2[a]



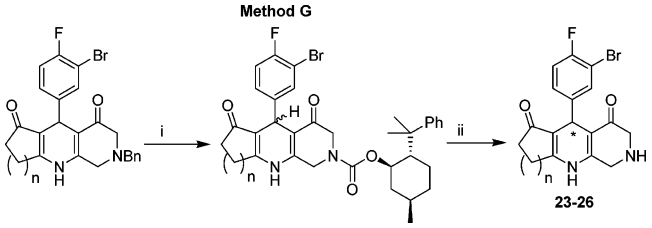
[a] Conditions: (i) NBS or pyridinium tribromide; (ii) 130 °C; (iii) R_1NH_2.

Scheme 3[a]



[a] Conditions: (i) BCl_3, $SOCl_2$; (R) mandelic acid; (ii) flash chromatography, NaOMe; (iii) pyridinium tribromide; (iv) 130 °C; (v) R_1NH_2.

Scheme 4[a]



[a] Conditions: (i) 8-phenylmenthol chloroformate; (ii) 48% HBr/AcOH.

Field-Stimulated Landrace Pig Detrusor (FS-LPD) Assay.[14] 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.[15] 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 P1075. Because of the different sensitivities of the two assays to muscarinic antagonists, each may model bladder overactivity of distinct etiology.

Results and Discussion

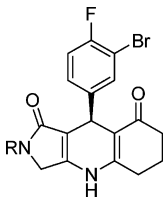
Analogues **7**−**14** containing a single oxygen incorporated into one ring (Table 1, see Figure 3 for ring fusions) demonstrated high potency at both GPB and FSLPD assays. For the γ-lactones **7**−**10**, stereochemistry was important to K_{ATP} activity in the GPB assay as the (*S*)-enantiomers **8** and **10** were more potent than the respective antipodes **7** and **9**. For the regioisomeric pyran ring fusions (rings **B** and **C**), little difference in potency was observed, as exemplified by examples **11**−**14**.

By comparison with the insertion of oxygen into one flanking ring, insertion of nitrogen as either a lactam NH, lactam N-Me, or piperidine NH produced the less potent compounds **15**−**23** (Table 1). Nonetheless, several of these analogues still possess substantial potency when compared to standards such as (−)-cromakalim (**1**). As was observed for the lactones in Table 1, stereochemistry was important for activity with either a lactam NH or piperidine NH in a flanking ring (compounds **15**−**16**, **23**−**26**). Interestingly, for ring fusion **D** (examples **15** and **16**) the preferred stereochemistry was *R*, opposite that for the lactones **7**−**10**. Compound **23** is interesting as a unique example of a K_{ATP} opener that possesses equivalent potency to (−)-cromakalim yet contains a basic nitrogen atom. With regard to stereochemistry and the *N*-methylated lactam nitrogen examples **17**−**20**, the six-membered carbocyclic analogues **19** and **20** showed similar potency, whereas the five-membered carbocyclic analogues **17** and **18** differed by over 10-fold in potency, with the (*R*)-stereochemistry being preferred. A similar phenomenon was described in our accompanying study with respect to stereochemistry and carbocyclic ring size. The two thiopyran analogues **27** and **28** showed intermediate potency between the pyran-containing (**13** and **14**) and piperidine-containing (**23**−**26**) examples.

The cyclic sulfone-containing variants **29**−**38** (Table 2) were generally found to possess slightly diminished potency compared to the carbocyclic variants in Table 1. One exception, however, was compound **32**, which displayed excellent potency at both GPB and FSLPD, even when compared to compound **10**. The preferred sense of absolute stereochemistry with respect to the oxygen-containing pyran ring of **32** is in agreement with that of the oxygen-containing lactone of **10**.[16] Likewise, the absolute stereochemistry of **32** with resepect to the sulfonyl group is in agreement with the preferred stereochemistry for the directly analogous carbocyclic analogue described in our companion paper.[17]

An extensive investigation was undertaken to evaluate both symmetrical and unsymmetrical core struc-

Table 4



compd	R	pEC$_{50}$ GPB[a,c]	pEC$_{50}$ FSLPD[b,d]
58	cyclopropyl	6.27(0.14)	NT
59	ethoxyethyl	6.27(0.13)	6.02 ± 0.12
60	*n*-propyl	<5	NT

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

tures containing heteroatoms in both the port and starboard sides of the dihydropyridine nucleus (Table 3).[18] The symmetrical oxygen- and sulfur-containing analogues **39**−**41** and **49** were all highly potent K_{ATP} openers. Among the oxygen-containing analogues, there was little to distinguish them in either GPB or FSLPD from a potency standpoint. In contrast, symmetrical nitrogen-containing compounds **45**−**48** showed considerably weaker activity than the nitrogen-containing analogues of Table 1. The weaker activity of **46** (N-Me on both sides of the DHP) is in accord with the differential activities for **17** and **18**, where it was demonstrated that tolerance to the N-Me group was stereospecific. The unsymmetrical analogues containing two oxygens (**43** and **44**) or an oxygen and a sulfur (**52** and **57**) displayed high potency similar to the symmetrical versions, with the (*S*)-enantiomer **44** exhibiting slightly greater potency than the (*R*)-enantiomer **43**. The unsymmetrical analogues in Table 3 with oxygen- and nitrogen-containing rings on opposite sides showed comparable potency to the nitrogen-containing analogues in Table 1. In these cases, the insertion of an oxygen into the flanking ring generally did not produce an enhancement in potency. Compound **54** appears to be an exception, as its potency in the GPB assay is greater than that of **17**−**20**.

To further explore the SAR around the analogues **15**, **16**, **19**, and **20**, a diverse array of substitutions off the γ-lactam nitrogen was investigated. With the availability of enantiomerically pure precursors (Scheme 3), these SAR studies were conducted in both the (*R*)- and (*S*)-series, employing parallel synthesis techniques and a variety of primary amines. The substitutions encompassed straight and branched chain alkyl, alkoxyalkyl, arylalkyl, heteroarylalkyl, and amino alkyl groups. Interestingly, whereas the tricyclic DHP core could be modified extensively with retention of K_{ATP} activity, lateral substitution was generally found to be poorly tolerated. Indeed, in the (*R*)-series all substitutions larger than methyl were found to be inactive. In the (*S*)-series only cyclopropyl (**58**) and ethoxyethyl (**59**) provided appreciable K_{ATP} activity (Table 4).

Several analogues were also evaluated for their ability to inhibit spontaneous bladder contractions in vitro, and the data are summarized in Table 5. Consistent with our previous findings, all compounds exhibited greater potency to relax spontaneously contracting bladder

Table 5

compd	pED$_{50}$ SHR[a]	pEC$_{50}$ FSLPD[b,d]	pEC$_{50}$ SLPD[c,d]	selectivity SLPD:FSLPD
6	6.37 ± 0.15	6.63 ± 0.15	7.64 ± 0.08	10
9	5.61 ± 0.03	5.96 ± 0.09	7.49 ± 0.15	34
39	6.40 ± 0.02	6.30 ± 0.15	7.63 ± 0.11	21
44	NA	6.58 ± 0.05	8.30 ± 0.18	52

[a] SHR = spontaneously hypertensive rat. The pED$_{50}$ refers to the negative log of the dose to produce a 50% reduction in blood pressure relative to the maximum achieved with the K_{ATP} standard P1075 (see Experimental Section for details). All compounds tested achieved maximal reductions in blood pressure equal to that attained with P1075. NA = not available. [b] FSLPD = field-stimulated Landrace pig detrusor strips. [c] SLPD = spontaneous Landrace pig detrusor strips. [d] Number of determinations ≥ 4; standard error shown.

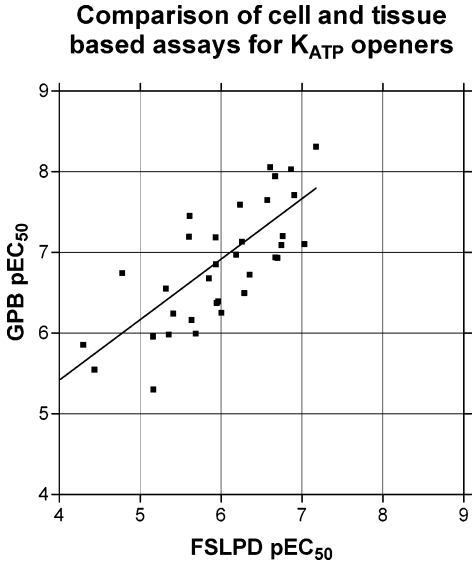


Figure 4. Plot of pEC$_{50}$ values for guinea pig bladder cells (GPB) vs field-stimulated Landrace pig detrusor (FSLPD). Slope = 0.75; r^2 = 0.48.

strips. Compounds **9**, **39**, and **44** showed greater selectivity for the spontaneous contractions relative to the earlier generation analogue **6**. Selectivity for spontaneous contractions may endow certain K_{ATP} openers with selectivity for diseased bladder contractions of myogenic origin relative to their effects on normal bladder function.

Examination of the collective data for this series of compounds in the two primary in vitro assays shows that the primary cell-based screen (GPB) offers some predictive value for the tissue assay (FSLPD), as indicated by the correlation plot (Figure 4). Generally, however, compounds tended to display greater potency in the GPB assay, as is also observed in the SLPD assay. Although the dataset is relatively small, the SLPD potencies of compounds appearing in this and our companion paper were better predicted by the GPB assay (Figure 5) than the FSLPD assay (Figure 6). For this reason, the biological results from the GPB assay were given greater weight than those from the FSLPD assay when interpreting inconsistent SAR trends across the two assays. Although the ability of compounds to inhibit spontaneous bladder contractions may be the most relevant for the condition of OAB, both the GPB and FSLPD assays are reasonably predictive, higher throughput assays that allow compounds to be funneled to the more labor intensive SLPD assay.

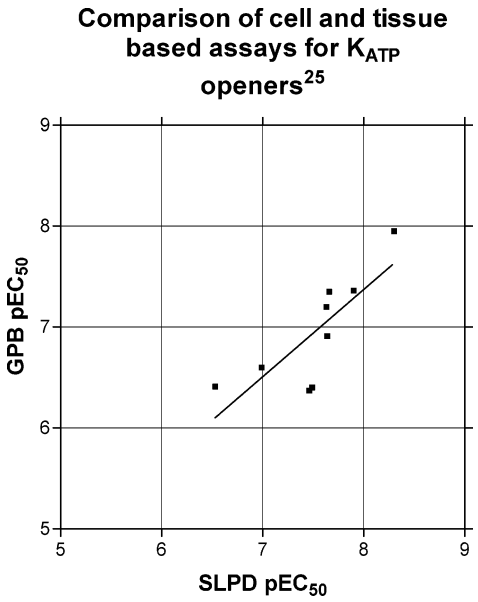


Figure 5. Plot of pEC_{50} values for guinea pig bladder cells (GPB) vs spontaneous Landrace pig detrusor (SLPD). Slope = 1.16; r^2 = 0.63.

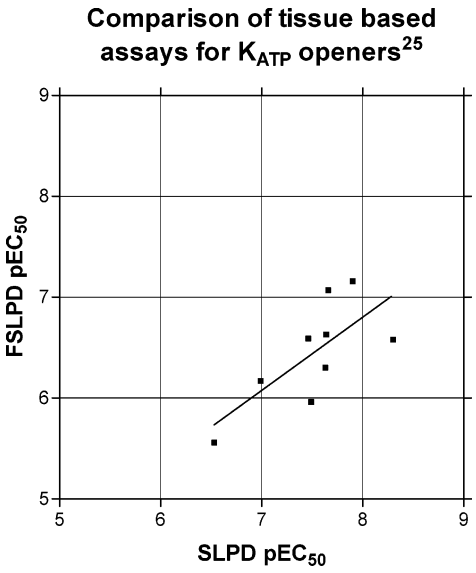


Figure 6. Plot of pEC_{50} values for field-stimulated Landrace pig detrusor (FSLPD) vs spontaneous Landrace pig detrusor (SLPD). Slope = 1.38; r^2 = 0.52.

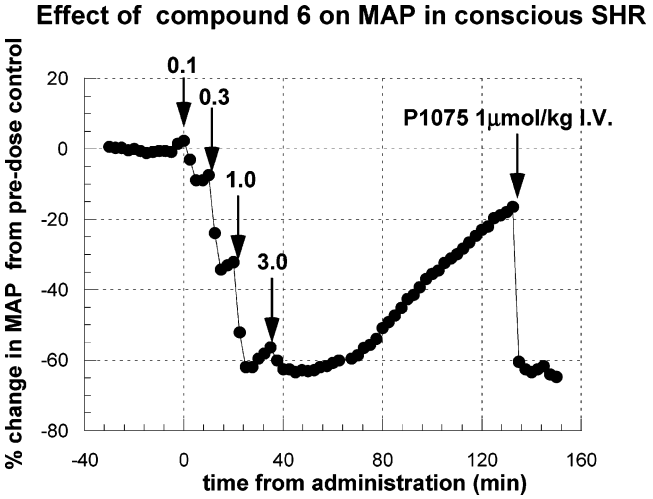


Figure 7. Effect of compound **6** on MAP when administered iv in a cumulative fashion to conscious spontaneously hypertensive rats. Doses shown are in μmol/kg. See Experimental Section for protocol details.

Different screening paradigms were investigated to determine if any of the structural features among the diverse array of potent K_{ATP} openers in Tables 1−4 led to improved selectivity versus cardiovascular effects. Ideally, selectivity would be measured directly in vivo; however, the laborious nature of such assays is prohibitive when screening a large set of compounds. It was necessary, therefore, to identify a relevant higher throughput screen for effects on hemodynamics. In vitro assays such as the rat aorta model were initially investigated; however, activity in this model did not correlate well with cardiovascular effects in vivo for a select group of K_{ATP} openers. Consequently, we chose to screen compounds for their ability to acutely reduce blood pressure on intravenous dosing in spontaneously hypertensive rats (SHR). A cumulative dosing protocol was used (see Figure 7) to generate a dose−response curve from which a pED_{50} could be determined. Effects at a given dose were measured over a short period (2.5 min) allowing for the minimization of differences in the pharmacokinetics of compounds. Even compounds such as nifedipine, with a short half-life, produced rapid, acute blood pressure responses that allowed generation of a full dose−response curve. It should be noted that such a screening paradigm allows for the measurement of only relative selectivity of compounds, as efficacy was determined in a separate in vitro bladder strip assay. The data shown in Table 5 from the SHR assay are typical for compounds from this dihydropyridine class. Potency to reduce MAP tracked with potency to relax bladder smooth muscle strips in vitro and none of these newer analogues demonstrated a significant improvement relative to **6**. Thus, although subtle differences in selectivity may exist in this compound set, the available assays for examining large sets of compounds have only sufficient precision to permit the measurement of significantly larger differences in intrinsic selectivity.

Conclusion

The results of Tables 1−4 indicate that significant variations in the flanking rings of the dihydropyridine are allowed with retention of K_{ATP} activity. Certain requirements must be met, however, with regard to the stereochemical placement of hydrogen-bond-accepting groups and especially hydrogen-bond-donating groups. Lateral substitution off the tricyclic system was poorly tolerated. Several of the analogues discovered in the course of these investigations containing oxygen in a flanking ring (**10**, **32**, **41**) rank among the most potent K_{ATP} openers known. These results also provide further evidence for the enhanced potency of K_{ATP} openers to inhibit spontaneous bladder contractions that may be related to diseased bladder contractions in OAB.

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, all melting points were 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. All single enantiomers described herein were enantiomerically pure to the level of detection of either ^{1}H NMR or chiral HPLC, depending upon the method of separation used.

Method A. 5-(3-Bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1*H*-thiopyrano[3,4-*b*]quinoline-4,6(3*H*,7*H*)-dione (28). A mixture of thiopyran-3,5-dione[19] (**c4**) (0.12 g, 1.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.20 g, 1.0 mmol), 3-aminocyclohex-2-en-1-one (**e2**) (0.11 g, 1.0 mmol), and EtOH (5 mL) was heated to 80 °C in a sealed tube for 60 h and cooled to ambient temperature. The resulting solid was collected by filtration, washed with EtOH, and dried to provide 0.13 g of **28**: ^{1}H NMR (DMSO-d_6) δ 1.77−1.88 (m, 1H), 1.89−1.98 (m, 1H), 2.25 (dd, 2H), 2.46−2.62 (m, 2H), 3.10 (dd, 1H), 3.48 (ddd, 2H), 3.82 (d, 1H), 4.96 (s, 1H), 7.15−7.24 (m, 2H), 7.41 (dd, 1H), 9.71 (s, 1H); MS (APCI$^-$) *m*/*z* 406 (M − H)$^-$. Anal. ($C_{18}H_{15}BrFNO_2S$) C, H, N.

Method B. 9-(3-Bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4*H*-pyrano[3,4-*b*]thieno[2,3-*e*]pyridin-8(7*H*)-one 1,1-Dioxide. A mixture of 5-amino-2*H*-pyran-3(6*H*)-one[20] (**e3**) (1.5 g, 13 mmol), 3-bromo-4-fluorobenzaldehyde (3.2 g, 16 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide (**c7**) (1.8 g, 13 mmol), and triethylamine (0.93 mL, 6.6 mmol) in EtOH (20 mL) was stirred in a sealed tube at 80 °C for 60 h, cooled, and concentrated to dryness. The residue was dissolved in EtOH (50 mL), treated with 1 M HCl/Et_2O (5 mL), heated to reflux for 5 min, and then cooled to room temperature. The resulting solid was collected by filtration, washed with EtOH, and dried under vacuum for 16 h to provide 3.2 g of the title compound: ^{1}H NMR (DMSO-d_6) δ 2.85 (m, 1H), 3.08 (m, 1H), 3.33−3.42 (m, 2H), 4.03 (s, 2H), 4.49 (AB q, 2H), 4.90 (s, 1H), 7.27 (m, 2H), 7.45 (dd, 1H), 10.14 (s, 1H); MS (ESI$^+$) *m*/*z* 414 (M + H)$^+$.

Method C. 10-(3-Bromo-4-fluorophenyl)-3,4,5,6,7,10-hexahydro-1*H*,9*H*-dipyrano[4,3-*b*:3,4-*e*]pyridine-1,9-dione (40). A mixture of dihydro-2*H*-pyran-2,4(3*H*)-dione[21] (**c9**) (0.456 g, 4.0 mmol) and 3-bromo-4-fluorobenzaldehyde (0.406 g, 2.0 mmol) was treated with a 2 M NH_3/MeOH (6.0 mmol, 3.0 mL) and stirred in a sealed tube at 75 °C for 72 h. After cooling to room temperature, the reaction mixture was concentrated and the residue purified by flash chromatography over silica gel, gradient eluting with EtOAc:CH_2Cl_2:MeOH (7:1:0.1 to 7:1:1) to provide 0.08 g of the title compound as a pale yellow solid: ^{1}H NMR (DMSO-d_6) δ 2.57 (ddd, 2H), 2.73 (ddd, 2 H), 4.16−4.22 (m, 2H), 4.27−4.33 (m, 2H), 4.76 (s, 1H), 7.23−7.27 (m, 2H), 7.44 (dd, 1H), 9.86 (bs, 1H); MS (APCI$^+$) *m*/*z* 394 (M + H)$^+$. Anal. ($C_{17}H_{13}BrFNO_4$) C, H, N.

Method D. Part 1. Methyl 4-(3-Bromo-4-fluorophenyl)-2-(bromomethyl)-5-oxo-4,5,6,8-tetrahydro-1*H*-pyrano[3,4-*b*]pyridine-3-carboxylate. A solution of 0.87 g (2.2 mmol) of methyl 4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-4,5,6,8-tetrahydro-1*H*-pyrano[3,4-*b*]pyridine-3-carboxylate [prepared from 2*H*-pyran-3,5(4*H*,6*H*)-dione (**c3**),[20] 3-bromo-4-fluorobenzaldehyde, and methyl (2*E*)-3-aminobut-2-enoate (**e5**) using method A] in $CHCl_3$ (10 mL) was cooled to −10 °C, treated with pyridine (0.21 mL, 2.6 mmol) and then pyridinium tribromide (0.84 g, 2.6 mmol), stirred for 1 h, diluted with CH_2Cl_2 (150 mL), and washed with 1 N HCl (25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and flash chromatographed over silica gel gradient eluting with MeOH:CH_2Cl_2 (1:99 to 2:98) to provide 0.68 g of the title compound that was carried directly on to part 2.

Method D. Part 2. 9-(3-Bromo-4-fluorophenyl)-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione. The intermediate from part 1 (0.30 g, 0.63 mmol) was heated neat under N_2 to 130 °C for 15 min and cooled to room temperature. The residue was treated with CH_2Cl_2, and the resulting solid was collected by filtration, washed with CH_2Cl_2, and dried to provide 0.074 g of the title compound as a white solid: mp 166−168 °C; ^{1}H NMR (DMSO-d_6) δ 4.06 (s, 2H), 4.54 (AB q, 2H), 4.75 (s, 1H), 4.88 (d, 1H), 5.03 (d, 1H), 7.28 (d, 2H), 7.48 (d, 1H), 10.50 (s, 1H); MS (ESI$^+$) *m*/*z* 380 (M + H)$^+$.

Method E. 9-(3-Bromo-4-fluorophenyl)-2-methyl-2,3,5,9-tetrahydropyrano[3,4-*b*]pyrrolo[3,4-*e*]pyridine-1,8(4*H*,7*H*)-dione (54). A solution of the intermediate from method D, part 1 (0.16 g, 0.34 mmol) and 2 M $MeNH_2$/MeOH (3.5 mL, 7.0 mmol) was stirred at room temperature for 16 h, concentrated, flash chromatographed on silica gel gradient eluting with MeOH:CH_2Cl_2 (5:95 to 10:90), and crystallized from EtOH, to provide 0.016 g of **54** as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.81 (s, 3H), 3.98 (d, 1H), 4.03 (s, 2H), 4.15 (d, 1H), 4.50 (AB q, 2H), 4.75 (s, 1H), 7.23 (m, 2H), 7.46 (dd, 1H), 10.11 (s, 1H); MS (ESI$^+$) *m*/*z* 393 (M + H)$^+$. Anal. ($C_{17}H_{14}BrFN_2O_3$·0.5H_2O) C, H, N.

Method F. Methyl (4*R*)-4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate and Methyl (4*S*)-4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate. Part 1. 4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylic Acid. BCl_3/CH_2Cl_2 (1 M, 200 mL) was added to a solution of 19.7 g (50 mmol) of methyl 4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate [prepared from 3-bromo-4-fluorobenzaldehyde, methyl (2*E*)-3-aminobut-2-enoate (**e5**), and cyclohexane-1,3-dione (**c2**) by method A] in 50 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred overnight at room temperature and diluted with ice−water (1 L) and EtOAc (0.75 L). The solid was collected, washed with EtOAc, and dried to provide 16.9 g of the title compound as a white powder: mp 225−228 °C; ^{1}H NMR (DMSO-d_6) δ 1.70−1.95 (m, 2H), 2.20 (t, 2H), 2.30 (s, 3H), 2.45 (m, 2H), 4.87 (s, 1H), 7.13 (m, 1H), 7.20 (t, 1H), 7.36 (d, 1H), 9.14 (s, 1H), 11.8 (br s, 1H); MS (ESI$^+$) *m*/*z* 380 (M + H)$^+$.

Part 2A. (2*R*′,4*R*)-({[4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinyl]carbonyl}-oxy)(phenyl)ethanoic Acid. To a solution of the intermediate from part 1 (16.9 g, 44.5 mmol) in DMF (150 mL) at −10 °C was added $SOCl_2$ (5.29 g, 44.5 mmol). After 1.5 h at −10 °C, (*R*)-mandelic acid (6.77 g, 44.5 mmol) and Et_3N (4.5 g, 44.5 mmol) were added, and the reaction was maintained at −10 °C for 2 h and then at room temperature for 1 h, followed by quenching with EtOAc:Et_2O (1:2) and water. The organic layer was dried, filtered, and concentrated to provide the crude diastereomeric mixture (20 g). The title compound was isolated as the more polar diastereomer after flash chromatography over silica gel eluting with MeOH:CH_2Cl_2:AcOH (10:89.5:0.5) to provide a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.70−1.81 (m, 1H), 1.85−1.94 (m, 1H), 2.20 (m, 2H), 2.34 (s, 3H), 2.48 (m, 2H), 4.87 (s, 1H), 7.13−7.28 (m, 3H), 7.38−7.45 (m, 5H), 9.37 (s, 1H).

Part 2B. (2′*R*,4*S*)-({[4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinyl]carbonyl}-oxy)(phenyl)ethanoic Acid. The less polar diastereomer was obtained from the above chromatographic separation as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.70−1.81 (m, 1H), 1.85−1.94 (m, 1H), 2.20 (m, 2H), 2.34 (s, 3H), 2.48 (m, 2H), 4.87 (s, 1H), 7.13−7.28 (m, 3H), 7.38−7.45 (m, 5H), 9.37 (s, 1H).

Part 3A. Methyl (4*R*)-4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate. To the intermediate from part 2A (257 mg, 0.5 mmol) in MeOH (50 mL), was added sodium (0.58 g, 25 mmol), and the reaction refluxed for 16 h. After concentration, the residue was treated with 2 M HCl to pH 7, diluted with water (50 mL), and extracted with CH_2Cl_2. The organics were dried ($MgSO_4$), filtered, and concentrated to provide 153 mg of the title compound as a white foam.

Part 3B. Methyl (4*S*)-4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate. The product from part 2B (257 mg, 0.5 mmol) was treated

according to the method of part 3A to provide 153 mg of the title compound as a white foamy solid. The absolute stereochemistry was determined by X-ray crystallographic analysis (see Supporting Information).

Method G. (−)-5-(3-Bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1*H*-cyclopenta[*b*][1,7]naphthyridine-4,6-dione Hydrochloride (23) and (+)-5-(3-Bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1*H*-cyclopenta[*b*][1,7]naphthyridine-4,6-dione Hydrochloride (24). Part 1. 2-Benzyl-5-(3-bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1*H*-cyclopenta[*b*][1,7]naphthyridine-4,6-dione. A mixture of 3-aminocyclopent-2-en-1-one (**e1**) (0.97 g, 10 mmol), 3-bromo-4-fluorobenzaldehyde (2.0 g, 10 mmol), and 1-benzylpiperidine-3,5-dione[22] (**c5**) (2.2 g, 10 mmol) in EtOH (10 mL) was heated to reflux for 72 h and cooled to room temperature. The solvent was evaporated and the residue purified by flash chromatography over silica gel eluting with EtOH:CH_2Cl_2 (5:95) to provide 3.0 g of the title compound: ^{1}H NMR (DMSO-d_6) δ 2.28 (m, 2H), 2.5−2.7 (m, 2H), 3.07 (AB qu, 2H), 3.4 (m, 2H), 3.65 (s, 2H), 4.65 (s, 1H), 7.15−7.45 (m, 8H), 10.25, (s, 1H). MS (ESI$^-$) *m*/*z* 465 (M − H)$^-$.

Part 2A. (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-(3-Bromo-4-fluorophenyl)-4,6-dioxo-1,3,4,5,6,7,8,9-octahydro-2*H*-cyclopenta[*b*][1,7]naphthyridine-2-carboxylate (less polar diastereomer). A solution of the product from part 1 (1.9 g, 4.0 mmol) in THF (30 mL) was treated with a solution of 1.45 g (4.92 mmol) of 8-phenylmenthyl chloroformate (prepared from (−)-8-phenylmenthol) in THF (10 mL), stirred for 3 days at room temperature, and partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated to provide a mixture of diastereomeric carbamates. The diastereomeric mixture was subjected to flash chromatography over silica gel eluting with hexane:EtOAc (20:80) to provide 0.32 g of the title compound as the less polar diastereomer and 0.9 g of mixed fractions containing both diastereomers: ^{1}H NMR (DMSO-d_6) δ 0.8 (m, 4H), 1.1 (s, 3H), 1.18 (m, 2H), 1.22 (s, 3H), 1.6 (m, 2H), 1.8 (m, 1H), 2.02 (m, 2H), 2.3 (m, 2H), 2.6 (m, 1H), 2.75 (m, 1H), 3.02 (d, 1H), 3.62 (d, 1H), 3.9 (d, 1H), 4.58 (d, 2H), 4.68 (s, 1H), 7.02−7.38 (m, 8H); MS (ESI$^-$) *m*/*z* 635 (M − H)$^-$.

Part 2B. (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-(3-Bromo-4-fluorophenyl)-4,6-dioxo-1,3,4,5,6,7,8,9-octahydro-2*H*-cyclopenta[*b*][1,7]naphthyridine-2-carboxylate (more polar diastereomer). The mixed fractions from above were crystallized from EtOH to provide 0.45 g of the title compound as the more polar diastereomer: ^{1}H NMR (DMSO-d_6) δ 0.82 (d, 3H), 1.02 (s, 3H), 1.18 (s, 3H), 1.18 (m, 2H), 1.58 (m, 2H), 1.68 (s, 1H), 1.98 (m, 2H), 2.3 (m, 2H), 2.61 (m, 1H), 2.75 (m, 1H), 3.2 (m, 1H), 3.6 (m, 2H), 4.0 (m, 1H), 4.52 (m, 2H), 4.55 (s, 1H), 6.45(m, 1H), 6.82 (m, 2H), 7.1 (m, 2H), 7.25 (m, 2H), 7.41 (m, 1H); MS (ESI$^-$) *m*/*z* 635 (M − H)$^-$.

Part 3A. (−)-5-(3-Bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1*H*-cyclopenta[*b*][1,7]naphthyridine-4,6-dione Hydrochloride (23). A solution of the product from part 2A (0.32 g, 0.52 mmol) in 48% HBr/AcOH (4 mL) was heated to 50 °C for 48 h, cooled to room temperature, neutralized with NH_4OH, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography over silica gel eluting with CH_2Cl_2 (saturated with NH_4OH):EtOH (90:10) to provide 0.10 g of **23** as the free base which was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −125.88° (DMSO); ^{1}H NMR (DMSO-d_6) (free base) δ 2.28 (t, 2H), 2.53−2.76 (m, 2H), 3.18 (s, 2H), 3.62 (d, 2H), 4.67 (s, 1H), 7.22 (d, 2H), 7.45 (d, 1H) 10.1 (s, 1H); MS (ESI$^-$) *m*/*z* 375 (M − H)$^-$. Anal. Calcd for $C_{17}H_{13}BrFN_2O_2\cdot HCl\cdot 0.5H_2O$: C, 48.43; H, 4.08; N, 6.28. Found: C, 48.42; H, 3.59; N, 6.64.

Part 3B. (+)-5-(3-Bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1*H*-cyclopenta[*b*][1,7]naphthyridine-4,6-dione Hydrochloride (24). A solution of the product from part 2B (0.25 g, 0.41 mmol) in 48% HBr/AcOH (3 mL) was heated for 3 days at 50 °C, cooled to room temperature, neutralized with NH_4OH, and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography over silica gel eluting with CH_2Cl_2 (saturated with NH_4OH):EtOH (90:10) to provide 0.070 g of **24** as a free base which was converted to the hydrochloride salt: $[\alpha]^{20}_D$ +117.64° (DMSO); ^{1}H NMR (DMSO-d_6) (free base) δ 2.28 (t, 2H), 2.52−2.65 (m, 2H), 3.18 (s, 2H), 3.52 (d, 2H), 4.68 (s, 1H), 7.2 (m, 2H), 7.43 (d, 1H) 10.1 (s, 1H); MS (ESI$^-$) *m*/*z* 375 (M − H)$^-$. Anal. ($C_{17}H_{13}BrFN_2O_2\cdot HCl\cdot 0.5H_2O$) C, H, N.

(−)-(8*S*)-(3-Bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1*H*-cyclopenta[*b*]furo[3,4-*e*]pyridine-1,7(3*H*)-dione (8) and (+)-(8*R*)-(3-Bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1*H*-cyclopenta[*b*]furo[3,4-*e*]pyridine-1,7(3*H*)-dione (7). 3-Bromo-4-fluorobenzaldehyde, methyl acetoacetate (**c6**), and 3-aminocyclopent-2-en-1-one (**e1**) were treated according to method A with the variations of MeOH for solvent, 65 °C for reaction temperature, and reaction time of 5 days to provide methyl 4-(3-bromo-4-fluorophenyl)-4,5,6,7-tetrahydro-2-methyl-5-oxo-1*H*-cyclopenta[*b*]pyridine-3-carboxylate: ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.60 (s, 3H), 4.90 (s, 1H), 6.33 (s, 1H), 6.98 (t, 1H), 7.23 (m, 1H), 7.37 (d, 1H). This intermediate (1.9 g, 5.0 mmol) in IPA (30 mL) was treated with NBS (890 mg, 5.0 mmol) and stirred at room temperature for 45 min. The solvent was evaporated and the crude product flash chromatographed over silica gel eluting with 2.5% MeOH/CH_2Cl_2 to provide 1.19 g methyl 4-(3-bromo-4-fluorophenyl)-2-(bromomethyl)-4,5,6,7-tetrahydro-5-oxo-1H-cyclopenta[*b*]pyridine-3-carboxylate: ^{1}H NMR ($CDCl_3$) δ 2.47 (m, 2H), 2.65 (m, 2H), 3.63 (s, 3H), 4.83 (AB q, 2H), 4.90 (s, 1H), 6.80 (br s, 1H), 7.00 (t, 1H), 7.23 (m, 1H), 7.40 (dd, 1H). This intermediate was reacted according to method D, part 2 at 180 °C for 1 h to provide the racemate that was separated into the individual enantiomers by chiral HPLC using an (*R*,*R*)-Whelk-O1 column eluting with hexane:MeOH:CH_2Cl_2 (50:34:16). The (−)-(*S*)-enantiomer 8 eluted first: $[\alpha]^{20}_D$ −80.8° (DMSO); ^{1}H NMR (DMSO-d_6) δ 2.35 (t, 2H), 2.70 (m, 2H), 4.60 (s, 1H), 4.98 (q, 2H), 7.26 (m, 2H), 7.50 (d, 1H), 10.71 (s, 1H); MS (ESI$^+$) *m*/*z* 364 (M + H)$^+$. Anal. ($C_{16}H_{11}BrFNO_3$) C, H, N. The (+)-(*R*)-enantiomer 7 eluted second: $[\alpha]^{20}_D$ +88.2° (DMSO); ^{1}H NMR (DMSO-d_6) δ 2.35 (t, 2H), 2.70 (m, 2H), 4.60 (s, 1H), 4.98 (q, 2H), 7.26 (m, 2H), 7.50 (d, 1H), 10.71 (s, 1H); MS (ESI$^+$) *m*/*z* 364 (M + H)$^+$. Anal. ($C_{16}H_{11}BrFNO_3$) C, H, N. The absolute stereochemistry for **7** and **8** was determined indirectly through independent synthesis of **8** from (4*S*)-methyl 4-(3-bromo-4-fluorophenyl)-4,5,6,7-tetrahydro-2-methyl-5-oxo-1*H*-cyclopenta[*b*]pyridine-3-carboxylate (see the Supporting Information for X-ray analysis) using the same method as described above. The enantiomerically pure (*S*)-ester intermediate, in turn, was obtained by chiral HPLC of the racemate over a Whelk-O1 column eluting with 80:13:7 hexane:MeOH:CH_2Cl_2.

(+)-(9*R*)-9-(3-Bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione (9). The product from method F, part 3A was treated according to method D at 180 °C for 1 h to provide **9** as a brown solid: $[\alpha]^{20}_D$ +171.4° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.92 (m, 2H), 2.25 (m, 2H), 2.57 (m, 2H), 4.68 (s, 1H), 4.88 (q, 2H), 7.23 (m, 2H), 7.44 (d, 1H), 10.18 (s, 1H); MS (APCI$^-$) *m*/*z* 376 (M − H)$^-$. Anal. ($C_{17}H_{13}BrFNO_3$) C, H, N.

(−)-(9*S*)-9-(3-Bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione (10). The product from method F, part 3B was treated as described in example **9** to provide **10** as a light pink powder. $[\alpha]^{20}_D$ −179.0° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.26 (m, 2H), 2.58 (m, 2H), 4.68 (s, 1H), 4.89 (q, 2H), 7.23 (m, 2H), 7.44 (d, 1H), 10.17 (s, 1H); MS (ESI$^-$) *m*/*z* 376 (M − H)$^-$. Anal. ($C_{17}H_{13}BrFNO_3\cdot 0.2H_2O$) C, H, N.

9-(3-Bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydrocyclopenta[*b*]pyrano[3,4-*e*]pyridine-1,8-dione (11). A mixture of dihydro-2*H*-pyran-2,4(3*H*)-dione (**c9**) (1.5 mmol, 171 mg), 3-bromo-4-fluorobenzaldehyde (1.5 mmol, 305 mg), and 3-amino-2-cyclopenten-1-one (**e1**) (1.5 mmol, 146 mg) was treated according to method A to provide 246 mg of **11**: ^{1}H NMR (DMSO-d_6) δ 2.28 (t, 2H), 2.52−2.86 (m, 4H), 4.20−4.38

(m, 2H), 4.63 (s, 1H), 7.20−7.27 (m, 2H), 7.45 (d, 1H), 10.27 (bs, 1H); MS (APCI$^+$) *m/z* 378 (M + H)$^+$. Anal. Calcd for $C_{17}H_{13}BrFNO_3$: C, 53.99; H, 3.46; N, 3.70. Found: C, 53.38; H, 3.76; N, 3.49.

10-(3-Bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-1*H*-pyrano[4,3-*b*]quinoline-1,9(5*H*)-dione (12). A mixture of dihydro-2*H*-pyran-2,4(3*H*)-dione (**c9**) (1.5 mmol, 171 mg), 3-bromo-4-fluorobenzaldehyde (1.5 mmol, 305 mg), and 3-amino-2-cyclohexen-1-one (**e2**) (1.5 mmol, 167 mg) was treated according to method A to provide 265 mg of **12**: ^{1}H NMR (DMSO-d_6) δ 1.73−2.00 (m, 2H), 2.19−2.29 (m, 2H), 2.54−2.80 (m, 4H), 4.10−4.35 (m, 2H), 4.80 (s, 1H), 7.18−7.23 (m, 2H), 7.39 (dd, 1H), 9.72 (bs, 1H); MS (APCI$^-$) *m/z* 390 (M − H)$^-$. Anal. ($C_{18}H_{15}BrFNO_3$) C, H, N.

5-(3-Bromo-4-fluorophenyl)-5,7,8,9-tetrahydrocyclopenta[*b*]pyrano[4,3-*e*]pyridine-4,6(1*H*,3*H*)-dione (13). A mixture of 5-amino-2*H*-pyran-3(6*H*)-one (**e3**) (0.23 g, 2.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.49 g, 2.4 mmol), and 1,3-cyclopentanedione (**c1**) (0.20 g, 2.0 mmol) was treated according to method B. The product was recrystallized from MeOH/CH_2Cl_2 to provide 0.14 g of **13**: ^{1}H NMR (DMSO-d_6) δ 2.31 (t, 2H), 2.59 (dt, 1H), 2.73 (dt, 1H), 4.04 (s, 2H), 4.53 (AB q, 2H), 4.71 (s, 1H), 7.22 (m, 2H), 7.43 (dd, 1H), 10.36 (bs, 1H); MS (ESI$^+$) *m/z* 378 (M + H)$^+$. Anal. ($C_{17}H_{13}BrFNO_3$) C, H, N.

5-(3-Bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1*H*-pyrano[3,4-*b*]quinoline-4,6(3*H*,7*H*)-dione (14). A mixture of 5-amino-2*H*-pyran-3(6*H*)-one (**e3**) (0.23 g, 2.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.49 g, 2.4 mmol), and 1,3-cyclohexanedione (**c2**) (0.23 g, 2.0 mmol) was treated according to method B. The product was recrystallized from MeOH/CH_2Cl_2 to provide 0.37 g of **14**: ^{1}H NMR (DMSO-d_6) δ 1.76−2.01 (m, 2H), 2.25 (t, 2H), 2.43−2.64 (m, 2H), 4.01 (s, 2H), 4.48 (AB q, 2H), 4.90 (s, 1H), 7.20 (m, 2H), 7.39 (dd, 1H), 9.82 (bs, 1H); MS (ESI$^+$) *m/z* 392 (M + H)$^+$. Anal. ($C_{18}H_{15}BrFHO_3$) C, H, N.

(+)-(9*R*)-9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1*H*-pyrrolo[3,4-*b*]quinoline-1,8(4*H*)-dione (15). The product from method F, part 3A was treated according to method D, part 1 and method E using NH_3 at room temperature for 20 h in a pressure bomb to provide **15** as a yellow powder: $[\alpha]^{20}_D$ +180.2° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 3.93 (q, 2H), 4.70 (s, 1H), 7.20 (m, 2H), 7.42 (d, 1H), 7.47 (s, 1H), 9.80 (s, 1H); MS (APCI$^-$) *m/z* 375 (M − H)$^-$. Anal. ($C_{17}H_{14}BrFN_2O_2\cdot 0.5H_2O$) C, H, N.

(−)-(9*S*)-9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1*H*-pyrrolo[3,4-*b*]quinoline-1,8(4*H*)-dione (16). The product from method F, part 3B was treated according to method D, part 1 and method E using NH_3 at room temperature for 20 h in a pressure bomb to provide **16** as a beige solid: $[\alpha]^{20}_D$ −169.4° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 3.93 (q, 2H), 4.69 (s, 1H), 7.19 (m, 2H), 7.42 (d, 1H), 7.48 (s, 1H), 9.80 (s, 1H); MS (ESI$^+$) *m/z* 377 (M + H)$^+$. Anal. ($C_{17}H_{14}BrFN_2O_2\cdot 0.4CH_2Cl_2$) C, H, N.

(+)-(8*R*)-(3-Bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[*b*]pyrrolo[3,4-*e*]pyridine-1,7-dione (17) and (−)-(8*S*)-(3-Bromo-4-fluorophenyl)-2-methyl-2,3,4,5,6,8-hexahydrocyclopenta[*b*]pyrrolo[3,4-*e*]pyridine-1,7-dione (18). Methyl 4-(3-bromo-4-fluorophenyl)-2-(bromomethyl)-4,5,6,7-tetrahydro-5-oxo-1*H*-cyclopenta[*b*]pyridine-3-carboxylate (0.11 g) from examples **7** and **8** was treated according to method D, part 1 and method E to provide 0.052 g of the title compound that was separated into the two enantiomers after chiral HPLC resolution (Chiralcel OD, 4.6 × 250 mm, hexane:EtOH, 90:10). The less polar enantiomer was **17**, a light yellow solid: $[\alpha]^{20}_D$ +68.5° (DMSO); ^{1}H NMR (DMSO-d_6) δ 2.30 (t, 2H), 2.55−2.67 (m, 2H), 2.80 (s, 3H), 4.08 (q, 2H), 4.56 (s, 1H), 7.21 (m, 2H), 7.44 (d, 1H); MS (ESI$^+$) *m/z* 377 (M + H)$^+$. Anal. ($C_{17}H_{14}BrFN_2O_2$) C, H, N. The more polar enantiomer was **18**: $[\alpha]^{20}_D$ −66.9° (DMSO); ^{1}H NMR (DMSO-d_6) δ 2.30 (t, 2H), 2.55−2.67 (m, 2H), 2.80 (s, 3H), 4.08 (q, 2H), 4.56 (s, 1H), 7.21 (m, 2H), 7.44 (d, 1H); MS (ESI$^+$) *m/z* 377 (M + H)$^+$. Anal. ($C_{17}H_{14}BrFN_2O_2\cdot 0.5H_2O$) C, H, N. A single-crystal X-ray confirmed the stereochemistry (see the Supporting Information).

(+)-(9*R*)-9-(3-Bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1*H*-pyrrolo[3,4-*b*]quinoline-1,8(4*H*)-dione (19). The product from method F, part 3A was treated according to method D, part 1 and method E to provide **19** as a white powder: $[\alpha]^{20}_D$ +152.15° (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.23 (m, 2H), 2.55 (m, 2H), 2.79 (s, 3H), 4.02 (q, 2H), 4.70 (s, 1H), 7.19 (m, 2H), 7.42 (d, 1H), 9.82 (s, 1H); MS (ESI$^+$) *m/z* 391 (M + H)$^+$. Anal. ($C_{18}H_{16}BrFN_2O_2\cdot 0.4CH_2Cl_2$) C, H, N.

(9*S*)-9-(3-Bromo-4-fluorophenyl)-2-methyl-2,3,5,6,7,9-hexahydro-1*H*-pyrrolo[3,4-*b*]quinoline-1,8(4*H*)-dione (20). The product from method F, part 3B was treated according to method D, part 1 and method E to provide **20** as a pale yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.24 (m, 2H), 2.55 (m, 2H), 2.78 (s, 3H), 4.02 (q, 2H), 4.69 (s, 1H), 7.18 (m, 2H), 7.43 (d, 1H), 9.80 (s, 1H); MS (ESI$^+$) *m/z* 391 (M + H)$^+$. Anal. ($C_{18}H_{16}BrFN_2O_2$) C, H, N.

9-(3-Bromo-4-fluorophenyl)-3,4,5,6,7,9-hexahydro-1*H*-cyclopenta[*b*][1,6]naphthyridine-1,8(2*H*)-dione (21). A mixture of 3-bromo-4-fluorobenzaldehyde (1 mmol, 203 mg), piperidine-2,4-dione[23] (**c10**) (1 mmol, 113 mg), and 3-aminocyclopent-2-en-1-one (**e1**) (1 mmol, 97 mg) was treated according to method A to provide 122 mg of **21**: ^{1}H NMR (DMSO-d_6) δ 2.25 (t, 2H), 2.40−2.70 (m, 4H), 3.15−3.35 (m, 2H), 4.70 (s, 1H), 7.07 (bs, 1H), 7.17−7.22 (m, 2H), 7.42 (dd, 1H), 9.83 (s, 1H); MS (APCI$^+$) *m/z* 377 (M + H)$^+$. Anal. ($C_{17}H_{14}BrFN_2O_2$) C, H, N.

10-(3-Bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydrobenzo[*b*][1,6]naphthyridine-1,9(2*H*,5*H*)-dione (22). A mixture of 3-bromo-4-fluorobenzaldehyde (1 mmol, 203 mg), piperidine-2,4-dione (**c10**) (1 mmol, 113 mg), and 3-aminocyclohex-2-en-1-one (**e2**) (1 mmol, 111 mg) was treated according to method A to provide 218 mg of **22**: ^{1}H NMR (DMSO-d_6) δ 1.70−1.97 (m, 2H), 2.15−2.25 (m, 2H), 2.36−2.59 (m, 4H), 3.13−3.23 (m, 2H), 4.90 (s, 1H), 7.00 (bs, 1H), 7.15−7.20 (m, 2H), 7.39 (dd, 1H), 9.28 (s, 1H); MS (ESI$^+$) *m/z* 391 (M + H)$^+$. Anal. ($C_{18}H_{16}BrFN_2O_2$) C, H, N.

(−)-5-(3-Bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[*b*][1,7]naphthyridine-4,6(1*H*,7*H*)-dione Hydrochloride (25) and (+)-5-(3-Bromo-4-fluorophenyl)-2,3,5,8,9,-10-hexahydrobenzo[*b*][1,7]naphthyridine-4,6(1*H*,7*H*)-dione Hydrochloride (26). A mixture of 3-aminocyclohex-2-en-1-one (**e2**) (0.55 g, 5.0 mmol), 3-bromo-4-fluorobenzaldehyde (1.01 g, 5.0 mmol) and 1-benzylpiperidine-3,5-dione (**c5**) (1.01 g, 5.0 mmol) was treated according to method G, part 1 to provide 0.84 g of 2-benzyl-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,-10-hexahydrobenzo[*b*][1,7]naphthyridine-4,6(1*H*,7*H*)-dione: ^{1}H NMR ($CDCl_3$) (free base) δ 2.0 (m, 2H), 2.67 (m, 2H), 2.48 (m, 2H), 3.05−3.48 (m, 4H), 3.7 (m, 2H), 5.1 (s, 1H), 6.05 (bs, 1H), 6.99 (t, 1H), 7.32 (m, 6H), 7.41 (dd, 1H). This intermediate (1.23 g, 2.5 mmol) was treated according to method G, part 2 to provide two diastereomers of (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-3,4,5,6,7,8,9,10-octahydrobenzo[*b*][1,7]naphthyridine-2(1*H*)-carboxylate. The less polar diastereomer (0.32 g): ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3H), 0.9 (m, 1H), 1.13 (m, 1H), 1.19 (s, 3H), 1.28 (m, 2H), 1.32 (s, 3H), 1.72 (m, 2H), 1.88 (m, 1H), 2.05 (m, 3H), 2.38 (m, 2H), 2.51 (m, 2H), 2.72 (d, 1H), 3.56 (d, 1H), 3.82 (d, 1H), 4.71 (m, 2H), 5.07 (s, 1H), 6.92 (t, 1H), 7.12 (m, 1H), 7.28 (m, 6H). The more polar diastereomer (0.24 g): ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3H), 0.92 (m, 1H), 1.13 (s, 3H), 1.18−1.32 (m, 6H), 1.73 (m, 2H), 1.92 (m, 1H), 2.05 (m, 3H), 2.38 (m, 2H), 2.53 (m, 2H), 2.81 (d, 1H), 3.2 (d, 1H), 3.9 (d, 1H), 4.56 (d, 1H), 4.75 (m, 1H), 5.1 (s, 1H), 6.41 (t, 1H), 6.8 (m, 2H), 7.05 (m, 1H), 7.12 (d, 1H), 7.31 (m, 1H), 7.4 (m, 1H), 7.5 (d, 1H). The less polar diastereomer (0.32 g) was reacted according to method G, part 3 to provide 0.125 g 25: $[\alpha]^{20}_D$ −10° (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 1.72−1.99 (m, 2H), 2.22 (t, 2H), 2.98 (m, 1H), 3.15 (s, 2H), 3.4 (m, 2H), 3.57 (s, 2H), 4.88 (s, 1H), 7.18 (m, 2H), 7.4 (d, 1H); MS (ESI$^-$) *m/z* 389 (M − H)$^-$. Anal. Calcd for $C_{18}H_{15}BrFN_2O_2\cdot HCl$: C, 50.67; H, 3.78; N, 6.57. Found: C, 50.18; H, 4.22; N, 6.16. The more polar diastereomer from above (0.24 g) was reacted according to method G, part 3 to provide 0.070 g of 26: $[\alpha]^{20}_D$ +9.52°

(CH_3CN); ^{1}H NMR (DMSO-d_6) δ 1.75−1.98 (m, 2H), 2.25 (t, 2H), 2.95 (s, 1H), 3.15 (s, 2H), 3.45 (m, 2H), 3.57 (s, 2H), 4.89 (s, 1H), 7.17 (m, 2H), 7.39 (d, 1H), 9.6 (s, 1H); MS (ESI$^-$) *m/z* 389 (M − H)$^-$. Anal. ($C_{18}H_{16}BrFN_2O_2$·HCl) C, H, N.

5-(3-Bromo-4-fluorophenyl)-5,7,8,9-tetrahydrocyclopenta[*b*]thiopyrano[4,3-*e*]pyridine-4,6(1*H*,3*H*)-dione (27). A mixture of 2*H*-thiopyran-3,5(4*H*,6*H*)-dione (**c4**), 3-bromo-4-fluorobenzaldehyde, and 3-aminocyclopent-2-en-1-one (**e1**) was treated according to method A and purified by flash chromatography on silica gel eluting with acetone:CH_2Cl_2 (1:1) to provide 0.13 g of **27**: ^{1}H NMR (DMSO-d_6) δ 2.28 (t, 2H), 2.48−2.73 (m, 2H), 3.14 (dd, 1H), 3.47 (dd, 1H), 3.54 (dd, 1H), 3.82 (dd, 1H), 4.72 (s, 1H), 7.18−7.25 (m, 2H), 7.42 (dd, 1H), 10.27 (s, 1H); MS (APCI$^+$) *m/z* 394 (M + H)$^+$. Anal. ($C_{17}H_{13}BrFNO_2S$) C, H, N.

8-(3-Bromo-4-fluorophenyl)-2,3,5,8-tetrahydrofuro[3,4-*b*]thieno[2,3-*e*]pyridin-7(4*H*)-one 1,1-Dioxide (29). A mixture of the dihydrothiophen-3(2*H*)-one 1,1-dioxide (**c7**) (1.29 g, 9.60 mmol), 3-bromo-4-fluorobenzaldehyde (2.03 g, 10.0 mmol), and methyl (2*E*)-3-aminobut-2-enoate (**e5**) (1.15 g, 10.0 mmol) was treated according to method B to provide 2.88 g of methyl 7-(3-bromo-4-fluorophenyl)-5-methyl-2,3,4,7-tetrahydrothieno[3,2-*b*]pyridine-6-carboxylate 1,1-dioxide: ^{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). This intermediate (0.83 g, 2.0 mmol) in $CHCl_3$ (40 mL) was treated with NBS (0.42 g, 2.4 mmol), stirred at room temperature for 30 min, concentrated to dryness, heated under N_2 to 130 °C for 15 min, and cooled to room temperature. The residue was purified by chromatography on silica gel eluting with MeOH:CH_2Cl_2 (3:97) to provide 0.085 g of **29**: ^{1}H NMR (DMSO-d_6) δ 2.80−2.92 (m, 1H), 2.99−3.12 (dt, 1H), 3.37−3.47 (m, 2H), 4.82 (s, 1H), 4.91 (AB q, 2H), 7.31 (m, 2H), 7.55 (dd, 1H), 10.40 (bs, 1H); MS (ESI$^+$) *m/z* 399 (M + H)$^+$. Anal. ($C_{15}H_{11}BrFO_4NS$) C, H, N.

(+)-9-(3-Bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2*H*-furo[3,4-*b*]thiopyrano[2,3-*e*]pyridin-8(5*H*)-one 1,1-Dioxide (31) and (−)-9-(3-Bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2*H*-furo[3,4-*b*]thiopyrano[2,3-*e*]pyridin-8(5*H*)-one 1,1-Dioxide (30). A mixture of 3-bromo-4-fluorobenzaldehyde (2.03 g, 10 mmol), methyl (2*E*)-3-aminobut-2-enoate (**e5**) (1.15 g, 10 mmol), and dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide (**c8**) (1.48 g, 10 mmol) in MeOH was treated according to method A at 65 °C for 24 h to provide 3.11 g of methyl 8-(3-bromo-4-fluorophenyl)-6-methyl-3,4,5,8-tetrahydro-2*H*-thiopyrano[3,2-*b*]pyridine-7-carboxylate 1,1-dioxide: ^{1}H NMR (DMSO-d_6) δ 2.18 (m, 2H), 2.27 (s, 3H), 2.43−2.55 (m, 2H), 3.14−3.22 (m, 2H), 3.58 (s, 3H), 4.97 (s, 1H), 7.19 (m, 1H), 7.25 (t, 1H), 7.36 (d, 1H), 9.12 (s, 1H). This intermediate (860 mg, 2.0 mmol) was treated according to method D, parts 1 and 2 to provide 345 mg of 9-(3-bromo-4-fluorophenyl)-3,4,6,9-tetrahydro-2*H*-furo[3,4-*b*]thiopyrano[2,3-*e*]pyridin-8(5*H*)-one 1,1-dioxide as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.18−2.22 (m, 2H), 2.56−2.61 (m, 2H), 3.18−3.23 (m, 2H), 4.86 (s, 1H), 4.87 (q, 2H), 7.28 (m, 2H), 7.47 (d, 1H), 10.03 (br s, 1H). To a suspension of this racemate (1.02 g, 2.46 mmol) in THF (10 mL) at 0 °C under N_2 was added slowly 1 M KOtBu/THF (2.46 mL), and the reaction warmed to room temperature for 10 min and cooled to 0 °C. A solution of 8-phenylmenthol chloroformate (0.727 g, 2.46 mmol, prepared from (−)-8-phenylmenthol) in THF (25 mL), was added. The reaction was warmed to room temperature 2 h, quenched in sat. $NaHCO_3$, and extracted with Et_2O:EtOAc (4:1). The organic portion was dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography on silica gel eluting with Et_2O:hexane (85:15) provided 750 mg of the less polar diastereomer and 655 mg of the more polar diastereomer. A solution of the less polar diastereomer (639 mg) in MeOH (10 mL) was treated with catalytic 25% NaOMe/MeOH under N_2. The solution slowly turned into a suspension. After completion of the reaction (evidenced by TLC), a few drops of AcOH were added, resulting in the formation of a precipitate that was isolated by filtration and dried to provide 210 mg of **31**: $[\alpha]^{20}_D$ +150.0° (DMSO); ^{1}H NMR (DMSO-d_6) δ 2.18−2.22 (m, 2H), 2.56−2.61 (m, 2H), 3.18−3.23 (m, 2H), 4.86 (s, 1H), 4.87 (q, 2H), 7.28 (m, 2H), 7.47 (d, 1H), 10.03 (br s, 1H); MS (ESI$^-$) *m/z* 412 (M − H)$^-$. Anal. ($C_{16}H_{13}BrFNO_4S$) C, H, N. The more polar diastereomer from above (655 mg) was reacted as described for the less polar diastereomer to provide 290 mg of **30** as a white solid: $[\alpha]^{20}_D$ −133.6° (DMSO); ^{1}H NMR (DMSO-d_6) δ 2.18−2.22 (m, 2H), 2.56−2.61 (m, 2H), 3.18−3.23 (m, 2H), 4.86 (s, 1H), 4.87 (q, 2H), 7.28 (m, 2H), 7.47 (d, 1H), 10.03 (br s, 1H); MS (ESI$^-$) *m/z* 412 (M − H)$^-$. Anal. ($C_{16}H_{13}BrFNO_4S$) C, H, N.

(+)-(9*R*)-(3-Bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4*H*-pyrano[3,4-*b*]thieno[2,3-*e*]pyridin-8(7*H*)-one 1,1-Dioxide (32) and (−)-9-(3-Bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4*H*-pyrano[3,4-*b*]thieno[2,3-*e*]pyridin-8(7*H*)-one 1,1-Dioxide (33). The racemic product from method B was separated into the individual enantiomers using the same protocol as used for examples **30** and **31** except eluting with 3:2:1 $CHCl_3$:hexanes:Et_2O during the separation of the diastereomeric intermediates. From the less polar diastereomeric intermediate (0.98 g, 1.4 mmol) was obtained 0.36 g of **32** (see the Supporting Information for X-ray crystal analysis): $[\alpha]^{23}_D$ +117° (*c* = 0.925, DMSO); ^{1}H NMR (DMSO-d_6) δ 2.85 (m, 1H), 3.08 (m, 1H), 3.33−3.42 (m, 2H), 4.03 (s, 2H), 4.49 (AB q, 2H), 4.90 (s, 1H), 7.27 (m, 2H), 7.45 (dd, 1H), 10.14 (s, 1H); MS (ESI$^+$) *m/z* 414 (M + H)$^+$. Anal. ($C_{16}H_{13}BrFNO_4S$): C, H, N. From the more polar diastereomeric intermediate (1.0 g, 15 mmol) was obtained 0.40 g of **33**: $[\alpha]^{23}_D$ −117° (*c* = 1.01, DMSO); ^{1}H NMR (DMSO-d_6) δ 2.85 (m, 1H), 3.08 (m, 1H), 3.33−3.42 (m, 2H), 4.03 (s, 2H), 4.49 (AB q, 2H), 4.90 (s, 1H), 7.27 (m, 2H), 7.45 (dd, 1H), 10.14 (s, 1H); MS (ESI$^+$) *m/z* 414 (M + H)$^+$. Anal. ($C_{16}H_{13}BrFNO_4S$): C, H, N.

10-(3-Bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2*H*,5*H*-pyrano[3,4-*b*]thiopyrano[2,3-*e*]pyridin-9(8*H*)-one 1,1-Dioxide (34). A mixture of 5-amino-2*H*-pyran-3(6*H*)-one (**e3**) (0.23 g, 2.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.49 g, 2.4 mmol), and dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide (**c8**) (0.30 g, 2.0 mmol) was treated according to method A to provide 0.25 g of **34**: ^{1}H NMR (DMSO-d_6) δ 2.22 (m, 2H), 2.41−2.56 (m, 1H), 2.64 (dt, 1H), 3.09−3.35 (m, 2H), 4.02 (s, 2H), 4.43 (AB q, 2H), 5.06 (s, 1H), 7.25 (m, 2H), 7.41 (dd, 1H), 9.67 (bs, 1H); MS (ESI$^+$) *m/z* 428 (M + H)$^+$. Anal. ($C_{17}H_{15}BrFNO_4S$) C, H, N.

8-(3-Bromo-4-fluorophenyl)-6-methyl-2,3,5,8-tetrahydropyrrolo[3,4-*b*]thieno[2,3-*e*]pyridin-7(4*H*)-one 1,1-Dioxide (35). Methyl 7-(3-bromo-4-fluorophenyl)-5-methyl-2,3,4,7-tetrahydrothieno[3,2-*b*]pyridine-6-carboxylate, 1,1-dioxide (52 mg, 0.13 mmol) from example **29** was treated according to method D, part 1 to provide an intermediate bromo derivative that was reacted directly with 2.0 M $MeNH_2$/MeOH (0.7 mL), stirred overnight at room temperature, and evaporated to dryness. The residue was flash chromatographed with 7.5% MeOH/CH_2Cl_2 to yield 26 mg of **35** as a light yellow solid: ^{1}H NMR (DMSO-d_6) δ 2.78 (s, 3H), 2.8−2.9 (m, 1H), 3.0−3.1 (m, 1H), 3.3−3.4 (m, 2H), 4.3 (AB q, 2H), 4.77 (s, 1H), 7.27 (m, 2H), 7.48 (d, 1H), 9.97 (s, 1H); MS (ESI$^-$) *m/z* 413 (M − H)$^-$. Anal. ($C_{16}H_{14}BrFN_2O_3S$·0.1H_2O) C, H, N.

9-(3-Bromo-4-fluorophenyl)-7-methyl-3,4,5,6,7,9-hexahydropyrrolo[3,4-*b*]thiopyrano[2,3-*e*]pyridin-8(2*H*)-one 1,1-Dioxide (36). A mixture of 3-bromo-4-fluorobenzaldehyde (2.03 g, 10 mmol), methyl (2*E*)-3-aminobut-2-enoate (**e5**) (1.15 g, 10 mmol), and dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide (**c8**) (1.48 g, 10 mmol) was treated according to method A to provide 3.11 g of methyl 8-(3-bromo-4-fluorophenyl)-6-methyl-3,4,5,8-tetrahydro-2*H*-thiopyrano[3,2-*b*]pyridine-7-carboxylate 1,1-dioxide: ^{1}H NMR (DMSO-d_6) δ 2.18 (m, 2H), 2.27 (s, 3H), 2.43−2.55 (m, 2H), 3.14−3.22 (m, 2H), 3.58 (s, 3H), 4.97 (s, 1H), 7.19 (m, 1H), 7.25 (t, 1H), 7.36 (d, 1H), 9.12 (s, 1H). This intermediate (107.5 mg, 0.25 mmol) was treated according to method D, part 1 and method E to provide 49 mg of **36** as a light yellow powder: ^{1}H NMR (DMSO-d_6) δ 2.18−2.24 (m, 2H), 2.58 (m, 2H), 2.78 (s, 3H), 3.16−3.22 (m, 2H), 3.98 (q, 2H), 4.86 (s, 1H), 7.26 (m, 2H), 7.43 (d, 1H), 9.60 (s, 1H); MS (ESI$^+$) *m/z* 427 (M + H)$^+$. Anal. Calcd for $C_{17}H_{16}BrFN_2O_3S$: C, 47.79; H, 3.77; N, 6.56. Found: C, 47.31; H, 4.03; N, 6.31.

9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno-[3,2-*b*][1,7]naphthyridin-8(4*H*)-one 1,1-Dioxide Hydrochloride (37). A solution of 1-benzylpiperidine-3,5-dione (**c5**) (0.55 g, 2.5 mmol) in EtOH (5 mL) was reacted with 2.0 M NH_3/EtOH (1.25 mL) for 4 h in a sealed tube, treated with dihydrothiophen-3(2*H*)-one 1,1-dioxide (**c7**) (0.33 g, 2.5 mmol) and 3-bromo-4-fluorobenzaldehyde (0.51 g, 2.5 mmol), stirred at 75 °C for 48 h, cooled, concentrated, and flash chromatographed over silica gel eluting with CH_2Cl_2/EtOH (90:10) to provide 0.28 g of 6-benzyl-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*][1,7]naphthyridin-8(4*H*)-one 1,1-dioxide: ^{1}H NMR (DMSO-d_6) δ 2.8 (m, 1H), 3.0 (m, 2H), 3.08−3.3 (m, 2H), 3.42 (m, 3H), 3.62 (m, 2H), 4.85 (s, 1H), 7.2−7.48 (m, 8H), 9.98 (s, 1H). This intermediate (0.22 g, 0.43 mmol) in CH_2Cl_2 (5 mL) was reacted with vinyl chloroformate (0.10 mL, 0.94 mmol) at room temperature for 24 h and partitioned between CH_2Cl_2/aq $NaHCO_3$. The organics were dried (Na_2SO_4), filtered, and concentrated to provide 0.28 g of vinyl 9-(3-bromo-4-fluorophenyl)-8-oxo-2,3,5,7,8,9-hexahydrothieno[3,2-*b*][1,7]-naphthyridine-6(4*H*)-carboxylate 1,1-dioxide: ^{1}H NMR (DMSO-d_6) δ 2.88 (m, 2H), 3.1 (m, 3H), 3.5 (m, 1H), 3.75 (q, 2H), 4.12 (s, 2H), 4.9 (s, 1H), 7.29 (m, 2H), 7.48 (d, 1H), 10.1 (s, 1H). This intermediate (0.28 g) in EtOH (5 mL) was reacted with 6 N HCl (1 mL) at reflux for 3 h, cooled to room temperature, concentrated, and flash chromatographed over silica gel eluting with CH_2Cl_2 (saturated with NH_4OH):EtOH (90:10) to provide 0.070 g of **37**: ^{1}H NMR (DMSO-d_6) δ 2.75 (m, 2H), 3.02 (m, 1H), 3.15 (s, 2H), 3.58 (m, 3H), 4.87 (s, 1H), 7.25 (d, 2H), 7.43 (d, 1H), 9.9 (s, 1H); MS (ESI$^-$) *m*/*z* 411 (M − H)$^-$. Anal. Calcd for $C_{16}H_{14}BrFN_2SO_3$·HCl·0.5C_2H_5OH: C, 43.19; H, 3.84; N, 5.93; Cl, 7.50. Found: C, 43.69; H, 3.85; N, 5.83; Cl, 7.66.

10-(3-Bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-2*H*-thiopyrano[3,2-*b*][1,7]naphthyridin-9(5*H*)-one 1,1-Dioxide Hydrochloride (38). A solution of 1-benzylpiperidine-3,5-dione (**c5**) (0.55 g, 2.5 mmol) in EtOH (5 mL) was reacted with 2.0 M NH_3/EtOH (1.25 mL, 2.5 mmol) for 30 min in a sealed tube, treated with dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide (**c8**) (0.36 g, 2.5 mmol) and 3-bromo-4-fluorobenzaldehyde (0.51 g, 2.5 mmol), stirred at 75 °C for 48 h, cooled, and concentrated. The residue was purified by flash chromatography over silica gel eluting with EtOH:CH_2Cl_2 (5:95) to provide 0.50 g of 7-benzyl-10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,-10-hexahydro-2*H*-thiopyrano[3,2-*b*][1,7]naphthyridin-9(5*H*)-one 1,1-dioxide: ^{1}H NMR (DMSO-d_6) δ 2.18 (m, 2H), 2.42 (m, 2H), 2.95 (m, 2H), 3.15 (m, 4H), 3.42 (m, 2H), 3.6 (q, 2H), 5.0 (s, 1H), 7.18−7.5 (m, 8H), 9.5 (s, 1H). This intermediate (0.48 g, 0.92 mmol) in THF (5 mL) was reacted with vinyl chloroformate (0.10 mL, 0.94 mmol) at room temperature for 24 h, the solvent was evaporated, and the residue was purified by flash chromatography over silica gel eluting with EtOH/CH_2Cl_2 (10:90) to provide 0.25 g of vinyl 10-(3-bromo-4-fluorophenyl)-9-oxo-3,4,6,8,9,10-hexahydro-2*H*-thiopyrano[3,2-*b*][1,7]-naphthyridine-7(5*H*)-carboxylate 1,1-dioxide: ^{1}H NMR (DMSO-d_6) δ 2.21 (m, 2H), 2.68 (m, 2H), 3.18 (m, 2H), 3.28 (m, 2H), 3.5 (m, 1H), 3.75 (q, 2H), 4.11 (s, 2H), 5.08 (s, 1H), 7.28 (m, 2H), 7.41 (d, 1H), 9.5 (br s, 1H). A solution of this intermediate (0.25 g) in EtOH was reacted with 6 N HCl (1 mL) at reflux for 2 h, cooled to room temperature, and concentrated. The residue was purified by flash chromatography over silica gel eluting with CH_2Cl_2 (saturated with NH_4OH):EtOH (85:15) to provide 0.09 g of **38**: ^{1}H NMR (DMSO-d_6) (free base) δ 2.2 (m, 2H), 2.6 (m, 2H), 3.15 (s, 2H), 3.22 (m, 2H), 3.52 (d, 2H), 5.02 (s, 1H), 7.22 (m, 2H), 7.4 (m, 1H), 9.5 (br s, 1H); MS (ESI$^-$) *m*/*z* 425 (M − H)$^-$. Anal. ($C_{17}H_{16}BrFN_2SO_3$·HCl·0.5C_2H_5OH) C, H, N.

8-(3-Bromo-4-fluorophenyl)-5,8-dihydro-1*H*,3*H*-difuro-[3,4-*b*:3,4-*e*]pyridine-1,7(4*H*)-dione (39). 3-Bromo-4-fluorobenzaldehyde (6.00 g, 29.6 mmol), ethyl acetoacetate (7.81 g, 60 mmol), and concentrated NH_4OH (6.2 mL, added in two portions over a period of 2 days) were reacted according to method C to provide 11.3 g of diethyl 4-(3-bromo-4-fluorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate as a light yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 6H), 2.35 (s, 6H), 4.10 (m, 4H), 4.94 (s, 1H), 5.56 (s, 1H), 6.95 (t, 1H), 7.18 (m, 1H), 7.42 (dd, 1H). This intermediate (1.27 g, 3.00 mmol) in MeOH (60 mL) was reacted with NBS (1.068 g, 6.00 mmol) for 1.5 h at room temperature and poured into water. The precipitate was collected and crystallized from acetone/hexane to provide 685 mg of diethyl 2,6-bis-(bromomethyl)-4-(3-bromo-4-fluorophenyl)-1,4-dihydro-3,5-pyridine dicarboxylate as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6H), 4.15 (m, 4H), 4.76 (AB q, 4H), 4.96 (s, 1H), 6.48 (s, 1H), 6.99 (t, 1H), 7.18 (m, 1H), 7.43 (dd, 1H). This intermediate (90 mg) was heated in an oil bath at 180 °C for 1 h, cooled to room temperature, and triturated with acetone. The solid was collected, washed with acetone, and dried to provide 32 mg of **39** as a light-yellow solid: ^{1}H NMR (DMSO-d_6) δ 4.69 (s, 1H), 4.98 (q, 4H), 7.32 (m, 2H), 7.57 (d, 1H), 10.73 (s, 1H); MS (ESI$^-$) *m*/*z* 364 (M − H)$^-$. Anal. ($C_{15}H_9BrFNO_4$) C, H, N.

5-(3-Bromo-4-fluorophenyl)-5,10-dihydro-1*H*,3*H*-dipyrano[3,4-*b*:4,3-*e*]pyridine-4,6(7*H*,9*H*)-dione (41). A mixture of dihydro-2*H*-pyran-2,4(3*H*)-dione (**c9**) (0.10 g, 0.88 mmol), 3-bromo-4-fluorobenzaldehyde (0.24 g, 1.2 mmol), and 5-amino-2*H*-pyran-3(6*H*)-one (**e3**) (0.10 g, 0.88 mmol) was treated according to method A to provide 0.20 g of **41**: ^{1}H NMR (DMSO-d_6) δ 4.06 (s, 4H), 4.41−4.60 (AB q, 4H), 4.94 (s, 1H), 7.19−7.32 (m, 2H), 7.42 (dd, 1H), 10.12 (br s, 1H); MS (APCI$^-$) *m*/*z* 392 (M − H)$^-$. Anal. ($C_{17}H_{13}BrFNO_4$·0.5H_2O) C, H, N.

9-(3-Bromo-4-fluorophenyl)-4,5,6,9-tetrahydro-1*H*-furo-[3,4-*b*]pyrano[3,4-*e*]pyridine-1,8(3*H*)-dione (42). A mixture of dihydro-2*H*-pyran-2,4(3*H*)-dione (**c9**) (0.171 g, 1.5 mmol), 3-bromo-4-fluorobenzaldehyde (0.304 g, 1.5 mmol), and methyl (2*E*)-3-aminobut-2-enoate (**e5**) (0.173 g, 1.5 mmol) was treated according to method A to provide 0.12 g of methyl 4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,5,7,8-tetrahydro-4*H*-pyrano-[4,3-*b*]pyridine-3-carboxylate. This intermediate (0.235 g, 0.59 mmol) was reacted according to method D, parts 1 and 2 but modified by conducting the cyclization in $CHCl_3$ (5 mL) at 50 °C for 12 h to provide 0.050 g of **42**: ^{1}H NMR (DMSO-d_6) δ 2.61 (ddd, 1H), 2.79 (ddd, 1H), 4.22−4.36 (m, 2H), 4.94 (s, 1H), 4.91 (ABq, 2H), 7.23−7.32 (m, 2H), 7.48 (dd, 1H), 10.34 (bs, 1H); MS (APCI$^+$) *m*/*z* 380 (M + H)$^+$. Anal. Calcd for $C_{16}H_{11}BrFNO_4$: C, 50.99; H, 3.47; N, 3.29. Found: C, 50.55; H, 2.92; N, 3.55.

(+)-(9*R*)-(3-Bromo-4-fluorophenyl)-5,9-dihydro-3*H*-furo-[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (43) and (−)-(9*S*)-(3-Bromo-4-fluorophenyl)-5,9-dihydro-3*H*-furo-[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (44). 9-(3-Bromo-4-fluorophenyl)-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione from method D was separated into the individual enantiomers by chiral chromatography on a Chiralpak AS column (5.0 cm inner diameter, 50 cm length, 20 micron packing) using hexane:EtOH (80:20) at a flow rate of 117 mL/min. From 227 mg of racemate in 100 mL of hot ethanol (three injections of 20, 40, and 40 mL) was obtained the less polar enantiomer which was repurified by flash chromatography on silica gel using a gradient of 1%−2% and 5% MeOH in CH_2Cl_2 to provide 0.080 g of **43**: [α] = +212 (*c* = 0.27, acetone); ^{1}H NMR (DMSO-d_6) δ 4.06 (s, 2H), 4.54 (AB q, 2H), 4.75 (s, 1H), 4.88 (d, 1H), 5.03 (d, 1H), 7.28 (d, 2H), 7.48 (d, 1H), 10.50 (s, 1H); MS (ESI$^+$) *m*/*z* 380 (M + H)$^+$. Anal. ($C_{16}H_{11}BrFNO_4$·0.19CH_2Cl_2) C, H, N. The absolute stereochemistry for **43** was determined via X-ray analysis (see the Supporting Information). From the preceding chiral chromatography was also obtained 0.080 g of the more polar enantiomer **44**: [α] = −212 (*c* = 0.25, acetone) ^{1}H NMR (DMSO-d_6) δ 4.06 (s, 2H), 4.54 (AB q, 2H), 4.75 (s, 1H), 4.88 (d, 1H), 5.03 (d, 1H), 7.28 (d, 2H), 7.48 (d, 1H), 10.50 (s, 1H); MS (ESI$^+$) *m*/*z* 380 (M + H)$^+$. Anal. ($C_{16}H_{11}BrFNO_4$·0.13CH_2Cl_2) C, H, N.

8-(3-Bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-*b*:3,4-*e*]pyridine-1,7-dione (45). Diethyl 2,6-bis-(bromomethyl)-4-(3-bromo-4-fluorophenyl)-1,4-dihydro-3,5-pyridine dicarboxylate from example **39** (0.29 g, 0.50 mmol) was treated with NH_3 (25 mL) in EtOH (25 mL) at room temperature for 2 days in a pressure bomb. The solvent was evaporated and the resultant solid triturated with hot EtOH/EtOAc. This solid was washed with water and then Et_2O and

dried to provide 26 mg of **45** as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 3.95 (q, 4H), 4.58 (s, 1H), 7.25 (d, 2H), 7.42 (s, 2H), 7.46 (s, 1H), 9.83 (s, 1H); MS (APCI$^+$) *m*/*z* 364 (M + H)$^+$. Anal. ($C_{15}H_{11}BrFN_3O_2 \cdot 0.3H_2O \cdot 0.5C_2H_6O$) C, H, N.

8-(3-Bromo-4-fluorophenyl)-2,6-dimethyl-2,3,4,5,6,8-hexahydrodipyrrolo[3,4-*b*:3,4-*e*]pyridine-1,7-dione (46). Diethyl 2,6-bis-(bromomethyl)-4-(3-bromo-4-fluorophenyl)-1,4-dihydro-3,5-pyridine dicarboxylate (0.812 g, 1.4 mmol) was treated according to method E to provide 183 mg of **46**: ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 6H), 4.05 (q, 4H), 4.59 (s, 1H), 7.22 (d, 2H), 7.45 (d, 1H), 9.88 (s, 1H); MS (APCI$^+$) *m*/*z* 392 (M + H)$^+$. Anal. ($C_{17}H_{15}BrFN_3O_2 \cdot 0.25\ H_2O$) C, H, N.

10-(3-Bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydropyrido[4,3-*b*][1,6]naphthyridine-1,9(2*H*,5*H*)-dione (47). A mixture of 3-bromo-4-fluorobenzaldehyde (1 mmol, 203 mg) and piperidine-2,4-dione (**c10**) (2 mmol, 226 mg) was treated according to method C to provide 150 mg of **47**: ^{1}H NMR (DMSO-d_6) δ 2.32−2.56 (m, 4H), 3.12−3.22 (m, 4H), 4.93 (s, 1H), 6.94 (bs, 2H), 7.18−7.22 (m, 2H), 7.42 (dd, 1H), 8.98 (s, 1H); MS (APCI$^+$) *m*/*z* 392 (M + H)$^+$. Anal. ($C_{17}H_{15}BrFN_3O_2$) C, H, N.

5-(3-Bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydropyrido[3,4-*b*][1,7]naphthyridine-4,6(1*H*,7*H*)-dione Dihydrochloride (48). A mixture of 1-benzylpiperidine-3,5-dione (**c5**) (2.2 g, 10 mmol) and 3-bromo-4-fluorobenzaldehyde (1.02 g, 5.0 mmol) was treated according to method C to provide 0.62 g of 2,8-dibenzyl-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydropyrido[3,4-*b*][1,7]naphthyridine-4,6(1*H*,7*H*)-dione: ^{1}H NMR (DMSO-d_6) δ 2.97 (d, 2H), 3.16 (m, 2H), 3.42 (m, 3H), 3.61 (q, 4H), 4.82 (s, 1H), 7.13−7.42 (m, 13H), 9.32 (s, 1H). This intermediate (0.5 g, 0.87 mmol) was debenzylated as in example **37** to provide 0.3 g of divinyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-4,5,6,7,9,10-hexahydropyrido[3,4-*b*][1,7]naphthyridine-2,8(1*H*,3*H*)-dicarboxylate: ^{1}H NMR (DMSO-d_6) δ 3.95 (d, 2H), 4.2 (d, 2H), 4.46 (d, 2H), 4.65 (d, 2H), 4.77−4.94 (m, 4H), 5.15 (s, 1H), 7.0 (t, 1H), 7.1 (d, 1H), 7.14 (d, 1H), 7.32 (m, 1H), 7.4 (m, 1H). This intermediate was deprotected using the same procedure as **37** to provide 0.12 g of **48**: ^{1}H NMR (DMSO-d_6) (free base) δ 3.78 (q, 4H), 4.22 (q, 4H), 4.95 (s, 1H), 7.22 (t, 1H), 7.32 (m, 1H), 7.48 (dd, 1H), 11.48 (s, 1H); MS (ESI$^-$) *m*/*z* 391 (M − H)$^-$. Anal. Calcd for $C_{17}H_{15}BrFN_3O_2 \cdot 2HCl$: C, 43.90; H, 3.68; N, 9.03. Found: C, 44.45; H, 3.86; N, 8.75.

5-(3-Bromo-4-fluorophenyl)-5,10-dihydro-1*H*,3*H*-bisthiopyrano[3,4-*b*:4′,3′-*e*]pyridine-4,6(7*H*,9*H*)-dione (49). A solution of 2*H*-thiopyran-3,5(4*H*,6*H*)-dione (**c4**) (0.51 g, 3.9 mmol) in EtOH (25 mL) was treated with concentrated H_2SO_4 (0.5 mL), heated to 80 °C under N_2 for 4 h, cooled to room temperature, and poured into a mixture of Et_2O (250 mL) and aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated to provide 0.55 g of crude 5-ethoxy-2*H*-thiopyran-3(6*H*)-one as an oil: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H), 3.24 (s, 2H), 3.34 (s, 2H), 3.93 (q, 2H), 5.37 (2, 1H); MS (DCI/NH_3): *m*/*z* 159 (M + H)$^+$. This intermediate was treated with 2 M NH_3/MeOH (40 mL), stirred for 40 h, concentrated, and flash chromatographed on silica eluting with 5%−10% MeOH/CH_2Cl_2 to provide 0.30 g of 5-amino-2*H*-thiopyran-3(6*H*)-one: ^{1}H NMR (DMSO-d_6) δ 3.03 (s, 2H), 3.32 (s, 2H), 4.94 (s, 1H), 6.95 (bs, 2H); MS (DCI/NH_3) *m*/*z* 130 (M + H)$^+$. A mixture of the intermediate enamine (0.065 g, 0.51 mmol), 3-bromo-4-fluorobenzaldehyde (0.13 g, 0.66 mmol), and thiopyran-3,5-dione (0.065 g, 0.51 mmol) was treated according to method A to provide 0.021 g of **49**: ^{1}H NMR (DMSO-d_6) δ 3.11 (dd, 2H), 3.45 (dd, 2H), 3.51 (dd, 2H), 3.81 (d, 2H), 5.01 (s, 1H), 7.19 (dt 1H), 7.25 (t 1H), 7.39 (dd, 1H), 9.90 (bs, 1H); MS (ESI$^+$) *m*/*z* 425 (M + H)$^+$. Anal. ($C_{17}H_{13}BrFO_2NS_2$) C, H, N.

8-(3-Bromo-4-fluorophenyl)-4,5,6,8-tetrahydro-1*H*-furo[3,4-*b*]pyrrolo[3,4-*e*]pyridine-1,7(3*H*)-dione (50). A mixture of pyrrolidine-2,4-dione[24] (**c11**) (2 mmol, 198 mg), 3-bromo-4-fluorobenzaldehyde (2 mmol, 406 mg), and methyl (2*E*)-3-aminobut-2-enoate (**e5**) (2 mmol) was treated according to method A to provide 165 mg of methyl 4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylate. This intermediate was reacted according to the procedure for **42** to provide 42 mg of **50**: ^{1}H NMR (DMSO-d_6) δ 4.00 (ABq, 2H), 4.61 (s, 1H), 4.91 (AB q, 2H), 7.24−7.30 (m, 2H), 7.50 (d, 1H), 7.58 (s, 1H); MS (APCI$^+$) *m*/*z* 365 (M + H)$^+$. Anal. ($C_{15}H_{10}N_2O_3FBr$ 1.0 H_2O) C, H, N.

9-(3-Bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-*b*][1,7]naphthyridine-1,8(3*H*,4*H*)-dione Hydrochloride (51). A mixture of methyl (2*E*)-3-aminobut-2-enoate (**e5**) (0.58 g, 5 mmol), 3-bromo-4-fluorobenzaldehyde (1.0 g, 5 mmol), and 1-benzylpiperidine-3,5-dione (**c5**) (1.1 g, 5 mmol) was treated according to method A and purified by flash chromatography over silica gel eluting with EtOH:CH_2Cl_2 (5:95) to provide 1.3 g of methyl 7-benzyl-4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro[1,7]naphthyridine-3-carboxylate. This intermediate (3.1 g) was reacted according to method D, parts 1 and 2 but modified by conducting the cyclization for 16 h in $CHCl_3$ at reflux to provide 2.1 g of 6-benzyl-9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-*b*][1,7]naphthyridine-1,8(3*H*,4*H*)-dione: ^{1}H NMR (DMSO-d_6) δ 3.08 (AB q, 2H), 3.5 (d, 2H), 3.65 (d,2H), 4.7 (s, 1H), 4.9 (AB q, 2H), 7.3 (m, 7H), 7.47 (m, 1H). 10.1 (1H). This intermediate (0.35 g, 0.75 mmol) was deprotected using the same procedure as in example **37** to provide 0.08 g of **51**: mp 255−257 °C; ^{1}H NMR (DMSO-d_6) (free base) δ 3.2 (s, 2H), 3.62 (s, 2H), 4.7 (s, 1H), 4.83 (d, 1H), 4.99 (d, 1H), 7.27 (m, 2H), 7.49 (dd, 1H), 10.25 (s, 1H); MS (ESI$^-$) *m*/*z* 377 (M − H)$^-$. Anal. ($C_{16}H_{11}BrFN_2O_3 \cdot HCl \cdot 0.5C_2H_5OH$) C, H, N.

9-(3-Bromo-4-fluorophenyl)-5,9-dihydro-3*H*-furo[3,4-*b*]-thiopyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (52). A mixture of the 2*H*-thiopyran-3,5(4*H*,6*H*)-dione (**c4**) (1.0 g, 7.7 mmol), 3-bromo-4-fluorobenzaldehyde (2.0 g, 10 mmol), and methyl (2*E*)-3-aminobut-2-enoate (**e5**) (1.1 g, 9.2 mmol) was treated according to method A to provide 1.8 g of methyl 4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-4,5,6,8-tetrahydro-1*H*-thiopyrano[3,4-*b*]pyridine-3-carboxylate. This intermediate (0.50 g, 1.2 mmol) was treated according to method D, parts 1 and 2 to provide 0.076 g of **52**: ^{1}H NMR (DMSO-d_6) δ 3.18 (dd, 1H), 3.49 (dd, 1H), 3.56 (dd, 1H), 3.82 (d, 1H), 4.74 (s, 1H), 4.73 (d 1H), 4.98 (d 1H), 7.26 (m 2H), 7.45 (dd, 1H), 10.38 (bs, 1H); MS (ESI$^+$) *m*/*z* 396 (M + H)$^+$. Anal. ($C_{16}H_{11}BrFO_3NS \cdot 0.5C_4H_8O_2$) C, H, N.

9-(3-Bromo-4-fluorophenyl)-2,3,5,9-tetrahydropyrano-[3,4-*b*]pyrrolo[3,4-*e*]pyridine-1,8(4*H*,7*H*)-dione (53). The product from method D, part 1 (0.22 g, 0.46 mmol) was treated according to method E with NH_3 (30 mL) in MeOH (30 mL) in a metal Parr reactor with stirring for 2.5 days at room temperature to provide 0.026 g of **53**: ^{1}H NMR (DMSO-d_6) δ 3.90 (d, 1H), 4.03 (s, 2H), 4.07 (d, 1H), 4.50 (AB q, 2H), 4.75 (s, 1H), 7.19−7.29 (m, 2H), 7.44 (dd, 1H), 7.59 (s, 1H), 10.09 (s, 1H); MS (ESI$^+$) *m*/*z* 379 (M + H)$^+$. Anal. ($C_{16}H_{12}BrFN_2O_3 \cdot 0.5H_2O$) C, H, N.

10-(3-Bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2*H*-pyrano[3,4-*b*][1,6]naphthyridine-1,9(5*H*,8*H*)-dione (55). A mixture of 5-amino-2*H*-pyran-3(6*H*)-one (**e3**),[20] 3-bromo-4-fluorobenzaldehyde, and piperidine-2,4-dione (**c10**) was treated according to method A to provide **55**: ^{1}H NMR (DMSO-d_6) δ 2.38−2.60 (m, 2H), 3.18−3.26 (m, 2H), 4.00 (s, 2H), 4.45 (AB q, 2H), 4.95 (s, 1H), 7.14 (s, 1H), 7.16−7.28 (m, 2H), 7.41 (dd, 1H), 9.59 (s, 1H); MS (APCI$^+$) *m*/*z* 393 (M + H)$^+$. Anal. ($C_{17}H_{14}BrFN_2O_3$) C, H, N.

5-(3-Bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1*H*-pyrano[3,4-*b*][1,7]naphthyridine-4,6(3*H*,7*H*)-dione Hydrochloride (56). A mixture of 5-amino-2*H*-pyran-3(6*H*)-one (**e3**), 3-bromo-4-fluorobenzaldehyde, 1-benzylpiperidine-3,5-dione (**c5**) was treated according to method A to provide 8-benzyl-5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1*H*-pyrano[3,4-*b*][1,7]naphthyridine-4,6(3*H*,7*H*)-dione. This intermediate (0.29 g, 0.69 mmol) was debenzylated using the two-step protocol for example **37** to provide 0.080 g of **56**: mp 232−235 °C; ^{1}H NMR (DMSO-d_6) δ 3.78 (AB q, 2H), 4.07 (s, 2H), 4.19 (s, 2H), 4.54 (AB q, 2H), 4.95 (s, 1H), 7.27 (m, 2H), 7.46 (dd, 1H), 9.86 (bs, 2H), 10.71 (s, 1H); MS (ESI$^+$) *m*/*z* 393 (M + H)$^+$. Anal. ($C_{17}H_{14}BrFN_2O_3 \cdot H_2O \cdot 0.25EtOH$) C, H, N.

5-(3-Bromo-4-fluorophenyl)-5,10-dihydro-1*H*,3*H*-pyrano-[3,4-*b*]thiopyrano[4,3-*e*]pyridine-4,6(7*H*,9*H*)-dione (57). A mixture of 5-amino-2*H*-pyran-3(6*H*)-one (**e3**) (0.23 g, 2.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.49 g, 2.4 mmol), 2*H*-thiopyran-3,5(4*H*,6*H*)-dione (**c4**) (0.26 g, 2.0 mmol) was treated according to method A to provide 0.37 g of **57**. ^{1}H NMR (DMSO-d_6) δ 3.12 (d, 1H), 3.50 (d, 2H), 3.81 (dd, 1H), 4.03 (s, 2H), 4.48 (AB q, 2H), 4.97 (s, 1H), 7.20 (ddd, 1H), 7.26 (t, 1H), 7.40 (dd, 1H), 9.98 (bs, 1H); MS (ESI$^+$) *m*/*z* 410 (M + H)$^+$. Anal. ($C_{17}H_{13}BrFNO_3S$) C, H, N.

(9*S*)-9-(3-Bromo-4-fluorophenyl)-2-(2-ethoxyethyl)-2,3,5,6,7,9-hexahydro-1*H*-pyrrolo[3,4-*b*]quinoline-1,8(4*H*)-dione (59). The product from method F, part 3B was treated according to method D, part 1 and method E (substituting 2-ethoxyethylamine for methylamine) to provide **59** as a yellow solid: [α] = −103.52 (DMSO); ^{1}H NMR (DMSO-d_6) δ 1.6 (t, 3H), 1.85−1.94 (m, 2H), 2.22−2.28 (m, 2H), 2.53−2.58 (m, 2H), 3.34−3.45 (m, 6H), 4.18 (q, 2H), 4.70 (s, 1H), 7.17−7.22 (m, 2H), 7.42 (d, 1H), 9.82 (s, 1H); MS (ESI$^+$) *m*/*z* 449 (M + H)$^+$. Anal. ($C_{21}H_{22}BrFN_2O_3$) C, H, N.

Biology. Conscious Spontaneously Hypertensive Rat (SHR) Assay. Male spontaneously hypertensive rats (300−350 g, Charles River Laboratories, Wilmington, MA) were anesthetized with methoxyflurane (Penthrane, Abbott Labs, North Chicago, IL). The left femoral artery and vein were catheterized using polyethylene (PE50) tubing for the measurement of arterial pressure and drug administration, respectively. The catheters were filled with a 0.9% saline solution containing 10 U of heparin/mL and were passed subcutaneously to a point behind the neck and exteriorized through a skin puncture. The rats were placed in Centrap restraining cages (12.5 × 4 × 3.5 In., Biodec, Inc., Cincinnati, OH) and allowed to recover from surgery for 2−3 h before dosing. The arterial catheter was connected to a Gould Statham p23ID transducer and the pressure waveform was recorded on a Grass 7D polygraph. Mean arterial pressure (MAP) (mmHg) and heart rate (HR) (beats/min) were determined on-line using a BUXCO cardiovascular analyzer (BUXCO Electronics, Sharon, CT) and stored on a MicroVAX II computer (Digital Equipment Corporation, Nashua, NH). After a 30 min predose control period, each rat was given a slow iv bolus of a test compound over a period of 1 min, and the MAP and HR were monitored for changes. Subsequent cumulative doses were given after MAP and HR changes had reached their respective maxima and responses had begun to return to baseline. At the end of each experiment, P1075 was administered at 1 μmol/kg iv bolus to establish a maximum response level for changes in MAP and confirm the site of iv drug injections. MAP and HR data were collected over a 2.5 min period at the point of maximum response for each dosing period, and the percent change from an average pre-dose control value was calculated. Dose−response curves were generated and the results were expressed as pED_{50} (−log ED_{50}). For iv dosing, compounds were dissolved in an aqueous solution containing equal parts of a hydroxypropyl-β-cyclodextrin solution (100 g/200 mL water) and sterile water.

Supporting Information Available: X-ray crystallographic analysis of various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Although the preferred sense of the absolute stereochemistry is the same for **10** and **32**, the stereochemical designation of R or S is opposite due to the priority of sulfur for example **32**.

(17) See examples **13** and **14** from the companion paper (Carroll, W. A.; et al. *J. Med. Chem.* **2004**, *47*, 3163−3179.

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