Effects of Substitution on 9-(3-Bromo-4-fluorophenyl)-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione, a Dihydropyridine ATP-Sensitive Potassium Channel Opener

Robert J. Altenbach,* Michael E. Brune, Steven A. Buckner, Michael J. Coghlan,† Anthony V. Daza, Adebola Fabiyi,‡ Murali Gopalakrishnan, Rodger F. Henry, Albert Khilevich,† Michael E. Kort, Ivan Milicic, Victoria E. Scott, Jamie C. Smith,§ Kristi L. Whiteaker, and William A. Carroll

Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064-6123

Received May 10, 2006

Structure−activity relationships were investigated on the tricyclic dihydropyridine (DHP) K_{ATP} openers 9-(3-bromo-4-fluorophenyl)-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (**6**) and 10-(3-bromo-4-fluorophenyl)-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (**65**). Substitution off the core of the DHP, absolute stereochemistry, and aromatic substitution were evaluated for K_{ATP} channel activity using Ltk− cells stably transfected with the Kir6.2/SUR2B exon 17− splice variant and in an electrically stimulated pig bladder strip assay. A select group of compounds was evaluated for in vitro inhibition of spontaneous bladder contractions. Several compounds were found to have the unique characteristic of partial efficacy in both the cell-based and electrically stimulated bladder strip assays but full efficacy in inhibiting spontaneous bladder strip contractions. For compound **23b**, this profile was mirrored in vivo where it was fully efficacious in inhibiting spontaneous myogenic bladder contractions but only partially able to reduce neurogenically mediated reflex bladder contractions.

Introduction

Overactive bladder (OAB) is a symptomatic diagnosis and is defined as the urgency to urinate with or without urge incontinence. OAB is usually accompanied by frequency and nocturia. The etiology of OAB has been linked to detrusor overactivity, which is characterized by involuntary detrusor contractions during the filling phase.[1] OAB has been reported to result from both myogenic and neurogenic origins.[2,3] The myogenic component is hypothesized to result from a reduction in the activity of the efferent nerves of the bladder. This reduction in efferent activity leads to alterations in the properties of the detrusor, which include increases in detrusor excitability and increases in the electrical coupling of the smooth muscle cells throughout the bladder wall. Many detrusor strips from unstable bladders show abnormal spontaneous mechanical activity. The neurogenic component is believed to result from damage to central inhibitory pathways or sensitization of peripheral afferent nerves of the bladder, both of which can unmask primitive voiding reflexes that trigger bladder overactivity.

ATP-sensitive potassium (K_{ATP}) channels[4] have been found in many tissues including smooth muscle in the vasculature and the bladder.[5] K_{ATP} channel openers[6] relax smooth muscle by increasing the permeability of the cell membrane to potassium ions, which results in hyperpolarization, decreased Ca^{2+} influx, and inhibition of contraction. K_{ATP} channel openers may be useful in the treatment of OAB because they have the potential to eliminate undesired bladder contractions during the filling phase by stabilizing the smooth muscle without affecting normal micturition.[7] For example, the K_{ATP} channel opener cromakalim (**2**) was shown to inhibit spontaneous contractions in vivo in pigs without compromising normal voiding.[8]

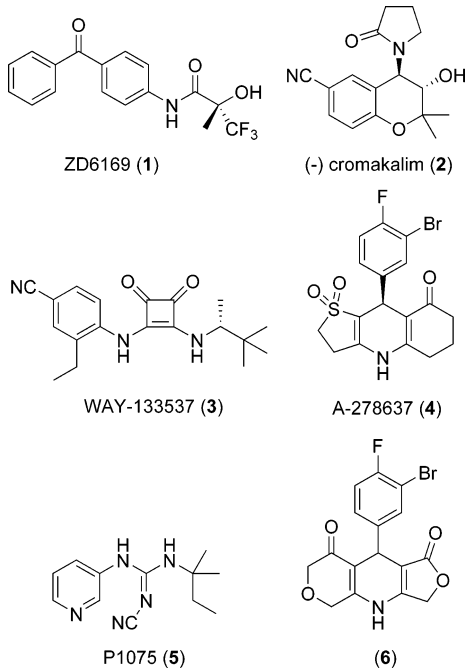


Figure 1.

The K_{ATP} channel openers ZD6169 (**1**)[9] and cromakalim (**2**)[10] have been evaluated clinically for OAB (Figure 1). ZD6169 was further evaluated but subsequently withdrawn from phase II trials perhaps because of an unfavorable side effect/efficacy profile[11] that may have included hypotensive effects. Recently, other K_{ATP} channel openers such as WAY-133537[12] (**3**) and A-278637[13] (**4**) have been reported to have selectivity for bladder versus cardiovascular effects in preclinical models.

We have recently published on a variety of tricyclic dihydropyridine (DHP) K_{ATP} channel openers,[14−17] several of which

* To whom correspondence should be addressed. Phone: 847-935- 4194. Fax: 847-937-9195. E-mail: Robert.j.altenbach@abbott.com.

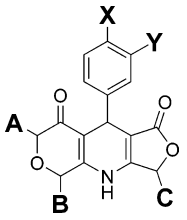
† Current address: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.

‡ Current address: John Radcliffe Hospital, Headley Way, Headington, Oxford, Oxfordshire, OX3 9DU.

§ Current address: Cumbre Inc., 1502 Viceroy Drive, Dallas, TX 75235.

10.1021/jm060549u CCC: $33.50
Published on Web 10/14/2006

Table 1. Substitutions to Compound **6** and Activity at Kir6.2/Sur2B 17− K_{ATP} Channels[a]



A	B	C	X, Y	isomer[b]	racemate	$pEC_{50} \pm SEM$ (% efficacy)	(+)-enantiomer	$pEC_{50} \pm SEM$ (% efficacy)	(−)-enantiomer	$pEC_{50} \pm SEM$ (% efficacy)
H	H	H	F, Br		**6**	7.34 ± 0.05 (92)[c]	**6a**[d]	7.20 ± 0.00 (107)[c]	**6b**	7.43 ± 0.17 (101)
Me	H	H	F, Br	cis	**7**	6.30 ± 0.44 (81)	**7a**	6.76 ± 0.13 (17)[c]	**7b**	6.29 ± 0.12 (94)[c]
Me	H	H	F, Br	trans	**8**	6.34 ± 0.04 (104)[c]	**8a**	7.14 ± 0.00 (15)[c]	**8b**	6.53 ± 0.12 (16)[c]
di-Me	H	H	F, Br		**9**	7.62 ± 0.04 (86)[c]	**9a**	7.57 ± 0.2 (104)	**9b**	5.55 (77)[e]
Et	H	H	F, Br	cis	**10**	<5[c]	**10a**	6.11 ± 0.12 (83)[c]	**10b**	5.86 ± 0.07 (46)[c]
Et	H	H	F, Br	trans	**11**	5.99 ± 0.16 (97)[c]				
H	Me	H	F, Br	cis	**12**	8.74 ± 0.33 (96)				
H	Me	H	F, Br	trans	**13**	6.99 ± 0.15 (73)				
H	di-Me	H	F, Br		**14**	6.92 ± 0.13 (73)				
H	Et	H	F, Br	cis	**15**	7.74 ± 0.22 (90)[c]				
H	Et	H	F, Br	trans	**16**	6.03 ± 0.14 (74)				
H	H	Me	F, Br	cis	**17**	8.26 ± 0.36 (100)[c]	**17a**	9.04 ± 0.12 (105)	**17b**[f]	7.29 ± 0.35 (89)
H	H	Me	F, Br	trans	**18**	6.00 ± 0.02 (75)[c]	**18a**	7.19 ± 0.10 (86)	**18b**	6.59 ± 0.07 (85)[c]
H	H	di-Me	F, Br		**19**	7.57 ± 0.05 (77)[c]				
H	H	Et	F, Br	cis	**20**	7.45 ± 0.01 (74)[c]	**20a**	8.41 ± 0.18 (101)[c]	**20b**	6.84 ± 0.08 (85)[c]
H	H	Et	F, Br	trans	**21**	7.02 ± 0.08 (40)	**21a**[d]	5.14 ± 0.09 (54)	**21b**	6.77 ± 0.10 (46)
H	H	*n*-Pr	F, Br	cis	**22**	8.29 ± 0.05 (90)[c]	**22a**	9.00. ± 0.06 (82)[c]	**22b**	8.43 ± 0.07 (66)
H	H	*n*-Pr	F, Br	trans	**23**	6.81 ± 0.14 (36)	**23a**	5.49 ± 0.07 (75)[c]	**23b**	7.56 ± 0.23 (45)
H	H	CH_2OMe	F, Br	cis	**24**	8.01 ± 0.05 (100)[c]				
H	H	CH_2OMe	F, Br	trans	**25**	7.64 ± 0.00 (103)[c]	**25a**	6.32 ± 0.2 (95)[c]	**25b**	7.64 ± 0.03(104)[c]
H	H	*i*-Pr	F, Br	cis	**26**	<5				
H	H	*i*-Pr	F, Br	trans	**27**	<5[c]				
H	H	*n*-Bu	F, Br	cis	**28**	7.53 (67)[e]				
H	H	*n*-Bu	F, Br	trans	**29**	5.66 (61)[e]	**29a**	5.29 ± 0.03 (62)	**29b**	6.07 ± 0.20 (68)[c]
H	H	*i*-Bu	F, Br	cis	**30**	7.56 (83)[e]				
H	H	*i*-Bu	F, Br	trans	**31**	<5[c]	**31a**	5.60 ± 0.10 (66)[c]	**31b**	@5 (59)[c]
H	H	*n*-Pn	F, Br	cis	**32**	<5[c]				
H	H	*n*-Pn	F, Br	trans	**33**	<5[c]				
H	H	Ph	F, Br	cis	**34**	6.59 ± 0.02 (68)[c]				
di-Me	H	Et	F, Br	cis	**35**	7.84 ± 0.12 (105)[c]				
di-Me	H	Et	F, Br	trans	**36**	6.55 ± 0.04 (70)[c]	**36a**	6.36 ± 0.13 (89)[c]	**36b**	6.26 ± 0.26 (34)[c]
H	di-Me	Et	F, Br	cis	**37**	5.76 ± 0.10 (59)[c]				
H	di-Me	Et	F, Br	trans	**38**	5.46 ± 0.15 (48)[c]	**38a**	5.80 ± 0.03 (77)[c]	**38b**	<5[c]
H	H	*n*-Pr	F, Cl	trans	**39**	7.17 ± 0.16 (42)[d]	**39a**	5.47 ± 0.02 (74)[d]	**39b**	7.04 ± 0.34 (39)[d]
H	H	*n*-Pr	F, I	trans	**41**	7.12 ± 0.00 (105)[d]	**41a**	5.71 ± 0.02 (81)[d]	**41b**	7.57 ± 0.02 (94)[d]
H	H	*n*-Pr	Cl, Cl	trans	**42**	6.22 ± 0.10 (95)[d]	**42a**	5.88 ± 0.09 (87)[d]	**42b**	5.70 ± 0.25 (62)[d]
H	H	*n*-Pr	Cl, Br	trans	**43**	6.76 ± 0.01 (120)[d]	**43a**	6.09 ± 0.08 (90)[d]	**43b**	6.82 ± 0.08 (99)[d]
H	H	*n*-Pr	Br, Cl	trans	**44**	6.37 ± 0.02 (97)[d]	**44a**	5.98 ± 0.01 (121)[d]	**44b**	6.36 ± 0.01 (92)[d]
H	H	*n*-Pr	Br, Br	trans	**45**	6.48 ± 0.06 (119)[d]	**45a**	5.94 ± 0.04 (104)[d]	**45b**	6.90 ± 0.05 108)[d]
H	H	*n*-Pr	Me, Br	trans	**46**	6.40 ± 0.03 (104)[d]	**46a**	5.46 ± 0.08 (81)[d]	**46b**	6.66 ± 0.08 (87)[d]
ZD-6169					**1**	5.87 ± 0.08 (100)				
(−)-cromakalim					**2**	6.22 ± 0.02 (83)				
WAY-133537					**3**	5.63 ± 0.07 (71)				
A-278637					**4**	6.80 ± 0.08 (90)				
P1075					**5**	7.28 ± 0.08 (101)				

[a] Number of observations is ≥3, unless otherwise specified. Values are expressed as the average $pEC_{50} \pm$ the standard error of the mean (SEM). The efficacy (in parentheses) is the average maximum response of each compound expressed as % relative to **5**. [b] Regiochemistry is reported as either cis or trans and is based on compounds **7**, **12**, and **17**, the structures of which were confirmed by X-ray. [c] $n = 2$. [d] Absolute stereochemistry confirmed by X-ray: **6a** is (*R*)-stereochemistry and **21a** is (*R*)-stereochemistry at the benzylic position. [e] $n = 1$. [f] Absolute stereochemistry of 3-fluoro-4-iodo analogue of compound **17b** confirmed by X-ray to be (*S*)-stereochemistry.

were shown to have greater potency for inhibiting spontaneous bladder contractions relative to their potencies to inhibit contractions elicited by electrical stimulation. In vitro selectivity for relaxing spontaneous bladder contractions over electrically stimulated bladder contractions may be predictive of in vivo selectivity for suppressing unstable bladder contractions versus normal micturition and/or cardiovascular effects. We were interested in exploring the effects of substitution on the DHP core with the objective of finding compounds that were even more selective for spontaneous versus electrically stimulated contractions. The tricyclic DHP **6**,[17] a potent K_{ATP} channel opener, was chosen as a scaffold. Compound **6** was attractive from a synthetic point of view because derivatives of **6** with substitutions at positions A, B, and C (see Table 1) could be readily synthesized. Additionally, the symmetrical bis-pyran, compound **65**, was also amenable to substitution, and derivatives of this compound were evaluated. We describe herein our findings.

Chemistry

The Hantzsch reaction was used to synthesize the substituted tricyclic DHPs described herein. An appropriate carbonyl-containing substrate selected from **c1**−**c12** (Figure 2) and an enamine selected from **e1**−**e17** (Figure 3) were reacted in EtOH at 80 °C to provide a DHP (method A, Scheme 1). In the

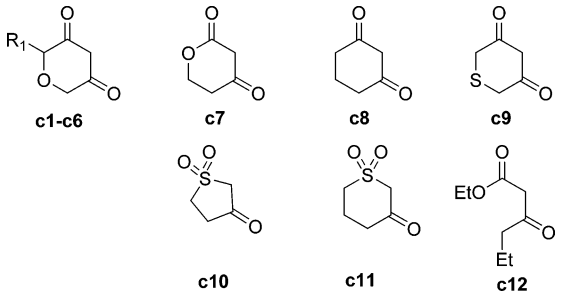


Figure 2. Carbonyl monomers: **c1**, R_1 = H; **c2**, R_1 = Me; **c3**, R_1 = di-Me; **c4**, R_1 = Et; **c5**, R_1 = di-Et; **c6**, R_1 = $-(CH_2)_4-$.

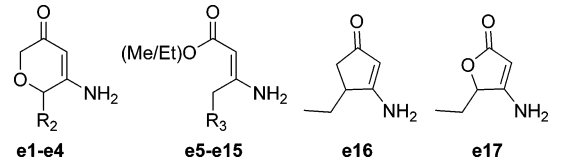
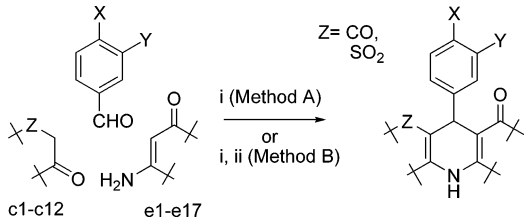


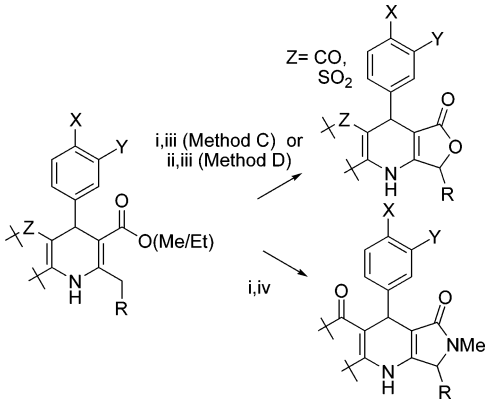
Figure 3. Enamine monomers: **e1**, R_2 = H; **e2**, R_2 = Me; **e3**, R_2 = di-Me; **e4**, R_2 = Et; **e5**, R_3 = H; **e6**, R_3 = Me; **e7**, R_3 = di-Me; **e8**, R_3 = Et; **e9**, R_3 = n-Pr; **e10**, R_3 = CH_2OMe; **e11**, R_3 = *i*-Pr; **e12**, R_3 = *n*-Bu; **e13**, R_3 = CH_2CHMe_2; **e14**, R_3 = *n*-Pn; **e15**, R_3 = Ph.

Scheme 1[a]



[a] Conditions: (i) EtOH, 80 °C, 16 h; (ii) 0.5 equiv of 1 M HCl in Et_2O, 80 °C, 45 min.

Scheme 2[a]



[a] Conditions: (i) pyridinium tribromide/pyridine, $CHCl_3$; (ii) NBS, $CHCl_3$; (iii) 130 °C, 15 min; (iv) $MeNH_2$, EtOH, 80 °C, 16 h.

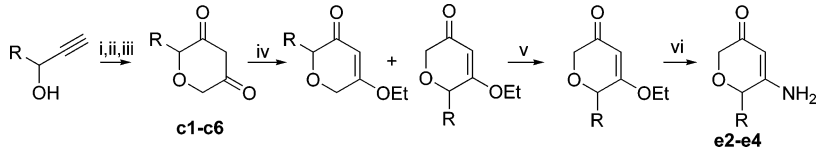
synthesis of compounds **70**−**78**, an intermediate believed to be a hemiaminal was observed in the reaction. Treatment of this mixture with 0.5 equiv of 1 M HCl resulted in a smooth conversion to the DHP (method B, Scheme 1). In the case where both the enamine and the carbonyl were cyclic, a tricyclic DHP was directly formed in the reaction. In the case where either the enamine or the carbonyl was acyclic, an intermediate bicyclic DHP ester was formed. These bicyclic esters were cyclized via a bromo intermediate to the lactone or the lactam as shown in Scheme 2. In the synthesis of thiopyrans **53** and **54**, the sequence in Scheme 2 was troublesome presumably because of bromination of the sulfur. Enamine **e17** and carbonyl **c9** were therefore used to generate these thio analogues directly via Scheme 1.

The syntheses of pyrandione carbonyls **c1**−**c6** and enamines **e1**−**e4** are shown in Scheme 3. By use of chemistry similar to that described by Morgan et al.,[18] pyrandiones **c1**−**c6**, were generated in three steps from appropriately substituted propargyl alcohols. Pyrandiones **c2**−**c6** were used in the Hantzsch reaction to synthesize DHPs with substitutions at positions A and E in Tables 1 and 3, respectively. The synthesis of DHPs with substitution at position B in Table 1 or position F in Table 3 required the use of enamines **e2**−**e4** in which the substituent is locked into position. Enamines **e2**−**e4** were generated from pyrandiones **c2**−**c4**, respectively. As shown in Scheme 3, treatment of a substituted pyrandione in EtOH with H_2SO_4 provided a mixture of vinyl ethers in approximately a 2:1 ratio in which the minor isomer contains the substituent in the position adjacent to the ethoxy group. This minor isomer was isolated by chromatography and smoothly converted with ammonia in ethanol to enamines **e2**−**e4**.

In Scheme 4, 3-ethoxy-2-cyclopenten-1-one was alkylated as described by Curran.[19] Similar to Scheme 3, the resulting vinyl ether was isomerized to a mixture of isomers. The desired minor isomer, 3-ethoxy-4-ethyl-cyclopent-2-enone, was isolated by chromatography and smoothly converted to enamine **e16**. In Scheme 5, ethyl-substituted tetronic acid, generated in three steps from diethyl malonate, was treated similarly to **c2**−**c4** to provide the vinyl ether that required relatively harsh conditions to provide a moderate yield of enamine **e17**.[20]

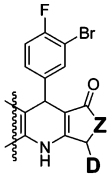
The substituted tricyclic DHPs were obtained from Schemes 1 and 2 as a mixture of cis and trans isomers, which were separated by crystallization and/or chromatography. In general, the cis isomers were more crystalline and more polar on silica gel than the corresponding trans isomers. Enantiomeric purification of individual isomers was accomplished using chiral chromatography. In the case of the compounds in Table 1, the enantiomers of the cis isomers were more easily separated than the trans. In particular, the enantiomers of the trans *n*-Pr derivative, **23**, were inseparable by chiral chromatography in our hands whereas the enantiomers of the cis *n*-Pr derivative, **22**, were easily separable. This problem was circumvented by using the finding that cis isomers of lactone-containing DHPs such as **22a** could be isomerized to a mixture of cis and trans isomers with retention of configuration of the carbon adjacent to the aromatic ring. As can be seen in Scheme 6, heating a solution of **22a** in 2 M NH_3 in EtOH resulted in the formation of a mixture of **23a** and **22a** that were separated by chromatography.

Scheme 3[a]



[a] Conditions: (i) NaH, THF; $BrCH_2CO_2Me$; (ii) $Hg(OAc)_2$, H_2O, H_2SO_4; (iii) KO-*t*-Bu, Et_2O, HO-*t*-Bu; (iv) catalytic H_2SO_4, EtOH; (v) chromatography; (vi) NH_3, EtOH.

Table 2. Modifications to Ring Systems of Substituted Compound **6** and Activity at Kir6.2/Sur2B 17− K_{ATP} Channels[a]



side ring	Z	D	isomer[b]	Cmpd, pEC_{50} ± SEM (%efficacy)	
	O	Et	*cis*	**47**	7.25±0.10 (87)
	O	Et	*trans*	**48**	6.60±0.15 (83)
	O	Et	*cis*	**49**	8.22±0.19 (94)[c]
	O	Et	*trans*	**50**	7.14±0.16 (74)[c]
	O	Et	*cis*	**51**	6.49±0.32 (71)[c]
	O	Et	*trans*	**52**	5.30±0.10 (54)[c]
	O	Et	*cis*	**53**	6.81±0.34 (74)[c]
	O	Et	*trans*	**54**	6.99±0.18 (15)[c]
	O	Me	*cis*	**55**	6.87±0.11 (93)[c]
	O	Me	*trans*	**56**	6.39±0.03 (86)[c]
	O	Me	*cis*	**57**	7.25±0.02 (102)[c]
	O	Me	*trans*	**58**	6.65±0.02 (99)[c]
	N-Me	Me	*cis*	**59**	8.56±0.08 (102)[c]
	N-Me	Me	*trans*	**60**	6.50±0.03 (92)[c]
	N-Me	Et	*cis*	**61**	<5[c]
	N-Me	Et	*trans*	**62**	<5[c]
	CH_2	Et	*cis*	**63**	8.93±0.01 (88)[c]
	CH_2	Et	*trans*	**64**	6.29±0.15 (89)[c]

[a] Number of observations is ≥3, unless otherwise specified. Values are expressed as the average pEC_{50} ± the standard error of the mean (SEM). The efficacy (in parentheses) is the average maximum response of each compound expressed as % relative to **5**. [b] Regiochemistry based on polarity on silica gel and similarity of ^{1}H NMR spectra to compounds in Table 1. [c] $n = 2$.

The relative and absolute stereochemistry of select compounds was confirmed by X-ray analysis. The racemates **7**, **12**, and **17** were all found to possess cis configuration. The single enantiomers **6a**, **21a**, **17b**,[21] and **75b** were found to possess (*R*)-, (*R*)-, (*S*)-, and (*S*)-stereochemistry at the benzylic positions, respectively. The assignment of cis vs trans for other derivatives was based on similarity of NMR spectra and the relative polarity on silica gel to the compounds whose structures were identified by X-ray analysis. Absolute stereochemistry of compounds of similar structure was assumed based on the order of elution from the chiral columns and the signs of rotation.

Biological Evaluation

Fluorometric Imaging Plate Reader (FLIPR) Membrane Potential Assay. Compounds were evaluated for potassium channel opening activity using Ltk− cells stably transfected with the Kir6.2/SUR2B exon 17− splice variant.[22] Functional activity at potassium channels was measured by evaluating changes in membrane potential using DIBAC dye in a 96-well cell-based kinetic assay system. Changes in fluorescence were measured by comparison to the effect elicited by **5**.[23] The maximal response of each compound is expressed as % relative to **5**. The observed effects were reversed by glyburide, confirming a K_{ATP} mechanism. Inhibition of K_{ATP} channel activity by sulfonylurea K_{ATP} channel blockers such as glyburide has been used to define K_{ATP} channels.[24] The average reversal induced by glyburide in the FLIPR assay for compounds described herein was 65%. This is in line with what we have observed for standard K_{ATP} channel openers such as compounds **1**, **2**, **3**, and **5**, which have an average reversal induced by glyburide of 64%.

Field-Stimulated Landrace Pig Detrusor (FSLPD) Assay.[25] 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.

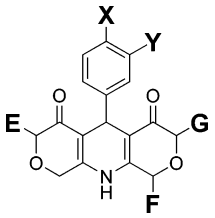
Spontaneous Landrace Pig Detrusor (SLPD) Assay.[26] Spontaneously contracting bladder strips were obtained from the area closer to the trigonal region of the bladder in Landrace pigs. The reduction of the area under the curve (AUC) by increasing concentrations of test agents was measured. These spontaneous 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. Because of the different sensitivities of FSLPD and LPD to muscarinic antagonists, each may model bladder overactivity of distinct etiology.

The DHPs described in this publication are structurally related to 1,4-dihydropyridine L-type calcium channel ligands such as nifedipine. Close analogues of the DHPs described in this publication have been tested in radioligand binding and functional studies and were shown to not interact with L-type calcium channels.[13a,27]

Results

Potassium Channel Opening Activity. Substitutions were initially made at positions A, B, and C of the DHP core of compound **6** (see Table 1). At position A, the cis and trans Me analogues, **7** and **8**, had reduced activity relative to **6** and were equipotent with each other. Interestingly, the di-Me derivative, **9**, picked up activity compared to the mono-Me analogues and

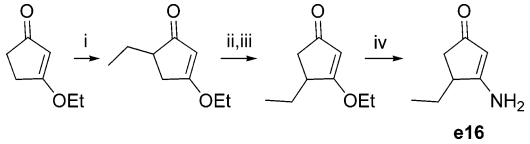
Table 3. Substitutions to Compound **65** and Activity at Kir6.2/Sur2B 17− K_{ATP} Channels[a]



E	F	X, Y	isomer[b,c]	racemate	$pEC_{50} \pm SEM$ (% efficacy)	(+)-enantiomer	$pEC_{50} \pm SEM$ (% efficacy)	(−)-enantiomer	$pEC_{50} \pm SEM$ (% efficacy)
H	H	F, Br		**65**	7.56 ± 0.16 (87)				
di-Me	H	F, Br		**66**	7.77 ± 0.13 (96)[d]				
di-Me	H	F, Br		**67**[b]	5.41 ± 0.32 (61)[d]				
$(CH_2)_4$	H	F, Br		**68**	<5[d]				
di-Et	H	F, Br		**69**	4.86 (42)[e]				
H	Et	F, Br	cis	**70**	7.85 ± 0.10 (60)[d]	**70a**	6.78 ± 0.10 (87)[d]	**70b**	7.70 ± 0.13 (94)[d]
H	Et	F, Br	trans	**71**	6.73 ± 0.06 (30)	**71a**	6.77 ± 0.34 (40)	**71b**	<5[d]
H	Et	F, Cl	trans	**72**	6.34 ± 0.01 (30)[d]	**72a**	5.44 ± 0.10 (66)[d]	**72b**	<5[d]
H	Et	F, I	trans	**73**	4.92 ± 0.07 (47)[d]	**73a**	5.89 ± 0.02 (69)[d]	**73b**	5.53 ± 0.13 (53)[d]
H	Et	Cl, Cl	trans	**74**	6.98 ± 0.12 (58)[d]	**74a**	6.33 ± 0.25 (118)[d]	**74b**	6.77 ± 0.18 (57)[d]
H	Et	Cl, Br	trans	**75**	5.79 ± 0.05 (70)[d]	**75a**	6.12 ± 0.07 (89)[d]	**75b**[c]	5.26 ± 0.03 (54)[d]
H	Et	Br, Cl	trans	**76**	6.00 ± 0.05 (46)[d]	**76a**	5.79 ± 0.23 (76)[d]	**76b**	6.61 ± 0.31 (37)[d]
H	Et	Br, Br	trans	**77**	6.87 ± 0.06 (76)[d]	**77a**	6.51 ± 0.13(120)[d]	**77b**	6.37 ± 0.14(104)[d]
H	Et	Me, Br	trans	**78**	5.8 ± 00.16 (70)[d]	**78a**	6.14 ± 0.06 (94)[d]	**78b**	5.25 ± 0.07 (56)[d]

[a] Number of observations is ≥3, unless otherwise specified. Values are expressed as the average pEC_{50} ± the standard error of the mean (SEM). The efficacy (in parentheses) is the average maximum response of each compound expressed as % relative to **5**. [b] G = hydrogen for all compounds except compound **67**, where G = di-Me. [c] Regiochemistry based on similarity to compound **75b** that was confirmed by X-ray to be trans with absolute (*S*)-stereochemistry at the benzylic position. [d] $n = 2$. [e] $n = 1$.

Scheme 4[a]



[a] Conditions: (i) LDA, THF, −78 °C; EtI, HMPA, THF; (ii) catalytic H_2SO_4, EtOH, 60 °C, 1 h; (iii) chromatography; (iv) concentrated aqueous NH_4OH, EtOH, 85 °C, 16 h.

was even slightly more potent than compound **6**. Evaluation of the enantiomers of **9** revealed a 2 orders of magnitude difference in potencies. This is in contrast to compounds **6**−**8** where there was only less than a 10-fold difference in potencies between their respective enantiomers. The mono-Et analogues, **10** and **11**, were less potent.

Methyl substitution at position B revealed a large difference in activity between the isomers, with the cis analogue **12** being approximately 50-fold more potent than the trans **13**. In contrast to substitution at position A, the di-Me derivative at position B, compound **14**, lost activity compared with compound **6**. The Et analogues **15** and **16**, although less potent than the corresponding Me analogues, followed the trend of cis being more potent than trans.

Because of the relative ease of synthesis of enamines of structures **e5**−**e15**, substitution at position C was explored most thoroughly. Similar to what was observed in substitution at position B, the cis Me derivative, **17**, was over 2 orders of magnitude more potent than the trans isomer, **18**. Evaluation of the enantiomers of **17** revealed that **17a** was 50-fold more potent than its antipode. The potency of dimethyl derivative **19** was between the potency of the cis and trans monomethyl analogues. Evaluation of the Et analogues **20** and **21** revealed that, as expected, the cis derivative **20** was more potent. Interestingly, the trans isomer **21** possessed partial agonist activity[28] with only 40% efficacy relative to **5**. The more potent enantiomer of **21**, compound **21b**, retained the partial agonist activity of the racemate. The cis and trans *n*-Pr derivatives, **22** and **23**, had the same pattern of potency and efficacy as **20** and **21**.

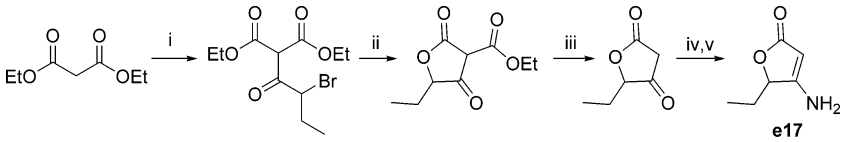
Further SAR was conducted at position C. The *i*-Pr derivatives **26** and **27** were inactive in the membrane potential assay. The CH_2OMe derivatives, compounds **24** and **25**, were similar in potency relative to the Et and *n*-Pr derivatives but were fully efficacious. Although the pEC_{50} values of the cis isomers of *n*-Bu and *i*-Bu, compounds **28** and **30**, remained >7, larger groups were found to be less potent. Several acids and esters were also examined, but these compounds all lost activity (pEC_{50} < 6) (compounds not shown).

We also investigated the effects of simultaneous substitutions. As was seen with derivatives **9** and **14**, the analogues with A = di-Me and C = Et (compounds **35** and **36**) were more potent than the analogues with B = di-Me and C = Et (compounds **37** and **38**). A slight increase in potency for compound **35** over **20** was observed. Although less potent than compound **21b**, compound **36b**, with the same stereochemistry at position C, also showed partial agonist activity.

To better understand the structural features conferring partial agonist activity to compounds such as **21b** and **23b**, we evaluated a variety of aromatic modifications on derivatives possessing trans *n*-Pr substitution at C (compounds **39**−**46**). Most derivatives lost potency relative to **23b**. Somewhat surprisingly, only the 4-F,3-Cl substitution retained partial agonist activity (compound **39b**).

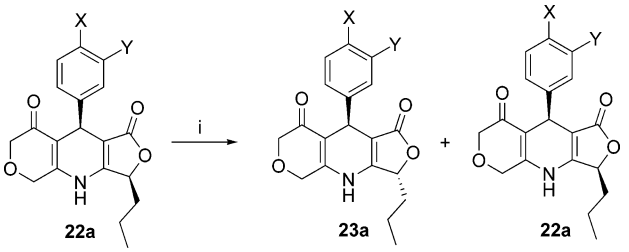
To further explore the SAR of the substituted tricyclic series, different ring systems were explored (Table 2). As was seen in Table 1, the cis isomers were approximately 10-fold more potent than the trans isomers. Relative to compounds **20** and **21**, the corresponding cyclohexanone derivatives, compounds **47** and **48**, lost potency and were fully efficacious. Replacement of the pyran with the γ-lactone (compounds **49** and **50**) resulted in a slight boost in potency, whereas the δ-lactone derivatives, **51** and **52**, lost potency by 10-fold. The cis thiopyran, **53**, lost potency relative to **20**, but the trans analogue, **54**, demonstrated

Scheme 5[a]



[a] Conditions: (i) Mg, EtOH, Δ; diethyl malonate, Δ; Et_2O, Δ; 0 °C, 2-bromobutyryl bromide; Δ; (ii) Et_3N, toluene; (iii) aqueous KOH, 2 h, then concentrated HCl; (iv) catalyst H_2SO_4, MeOH; (v) NH_3/MeOH, 80 °C, 16 h.

Scheme 6[a]



[a] Conditions: (i) 2 M NH_3 in EtOH, Δ, 16 h.

a very low efficacy of 15%. The sulfone derivatives, compounds **55**−**58**, all lost potency relative to the corresponding pyran derivatives. Modifications to the lactone ring were also explored. Replacement of the oxygen of the lactone with a *N*-Me led to compounds with potencies similar to the potencies of **17** and **18** in the case where D = Me (**59** and **60**) but were inactive in the case of D = Et (**61** and **62**). Replacement of the oxygen of the lactone with the CH_2 group led to over a 10-fold boost in potency in the case of the cis isomer **63** compared to lactone **20**.

The symmetrical pyran DHP, compound **65**, was also amenable to substitution (see Table 3). Di-Me substitution at position E, compound **66**, led to retention of activity relative to **65**, but larger groups (compounds **68** and **69**) at E and di-Me substitution at both E and G (compound **67**) led to a significant loss of activity. We investigated the effects of Et substitution at position F of **65**. Similar to the derivatives of compound **6** in Table 1, the cis derivative, **70**, was more potent than the trans, **71**. Compound **71** was separated into its enantiomers, and compound **71a**, like the racemate **71**, possessed reduced efficacy.

To investigate the significance of aromatic substitution on the partial agonism of compound **71**, derivatives of compound **71** were evaluated. Partial agonism was observed with the 4-Cl,3-Cl and 4-Br,3-Cl derivatives (compounds **74b** and **76b**, respectively). Interestingly, compound **71a** is an outlier in terms of absolute stereochemistry, having opposite stereochemistry ((*R*)-stereochemistry at the benzylic position) from the other compounds possessing partial agonist activity in FLIPR, namely, **21b**, **36b**, **23b**, **39b**, **74b**, and **76b**.

The impact of aromatic substitution on the partial agonism of compound **71** diverged from that of compound **23**, wherein only the smaller F,Cl analogue retained partial agonistic activity. This disparity, along with the lack of partial agonism in the analogues described in Table 2, indicates that the structural requirements for partial agonism by DHPs are specific and vary between different DHP cores.

From the above SAR, substitution on the tricyclic DHP core was most allowed at positions adjacent to the NH of the molecule where longer chains up to *n*-Bu retained K_{ATP} channel opening activity. Increasing the steric bulk near the NH of the molecule, for example, the *i*-Pr derivatives **26** and **27**, as well as the di-Me derivative **14**, resulted in a loss of activity. Dimethyl substitution next to the carbonyl maintained or slightly

Table 4. Functional K_{ATP} Activity in Isolated Bladder Strips

	pEC_{50} (% efficacy)[a]	
compd	FSLPD[b]	SLPD[c]
1	5.56 ± 0.13 (99)	6.53 ± 0.32 (100)
2	6.59 ± 0.19 (99)	7.46 ± 0.20 (100)
3	6.17 ± 0.13 (94)	6.99 ± 0.06 (100)
5	7.07 ± 0.10 (99)	7.66 ± 0.16 (100)
6a	6.23 ± 0.14 (95)	
6b	6.67 ± 0.05 (88)	9.17 ± 0.04 (100)[d]
10a	5.57 ± 0.18 (86)[d]	
10b	6.05 ± 0.39 (95)[d]	
17a	7.45 ± 0.31 (97)	
21	6.31 ± 0.37 (88)[e]	
21a	5.53 ± 0.03 (94)	
21b	6.55 ± 0.07 (77)	7.72 ± 0.58 (96)[e]
23	6.10 ± 0.10 (90)	
23b	6.29 ± 0.26 (34)	7.54 ± 0.10 (99)
26	5.92 ± 0.02 (97)[d]	
29b	5.78 ± 0.22 (51)	6.48 ± 0.09 (100)[d]
30	6.89 ± 0.38 (74)	
31b	6.99 ± 0.17 (35)[d]	
34	5.89 ± 0.24 (91)	
39b	6.89 ± 0.17 (66)	
41b	6.64 ± 0.35 (86)	
54	6.05 ± 0.24 (100)[e]	
54b	6.02 ± 0.11 (38)	
65	6.90 ± 0.13 (97)	
71a	5.69 ± 0.19 (54)	6.89 ± 0.34 (98)
74b	5.64 ± 0.34 (41)[e]	7.26 ± 0.65 (92)[d]
76b	4.87 ± 0.16 (38)	6.61 ± 0.63 (97)[d]

[a] pEC_{50} is expressed as a mean ± SEM, with % efficacy relative to **5** in parentheses. $n \geq 4$ unless otherwise indincated. [b] Field stimulated Landrace pig detrusor strips. [c] Spontaneous Landrace pig detrusor strips. [d] $n = 2$. [e] $n = 3$.

increased activity, as in compounds **9**, **35**, and **66**. Larger substitutions next to the carbonyl resulted in a loss of activity.

FSLPD. To further investigate the potassium channel opening activity of these substituted tricyclic DHPs, we examined several for their ability to relax field-stimulated pig detrusor strips (see Table 4). Compounds that were fully efficacious in FLIPR (efficacy of >60%) were also fully efficacious in FSLPD.

Compounds that showed partial agonist activity in FLIPR were also evaluated in FSLPD. Interestingly, racemic compounds such as **21**, **23**, and **54** that were partial agonists in FLIPR were full agonists in FSLPD. For example, the racemic trans ethyl derivative, compound **21**, which had only 40% efficacy in FLIPR, was a full agonist in FSLPD (88%). The more potent enantiomer of **21**, compound **21b**, did display a reduced efficacy in FSLPD relative to **21** with 77% efficacy. Single enantiomers, compounds **23b**, **29b**, **31b**, **39b**, **71a**, **74b**, and **76b** that had reduced activity in FLIPR (45%, 68%, 59%, 39%, 40%, 57%, and 37%) also had reduced efficacy in FSLPD (30%, 51%, 35%, 66%, 54%, 41%, and 38%).

Plots were generated in order to evaluate if potency in FLIPR predicts potency in FSLPD.[29] As can be seen from Figure 4, the predictive value was best for compounds that were full agonists in FLIPR (plot B, $r^2 = 0.84$) and worst for partial

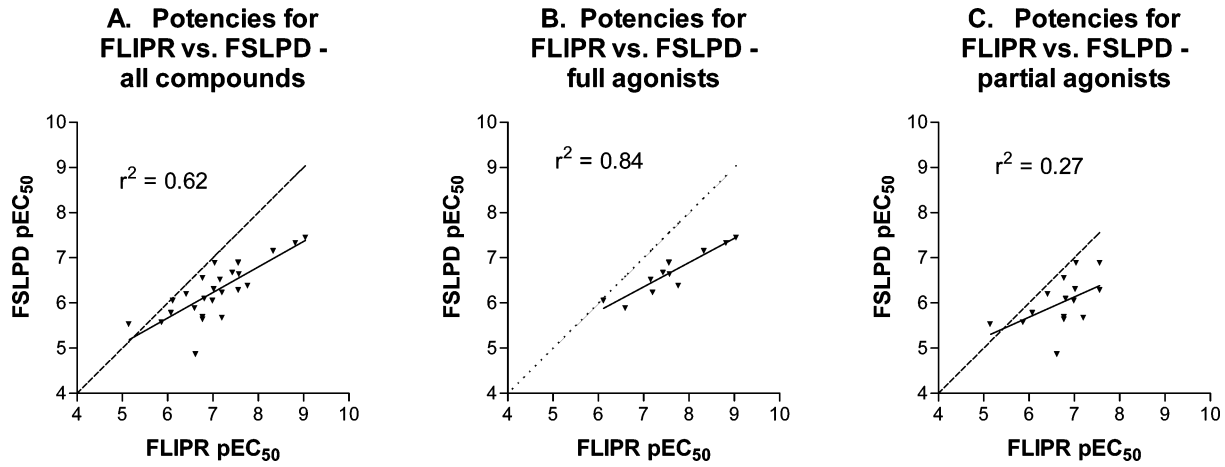


Figure 4. Comparison of potencies between FLIPR and FSLDP.

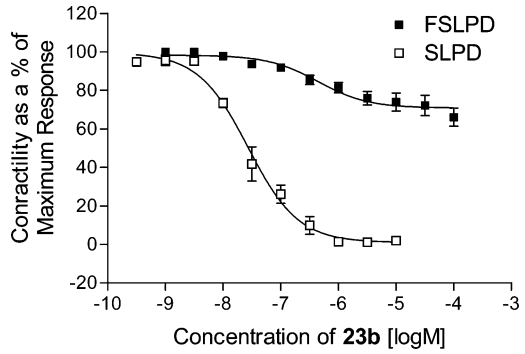


Figure 5. Comparison of FSLPD with SLPD for **23b**.

agonists (plot C, $r^2 = 0.27$). Overall, compounds that were weaker in FLIPR ($pEC_{50} \approx 6$) had similar potencies in FSLPD whereas more potent compounds ($pEC_{50} > 7$) in FLIPR were over an order of magnitude less potent in FSLPD.

SLPD. Several of the compounds were evaluated for their K_{ATP} channel opening activity in SLPD (see Table 4). As seen with other K_{ATP} channel openers,[16,17,26] all of the compounds displayed greater potency to relax spontaneous bladder contractions than to inhibit those elicited by electrical stimulation. Interestingly, all of the compounds, including the ones that were partial agonists in FSLPD, were fully efficacious in SLPD.

Functional selectivity can be achieved by increasing the separation between the potencies for the desired and undesired responses. Functional selectivity can also be achieved by reducing or eliminating the efficacy of the undesired response. The partial agonists described herein are more potent for relaxing SLPD over FSLPD and have reduced efficacy in the FSLPD model.

Table 5. Compound **23b** in Neurogenic vs Myogenic Rat Models[a]

concn (μmol/kg)	neurogenic model		myogenic model	
	% Δ AUC	% Δ MAP	% Δ AUC	% Δ MAP
0.03			−4.2 (14.3)[b]	−5.1 (1.2)[b]
0.1			−19.1 (11.4)	−9.6 (1.3)
0.3	−16 (7.7)[b]	−22.6 (4.0)[b]	−46.7 (10.4)	−23.6 (2.7)
1	−31.9 (4.1)	−43.8 (1.9)	−93.1 (6.1)	−40.7 (1.6)
3	−37.4 (4)[c]	−49.7 (2.4)[c]		

[a] Data expressed as % reduction in the area under the curve (AUC) of bladder contractions. Standard error of the mean (SEM) is in parentheses. Number of observations *n* is 7 unless otherwise indincated. [b] $n = 3$. [c] $n = 4$.

As can be seen in Figure 5, compound **23b** was fully efficacious in SLPD but only partially efficacious in FSLPD. This agent has a unique pharmacological profile compared to prototypical K_{ATP} channel openers such as **1** and **3**, which are all fully efficacious in both SLPD and FSLPD. This agent is also different from tolterodine, a muscarinic antagonist used clinically to treat OAB that acts via neurogenic mechanisms. Tolterodine is partially efficacious for relaxing FSLPD ($pEC_{50} = 7.1 \pm 0.17$ with 50% efficacy) but is inactive at relaxing SLPD.[26] Spontaneous contractions in detrusor tissue are believed to be myogenic in origin.[2] We hypothesized that a compound such as **23b** might be more selective in vivo for relaxing myogenic contractions over neurogenic contractions.

In Vivo. Compound **23b** was evaluated in the partial outlet obstructed rat and in the urethral ligated rat, using models of spontaneous myogenic bladder contractions and volume-induced reflex neurogenic bladder contractions, respectively.[30] The results are displayed in Figure 6 and Table 5. As can be seen from the plots, compound **23b** was completely effective at eliminating myogenic bladder contractions, whereas it was only

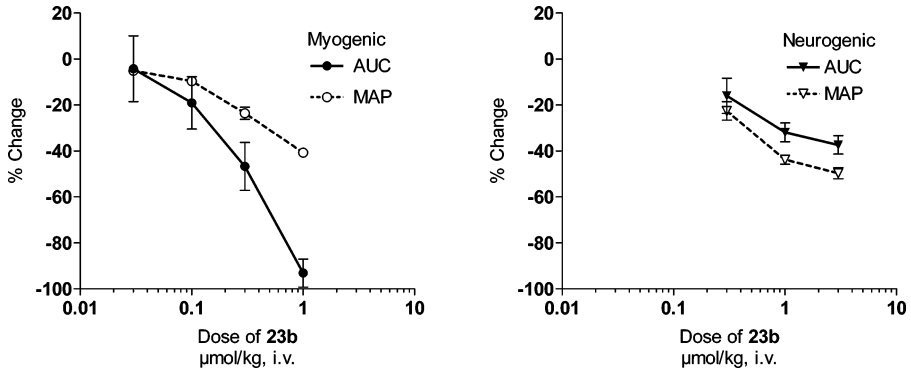


Figure 6. Compound **23b**: myogenic vs neurogenic activity in vivo.

partially efficacious against neurogenically mediated contractions at a dose 3-fold higher. At the doses tested, these effects on myogenic and neurogenic contractile activity parallel what was observed in vitro.

Blood pressure effects were monitored simultaneously in the two models and were similar in both assays. Over the dose range examined, compound **23b** reduced MAP in parallel with effects on inhibiting reflex neurogenic contractions. A maximum reduction in MAP of 49.7% was observed at 3 mmol/kg iv. Solubility limitations prevented the exploration of higher doses to assess whether the MAP effects plateaued at this level. Nonetheless, the magnitude of the MAP effects observed at the approximate ED_{50} (0.3 mmol/kg) for inhibition of spontaneous bladder contractions was similar to that seen with ZD6169 and cromakalim.[30]

Similar to compound **23b**, other K_{ATP} channel openers tested in vivo also relaxed myogenic contractions more potently than neurogenic contractions.[30] But unlike the other K_{ATP} channel openers, the efficacy of compound **23b** plateaus at about 40% in the neurogenic model. The in vivo profile of compound **23b** parallels what was observed in the in vitro functional models. Compound **23b** fully relaxed SLPD but only partially relaxed FSLPD. As previously reported, tolterodine in the above in vivo models partially relaxed neurogenic contractions but had no effect on myogenic contractions.[30] Interestingly, the in vivo results for tolterodine also parallel the in vitro results, wherein tolterodine was 50% efficacious in relaxing FSLPD but was essentially inactive in suppressing contraction in SLPD.[26]

The in vivo myogenic and neurogenic models may represent unstable nonvoiding bladder contractions of myogenic origin and normal bladder function, respectively. The lack of activity of a muscarinic antagonist such as tolterodine in the myogenic models supports the hypothesis that these spontaneous bladder contractions are of smooth muscle origin. Normal bladder function is largely driven by parasympathetic neurons. The efficacy seen with tolterodine in the neurogenic model indicates that parasympathetic activity contributes in part to these reflex contractions.

Achieving high selectivity for relaxing myogenic contractions over neurogenic contractions in vivo may represent an approach to inhibiting disease-related involuntary bladder contractions without disrupting normal voiding function. Currently, OAB is clinically treated with muscarinic antagonists such as tolterodine. Muscarinic antagonists reduce the efferent activity to the bladder, which is innervated mainly by parasympathetic neurons. Because these agents reduce the overall efferent activity to the bladder, they may inhibit to some extent the normal micturition reflexes of the bladder at higher doses. K_{ATP} channel openers such as **23b**, with reduced efficacy for neurogenically mediated bladder contractions, represent a novel approach toward identifying agents with potential to more selectively inhibit disease-related bladder contractions of myogenic origin. It remains to be determined if further optimization of this pharmacological profile can yield agents with acceptable selectivity versus cardiovascular effects.

Conclusion

In conclusion, we have demonstrated that substitution is allowed on the flanking rings of compounds **6** and **65**. In general, smaller groups such as Me in a cis fashion on the carbon adjacent to the NH of the DHP provided a boost in potency in FLIPR and FSLPD. Separation of enantiomers of derivatives of compound **6** revealed that (*R*)-stereochemistry at the benzylic position was the more potent enantiomer in the cis isomers, whereas (*S*)-stereochemistry at the benzylic position was, in general, the more potent enantiomer in the trans isomers. Partial agonist activity in FLIPR and FSLPD was observed with several Et and Pr trans substituted compounds. These agents were potent and full agonists at relaxing SLPD and thus were highly selective for spontaneous (SLPD) versus field-stimulated (FSLPD) bladder strips. In vivo, compound **23b** fully inhibited myogenic contractions but only partially inhibited neurogenic contractions. This unique pharmacological profile of selectively relaxing myogenic contractions over neurogenic contractions may be useful as an alternative treatment for 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. Tricyclic DHPs for which melting points are not reported were isolated as amorphous solids. 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 F254 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 chiral HPLC.

Synthesis of Carbonyl Monomers: 2-Methyl-2*H*-pyran-3,5-(4*H*,6*H*)-dione (c2). A mechanically stirred suspension of NaH (60% dispersion in mineral oil, 10 g, 0.25 mol) in THF (160 mL) at 0 °C under N_2 was treated with a solution of 3-butyn-2-ol (21 g, 0.30 mol) in THF (35 mL) over 30 min, stirred for 35 min, treated with a solution of methyl bromoacetate in THF (50 mL) over 10 min, stirred for 30 min at 0 °C, stirred at room temperature for 16 h, and treated with 2 M HCl (150 mL). The organic layer was isolated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and distilled under vacuum (75−90 °C at 15 mmHg) to provide methyl [(1-methyl-2-propynyl)-oxy]acetate (20 g). ^{1}H NMR ($CDCl_3$) δ 1.51 (d, 3H), 2.46 (d, 1H), 3.76 (s, 3H), 4.25 (AB q, 2H), 4.39 (dq, 1H). This product (20 g, 0.14 mol) in MeOH (700 mL) was treated with $Hg(OAc)_2$ (4.6 g, 0.014 mol), treated with concentrated H_2SO_4 (0.5 mL), heated to reflux for 1 h, concentrated to approximately 100 mL total volume, treated with 1 M HCl (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The extractions were combined, dried ($MgSO_4$), filtered, and concentrated to provide methyl (1-methyl-2-oxopropoxy)-acetate. ^{1}H NMR ($CDCl_3$) δ 1.37 (d, 3H), 2.31 (s, 3H), 3.76 (s, 3H), 3.96 (q, 1H), 4.15 (AB q, 2H). A mechanically stirred solution of KO-*t*-Bu in *t*-BuOH (1 M, 203 mL) under N_2 was treated with anhydrous ether (125 mL), cooled to 0 °C, treated with the product from above (15.5 g, 97 mmol) in ether (55 mL) over 2 min, stirred for 10 min, and then treated with 2 M HCl (240 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel, eluting with hexane/EtOAc/HCO_2H/H_2O (200:200:1:1) to provide **c2**. ^{1}H NMR ($CDCl_3$) δ 1.48 (d, 3H), 3.43 (d, 1H), 3.92 (d, 1H), 3.97 (q, 1H), 4.04 (d, 1H), 4.44 (d, 1H).

2,2-Dimethyl-2*H*-pyran-3,5(4*H*,6*H*)-dione (c3). 2-Methyl-3-butyn-2-ol was processed as described for compound **c2** to provide the crude product, which was treated with 10% CH_2Cl_2 in hexane (5 mL) and stored at 0 °C for 1 h. The resulting crystals were collected by filtration, washed with a cold solution of 10% CH_2Cl_2 in hexane, and dried to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6H), 4.16 (s, 2H), 5.20 (s, 1H), 11.70 (s, 1H).

2-Ethylpyran-3,5-dione (c4). 1-Pentyn-3-ol was processed as described for compound **c2** to provide the title compound, which

was not chromatographed. ^{1}H NMR (DMSO) δ 0.90 (t, J = 7.46 Hz, 3 H), 1.56−1.84 (m, 2 H), 3.87−3.97 (m, 1 H), 4.14 (s, 2 H), 5.30 (s, 1 H).

2,2-Diethylpyran-3,5-dione (c5). 3-Ethyl-1-pentyn-3-ol was processed as described for compound **c2** to provide the title compound, which was not chromatographed. ^{1}H NMR (DMSO) δ 0.80 (t, J = 7.29 Hz, 6H), 1.54 (m, 2H), 1.74 (m, 2H), 4.16 (s, 2H), 5.25 (s, 1H).

6-Oxaspiro[4.5]decane-8,10-dione (c6). 1-Ethynylcyclopentanol was processed as described for compound **c2** to provide the title compound, which was not chromatographed. ^{1}H NMR (DMSO-d_6) δ 1.60−1.72 (m, 4H), 1.72−1.91 (m, 4H), 4.14 (s, 2H), 5.27 (s, 1H), 11.5 (bs, 1H).

Synthesis of Enamine Monomers: 5-Amino-6-methyl-2*H*-pyran-3(6*H*)-one (e2). Compound **c2** (3.0 g, 23 mmol) was dissolved in EtOH (50 mL), treated with concentrated H_2SO_4 (5 drops), heated to reflux for 3 h, and concentrated. The residue was purified by chromatography, eluting with 10:1, 5:1, and then 2:1 hexane/EtOAc to provide 5-ethoxy-2-methyl-2*H*-pyran-3(6*H*)-one (^{1}H NMR (DMSO-d_6) δ 1.38 (t, 3H), 1.40 (d, 3H), 3.89−4.06 (m, 3H), 4.29 (s, 2H), 5.41 (s, 1H)) as the faster moving isomer and 5-ethoxy-6-methyl-2*H*-pyran-3(6*H*)-one (^{1}H NMR (DMSO-d_6) δ 1.39 (t, 3H), 1.44 (d, 3H), 3.91−4.01 (m, 2H), 4.03 (dd, 1H), 4.21 (d, 1H), 4.37 (q, 1H), 5.41 (s, 1H)) as the slower moving isomer in a 2:1 ratio. The slower moving 5-ethoxy-6-methyl-2*H*-pyran-3(6*H*)-one was treated with NH_3 saturated EtOH (60 mL), stirred at room temperature for 16 h, and concentrated to provide the title compound (0.52 g). ^{1}H NMR (DMSO-d_6) δ 1.38 (d, 3H), 3.77 (d, 1H), 3.91 (d, 1H), 4.32 (q, 1H), 4.96 (s, 1H), 6.84 (bs, 1H), 7.07 (bs, 1H).

5-Amino-6,6-dimethyl-6*H*-pyran-3-one (e3). Compound **c3** was treated as described for compound **e2** to provide the title compound. ^{1}H NMR (DMSO-d_6) δ 1.38 (s, 6H), 3.86 (s, 2H), 4.90 (s, 1H), 6.92 (s, 2H).

5-Amino-6-ethyl-6*H*-pyran-3-one (e4). Compound **c4** was treated as described for compound **e2** to provide the title compound. ^{1}H NMR (DMSO-d_6) δ 0.95 (t, J = 7.29 Hz, 3H), 1.65−1.88 (m, 2H), 3.38−3.49 (m, 1H), 3.74 (d, J = 15.94 Hz, 1H), 3.89 (d, J = 15.94 Hz, 1H), 4.10 (dd, J = 8.99, 3.56 Hz, 1H), 4.97 (s, 1H), 6.97 (bs, 2H).

3-Aminopent-2-enoic Acid Methyl Ester (e6). A mixture of methyl 3-oxopentanoate (10 g, 77 mmol) and 2 M NH_3 in EtOH (100 mL) was heated to 80 °C for 16 h in a sealed tube. After cooling, the mixture was concentrated to dryness to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.63 Hz, 3H), 2.17 (q, J = 7.46 Hz, 2H), 3.65 (s, 3H), 4.56 (s, 1H).

Ethyl (2*E*)-3-Amino-4-methyl-2-pentenoate (e7). Ethyl 4-methyl-3-oxopentanoate was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 6H), 1.26 (t, 3H), 2.32 (m, 1H), 4.11 (q, 2H), 4.57 (s, 1H)

3-Aminohex-2-enoic Acid Methyl Ester (e8). Methyl butyryl acetate was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.29 Hz, 3H), 1.26 (t, J = 7.12 Hz, 3H), 1.51−1.65 (m, 2H), 2.10 (t, J = 7.80 Hz, 2H), 4.11 (q, J = 7.12 Hz, 2H), 4.54 (s, 1H).

3-Aminohept-2-enoic Acid Ethyl Ester (e9). 3-Oxoenanthic acid ethyl ester was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.29 Hz, 3H), 1.26 (t, J = 7.12 Hz, 3H), 1.30−1.43 (m, 2H), 1.48−1.59 (m, 2H), 2.12 (t, J = 7.80 Hz, 2H), 4.11 (q, J = 7.12 Hz, 2H), 4.54 (s, 1H).

3-Amino-5-methoxypent-2-enoic Acid Methyl Ester (e10). 5-Methoxy-3-oxovaleric acid methyl ester was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 2.38 (t, J = 5.76 Hz, 2H), 3.36 (s, 3H), 3.58 (t, J = 5.42 Hz, 2H), 3.64 (s, 3H), 4.49 (s, 1H); MS (DCI/NH_3) m/z 160 $(M + H)^+$.

3-Amino-5-methylhex-2-enoic Acid Methyl Ester (e11). 5-Methyl-3-oxohexanoic acid methyl ester[31] was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3H), 0.96 (s, 3H), 1.78−2.01 (m, 3H), 3.65 (s, 3H), 4.52 (s, 1H).

3-Aminooct-2-enoic Acid Methyl Ester (e12). 3-Oxooctanoic acid methyl ester[32] was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.78 Hz, 3H), 1.28−1.35 (m, 4H), 1.49−1.60 (m, 2H), 2.08−2.15 (m, 2H), 3.64 (s, 3H), 4.54 (s, 1H); MS (DCI/NH_3) m/z 172 $(M + H)^+$.

3-Amino-6-methylhept-2-enoic Acid Methyl Ester (e13). 6-Methyl-3-oxoheptanoic acid methyl ester[33] was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.78 Hz, 6H), 1.38−1.49 (m, 2H), 1.52−1.70 (m, 1H), 2.08−2.17 (m, 2H), 3.64 (s, 3H), 4.55 (s, 1H).

3-Aminonon-2-enoic Acid Methyl Ester (e14). 3-Oxononanoic acid methyl ester[32] was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.78 Hz, 3H), 1.23−1.39 (m, 6H), 1.46−1.61 (m, 2H), 2.09−2.15 (m, 2H), 3.64 (s, 3H), 4.54 (s, 1H); MS (DCI/NH_3) m/z 186 $(M + H)^+$.

3-Amino-4-phenylbut-2-enoic Acid Ethyl Ester (e15). 3-Oxo-4-phenylbutyric acid ethyl ester[34] was treated as described for compound **e6** to provide the title compound. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.12 Hz, 3H), 3.46 (s, 2H), 4.12 (q, J = 7.12 Hz, 2H), 4.64 (s, 1H), 7.21−7.37 (m, 5H).

3-Amino-4-ethylcyclopent-2-enone (e16). A solution of diisopropylethylamine (7.5 mL, 54 mmol) in THF (30 mL) under N_2 at −78 °C was treated over 5 min with *n*-BuLi (2.5 M in hexanes, 21 mL, 52 mmol), stirred for 30 min, treated with a solution of 3-ethoxy-2-cyclopenten-1-one (5 g, 40 mmol) in THF (30 mL) dropwise, stirred for 45 min, treated with a solution of EtI (4.8 mL, 60 mmol) and HMPA (14 mL, 80 mmol) in THF (30 mL), and stirred at room temperature overnight. The mixture was diluted with Et_2O (250 mL), washed with H_2O (125 mL), washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in EtOH (200 mL), treated with concentrated H_2SO_4 (1 mL), refluxed for 1 h, cooled, concentrated to 50 mL, treated with $NaHCO_3$ solution (100 mL), and extracted with Et_2O (3 × 100 mL). The combined Et_2O layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 4 g of crude product. The crude product was chromatographed via multiple injections on a YMC column, eluting with 3% EtOH in hexane to provide 1.09 g (18%) of 3-ethoxy-5-ethylcyclopent-2-enone (^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.46 Hz, 3H), 1.35−1.54 (m, 1H), 1.41 (t, J = 7.12 Hz, 3H), 1.77−1.93 (m, 1H), 2.29 (ddd, J = 17.63, 2.71, 1.02 Hz, 1H), 2.37−2.47 (m, 1H), 2.74 (ddd, J = 17.55, 7.21, 1.02 Hz, 1H), 4.04 (q, J = 7.12 Hz, 2H), 5.24 (s, 1H)) as the less polar isomer and 1.13 g (18%) of 3-ethoxy-4-ethylcyclopent-2-enone (^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.46 Hz, 3H), 1.33−1.52 (m, 1H), 1.43 (t, J = 7.12 Hz, 3H), 1.76−1.92 (m, 1H), 2.12 (dd, J = 17.80, 2.54 Hz, 1H), 2.57 (dd, J = 17.97, 7.12 Hz, 1H), 2.71−2.85 (m, 1H), 3.95−4.11 (m, 2H), 5.24 (s, 1H)) as the more polar isomer. A solution of 3-ethoxy-4-ethylcyclopent-2-enone (1.13 g, 7.3 mmol) in EtOH (10 mL) was treated with 28% aqueous NH_4OH (5 mL), heated to 85 °C for 16 h, cooled, and concentrated to dryness to provide 0.9 g (98%) of the title compound. ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 7.29 Hz, 3H), 1.25−1.42 (m, 1H), 1.69−1.85 (m, 1H), 1.80 (dd, J = 17.12, 2.54 Hz, 1H), 2.25 (dd, J = 17.29, 7.46 Hz, 1H), 2.57−2.67 (m, 1H), 4.74 (s, 1H), 6.98 (s, 1H), 7.29 (s, 1H); MS (ESI+) m/z 126 $(M + H)^+$; MS (ESI−) m/z 124 $(M - H)^-$.

General Methods for Synthesizing Final Products. Method A: Methyl 4-(3-Bromo-4-fluorophenyl)-2,6-dimethyl-5-oxo-4,5,6,8-tetrahydro-1*H*-pyrano[3,4-*b*]pyridine-3-carboxylate. Carbonyl **c2** (1.3 g, 10 mmol), 3-bromo-4-fluorobenzaldehyde (2.4 g, 12 mmol), and methyl 3-aminocrotonate (**e5**) (1.2 g, 10 mmol) in EtOH (10 mL) were heated at 80 °C in a sealed tube for 16 h. After cooling to room temperature, the mixture was filtered and the filtercake washed with EtOH and dried to provide the title compound. The filtrate was concentrated and chromatographed on silica gel, eluting with a gradient of 1%, 2%, and 5% MeOH in CH_2Cl_2 to provide additional quantities of the title compound: 1.03 g total (25% yield). MS (ESI+) m/z 410 $(M + H)^+$; MS (ESI−) m/z 408 $(M - H)^-$.

Method B: *cis*-10-(3-Bromo-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (70) and *trans*-10-(3-Bromo-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (71). A mixture of enamine

e4 (1.3 g, 9.2 mmol), 4-bromo-3-fluorobenzaldehyde (2.4 g, 12 mmol), and pyran-3,5-dione[35] **c1** (1.3 g, 11 mmol) in EtOH (16 mL) was heated to 80 °C in a sealed tube for 20 h, cooled to room temperature, treated with a 1 M solution of HCl in Et_2O (5 mL), heated to 80 °C for 45 min, cooled to room temperature, and concentrated to dryness. The residue, which contained a mixture of cis and trans isomers, was purified by chromatography using a gradient of 2%, 3%, and 4% EtOH in CH_2Cl_2 to provide **71** (1.3 g, 33%, less polar; mp 244−245 °C; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, 3H), 1.59−1.67 (m, 1H), 1.89−2.03 (m, 1H), 3.93 (d, 1H), 4.03 (s, 2H), 4.22 (d, 1H), 4.42 (dd, 1H), 4.51 (AB q, 2H), 4.92 (s, 1H), 7.18−7.30 (m, 2H), 7.41 (dd, 1H), 9.96 (s, 1H); MS (ESI+) *m*/*z* 422 (M + H)$^+$; MS (ESI−) *m*/*z* 420 (M − H)$^-$; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N) and **70** (1.6 g, 41%, more polar; mp 221−226 °C; ^{1}H NMR (DMSO-d_6) δ 0.96 (t, J = 7.29 Hz, 3H), 1.91−2.03 (m, 2H), 3.98−4.15 (m, 4H), 4.42−4.51 (m, 2H), 4.63 (d, J = 16.28 Hz, 1H), 4.96 (s, 1H), 7.17 (ddd, J = 8.39, 5.00, 2.20 Hz, 1H), 7.27 (t, J = 8.65 Hz, 1H), 7.37 (dd, J = 6.78, 2.03 Hz, 1H), 9.54 (s, 1H); MS (ESI+) *m*/*z* 422 (M + H)$^+$; MS (ESI−) *m*/*z* 420 (M − H)$^-$; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N).

Method C: (*cis*)-9-(3-Bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (7) and (*trans*)-9-(3-Bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (8). The product from method A (1.0 g, 2.5 mmol) was dissolved in $CHCl_3$ (15 mL) under N_2, cooled to 0 °C, treated with pyridine (0.24 mL, 3.0 mmol) and pyridinium tribromide (0.97 g, 3.0 mmol), stirred at 0 °C for 20 min, diluted with CH_2Cl_2 (100 mL), and treated with 1 M HCl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, heated neat to 130 °C under N_2 for 15 min, and cooled to room temperature. The residue was purified by chromatography on silica gel, eluting with 40:38:1:1 hexane/EtOAc/HCO_2H/H_2O to provide the trans isomer (compound **8**) as the faster moving isomer and the cis isomer (compound **7**) as the slower moving isomer. Both isomers were crystallized from CH_2Cl_2. Compound **7**: mp 234−239 °C; ^{1}H NMR (DMSO-d_6) δ 1.16 (d, 3H), 4.11 (q, 1H), 4.55 (s, 2H), 4.72 (s, 1H), 4.86 (dd, 1H), 5.01 (d, 1H), 7.22−7.32 (m, 2H), 7.46 (dd, 1H), 10.45 (bs, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N. Compound **8**: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, 3H), 4.12 (q, 1H), 4.48 (d, 1H), 4.65 (d, 1H), 4.68 (s, 1H), 4.86 (dd, 1H), 4.99 (d, 1H), 7.24−7.28 (m, 2H), 7.48 (dd, 1H), 10.42 (bs, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{17}H_{13}NO_4FBr\cdot 0.2CH_2Cl_2$) C, H, N.

4-(3-Bromo-4-fluorophenyl)-2-isopropyl-5-oxo-4,5,6,8-tetrahydro-1*H*-pyrano[3,4-*b*]pyridine-3-carboxylic Acid Ethyl Ester. Pyran-3,5-dione[35] (**c1**) (0.30 g, 2.6 mmol), 3-bromo-4-fluorobenzaldehyde (0.70 g, 3.4 mmol), and enamine **e7** (0.50 g, 3.2 mmol) via method A (0.75 g, 53%) provided the title compound.

Method D: 9-(3-Bromo-4-fluorophenyl)-3,3-dimethyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (19). The compound from above (4-(3-bromo-4-fluorophenyl)-2-isopropyl-5-oxo-4,5,6,8-tetrahydro-1*H*-pyrano[3,4-*b*]pyridine-3-carboxylic acid ethyl ester) (0.58 g, 1.3 mmol) was dissolved in $CHCl_3$ (20 mL), treated with NBS (0.29 g, 1.6 mmol), stirred at RT for 30 min, refluxed for 1.5 h, concentrated to dryness, heated neat to 130 °C for 15 min, cooled, chromatographed (2% and then 5% MeOH in CH_2Cl_2) and crystallized from EtOAc/hexane to provide **19** (127 mg, 19%). mp 219−221 °C; ^{1}H NMR (DMSO-d_6) δ 1.49 (s, 3H), 1.50 (s, 3H), 4.06 (s, 2H), 4.57 (AB q, 2H), 4.73 (s, 1H), 7.22 (m, 1H), 7.29 (t, 1H), 7.47 (dd, 1H), 10.44 (bs, 1H); MS (ESI+) *m*/*z* 408 (M + H)$^+$, 425 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}NO_4FBr$) C, H, N.

(+)-*cis*-9-(3-Bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (7a) and (−)-*cis*-9-(3-Bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (7b). The enantiomers of compound **7** (430 mg) were separated using a Chiralcel OJ column, eluting with 3:1 hexane/EtOH to provide **7b** (less polar; mp 267−277 °C; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ −232 (*c* 0.26, acetone)) and **7a** (more polar; mp 261−274 °C; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ +274 (*c* 0.28, acetone)).

(+)-*trans*-9-(3-Bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (8a) and (−)-*trans*-9-(3-Bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (8b). The enantiomers of compound **8** (330 mg) were separated using a (*R*,*R*)-Whelk-O1 column, eluting with 3:2:1 hexane/CH_3OH/CH_2Cl_2 to provide **8b** (less polar; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ − 78 (*c* 0.27, acetone)) and **8a** (more polar; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ +88 (*c* 0.27, acetone)).

9-(3-Bromo-4-fluorophenyl)-7,7-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (9). Carbonyl **c3** (0.50 g, 3.5 mmol), 3-bromo-4-fluorobenzaldehyde (0.88 g, 4.2 mmol), and methyl 3-aminocrotonate (0.40 g, 3.5 mmol) via methods A and C provided the title compound (0.31 g, 22%): mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.15 (s, 3H), 1.26 (s, 3H), 4.55 (s, 2H), 4.68 (s, 1H), 4.83 (dd, 1H), 4.98 (d, 1H), 7.26 (m, 2H), 7.46 (dd, 1H), 10.40 (s, 1H); MS (APCI+) *m*/*z* 408 (M + H)$^+$; Anal. ($C_{18}H_{15}BrFNO_4\cdot 0.1CHCl_3$) C, H, N.

(+)-9-(3-Bromo-4-fluorophenyl)-7,7-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (9a) and (−)-9-(3-Bromo-4-fluorophenyl)-7,7-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (9b). The enantiomers of compound **9** (500 mg) were separated using a Chiralpak AS column, eluting with 6:4 hexane/EtOH to provide **9a** (less polar; mp 246−252 °C; Anal. ($C_{18}H_{15}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ +199 (*c* 0.28, acetone)) and **9b** (more polar; mp 242−250 °C; Anal. ($C_{18}H_{15}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ −235 (*c* 0.24, acetone)), each of which were individually rechromatographed with 2% and 5% MeOH in CH_2Cl_2.

***cis*-9-(3-Bromo-4-fluorophenyl)-7-ethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (10) and *trans*-9-(3-Bromo-4-fluorophenyl)-7-ethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (11).** Carbonyl **c4** (0.50 g, 3.5 mmol), 3-bromo-4-fluorobenzaldehyde (0.88 g, 4.2 mmol), and methyl 3-aminocrotonate (0.40 g, 3.5 mmol) via method A (42% yield) and method C provided **11** as the less polar product (75 mg, 5%) and **10** as the more polar product (125 mg, 9%). Compound **11**: ^{1}H NMR (DMSO-d_6) δ 0.89 (t, J = 7.46 Hz, 3H), 1.59−1.72 (m, 2H), 3.89 (t, J = 7.12 Hz, 1H), 4.48 (d, J = 16.27 Hz, 1H), 4.62 (d, J = 15.93 Hz, 1H), 4.67 (s, 1H), 4.86 (dd, J = 16.27, 1.02 Hz, 1H), 4.99 (d, J = 16.61 Hz, 1H), 7.26 (dd, J = 6.10, 1.02 Hz, 2H), 7.46−7.50 (m, 1H), 10.41 (s, 1H); mp 227−233 °C; MS (ESI+) *m*/*z* 408 (M + H)$^+$, 425 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_4$) C, H, N. Compound **10**: ^{1}H NMR (DMSO-d_6) δ 0.76 (t, J = 7.29 Hz, 3H), 1.45−1.60 (m, 1H), 1.69−1.81 (m, 1H), 3.95 (ddd, J = 7.12, 3.73, 1.02 Hz, 1H), 4.49−4.64 (m, 2H), 4.76 (s, 1H), 4.86 (dd, J = 16.27, 1.36 Hz, 1H), 5.01 (d, J = 16.27 Hz, 1H), 7.25−7.30 (m, 2H), 7.42−7.47 (m, 1H), 10.45 (s, 1H); mp 227−229 °C; MS (ESI+) *m*/*z* 408 (M + H)$^+$, 425 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_4$) C, H, N.

(+)-*cis*-9-(3-Bromo-4-fluorophenyl)-7-ethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (10a) and (−)-*cis*-9-(3-Bromo-4-fluorophenyl)-7-ethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (10b). The enantiomers of compound **10** (80 mg) were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **10a** (less polar, 35 mg; Anal. ($C_{18}H_{15}BrFNO_4\cdot 0.25$ acetone) C, H, N; $[\alpha]^{23}_D$ +235 (*c* 0.27, acetone)) and **10b** (more polar, 30 mg; Anal. ($C_{18}H_{15}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ −235 (*c* 0.18, acetone)).

(*cis*)-9-(3-Bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (12) and (*trans*)-9-(3-Bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (13). Enamine **e2** (0.50 g, 3.9 mmol), 3-bromo-4-fluorobenzaldehyde (0.96 g, 4.7 mmol), and methyl acetoacetate (0.46 g, 3.9 mmol) via method A (0.97 g, 61%), heating for 60 h instead of 16 h, and method C, but

eluting with 40:38:1:1, 30:38:1:1, and then 20:38:1:1 hexanes/EtOAc/HCO_2H/H_2O, provided **13** (55 mg, 4%) (less polar, crystallized from EtOAc/hexanes; mp 240−243 °C; ^{1}H NMR (DMSO-d_6) δ 1.50 (d, 3H), 3.96 (d, 1H), 4.24 (d, 1H), 4.72−4.80 (m, 2H), 4.88 (d, 1H), 5.01 (d, 1H), 7.25−7.29 (m, 2H), 7.48 (dd, 1H), 10.32 (bs, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{17}H_{13}NO_4FBr$ 0.25 H_2O) C, H, N)) and **12** (140 mg, 9%) (more polar, crystallized from EtOAc/hexane; mp 260−263 °C; ^{1}H NMR (DMSO-d_6) δ 1.52 (d, 3H), 4.07 (s, 2H), 4.66 (q, 1H), 4.77 (s, 1H), 4.86 (dd, 1H), 5.02 (d, 1H), 7.20−7.26 (m, 1H), 7.29 (t, 1H), 7.46 (dd, 1H), 10.12 (bs, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N)).

9-(3-Bromo-4-fluorophenyl)-5,5-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (14). Enamine **e3** (0.52 g, 3.7 mmol), 3-bromo-4-fluorobenzaldehyde (0.89 g, 4.4 mmol), methyl acetoacetate (0.43 g, 3.7 mmol) via method A, heating for 60 h instead of 16 h (0.60 g, 38%), and method C, but purified with 2% MeOH in CH_2Cl_2, provided **14** (recrystallized from EtOAc/hexane, 125 mg, 8%). ^{1}H NMR (DMSO-d_6) δ 1.51 (s, 3H), 1.54 (s, 3H), 3.98 (d, *J* = 16.95 Hz, 1H), 4.24 (d, *J* = 16.61 Hz, 1H), 4.76 (s, 1H), 4.89 (dd, *J* = 16.61, 1.36 Hz, 1H), 5.02 (d, *J* = 16.61 Hz, 1H), 7.22 (ddd, *J* = 8.48, 5.09, 2.03 Hz, 1H), 7.29 (t, *J* = 8.65 Hz, 1H), 7.46 (dd, *J* = 6.78, 2.03 Hz, 1H), 10.05 (s, 1H); mp >260 °C; MS (ESI+) *m*/*z* 408 (M + H)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_4$) C, H, N.

(*cis*)-9-(3-Bromo-4-fluorophenyl)-5-ethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (15) and (*trans*)-9-(3-Bromo-4-fluorophenyl)-5-ethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (16). Enamine **e4** (0.50 g, 3.5 mmol), 3-bromo-4-fluorobenzaldehyde (0.94 g, 4.6 mmol), and methyl acetoacetate (0.50 g, 4.3 mmol) via method A (0.70 g, 47%) and method C provided **16** (less polar, 87 mg, 15%; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, *J* = 7.12 Hz, 3H), 1.63−1.78 (m, 1H), 1.93−2.06 (m, 1H), 3.94 (d, *J* = 16.95 Hz, 1H), 4.19 (d, *J* = 16.62 Hz, 1H), 4.47 (dd, *J* = 10.51, 2.71 Hz, 1H), 4.74 (s, 1H), 4.87 (d, *J* = 16.28 Hz, 1H), 5.01 (d, *J* = 16.62 Hz, 1H), 7.27 (d, *J* = 7.12 Hz, 2H), 7.48 (d, *J* = 6.78 Hz, 1H), 10.34 (s, 1H); MS (ESI+) *m*/*z* 408 (M + H)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_4$·0.5 acetone) C, H, N)) and compound **15** (more polar, 120 mg, rechromatographed using 2:1 hexane/acetone; mp 236−240 °C (dec); ^{1}H NMR (DMSO-d_6) δ 0.98 (t, *J* = 7.29 Hz, 3H), 1.89−2.00 (m, 2H), 4.08 (AB q, 2H), 4.54 (t, *J* = 5.09 Hz, 1H), 4.76 (s, 1H), 4.85 (dd, *J* = 16.28, 1.02 Hz, 1H), 5.02 (d, *J* = 16.28 Hz, 1H), 7.22 (ddd, *J* = 8.48, 4.92, 2.20 Hz, 1H), 7.29 (t, *J* = 8.65 Hz, 1H), 7.44 (dd, *J* = 6.61, 2.20 Hz, 1H), 10.15 (s, 1H); MS (ESI+) *m*/*z* 408 (M + H)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_4$) C, H, N).

(*cis*)-9-(3-Bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (17) and (*trans*)-9-(3-Bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (18). 5-Amino-6*H*-pyran-3-one[35] (**e1**) (0.82 g, 7.3 mmol), 3-bromo-4-fluorobenzaldehyde (1.8 g, 8.7 mmol), and methyl 3-oxopentanoate (1.0 g, 7.3 mmol) via method A (0.53 g, 18%) and method C, eluting with 40:38:1:1, 30:38:1:1, and then 20:38:1:1 hexanes/EtOAc/HCO_2H/H_2O, provided compound **18** (70 mg, 2%) (less polar; mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 1.43 (d, 3H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.74 (s, 1H), 5.26 (q, 1H), 7.26−7.30 (m, 2H), 7.49 (d, 1H), 10.44 (bs, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N)) and compound **17** (77 mg, 3%) (more polar; mp 213-216 °C; ^{1}H NMR (DMSO-d_6) δ 1.45 (d, 3H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.75 (s, 1H), 5.15 (q, 1H), 7.19−7.25 (m, 1H), 7.29 (t, 1H), 7.47 (dd, 1H), 10.48 (bs, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N).

(+)-(*cis*)-9-(3-Bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (17a) and (−)-(*cis*)-9-(3-Bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (17b). The enantiomers of compound **17** (470 mg) were separated using a Chiralpak AS column, eluting with 1:1 EtOH/hexane to provide **17a** (95 mg, less polar, rechromatographed with 2% MeOH in CH_2Cl_2; mp 230−233 °C; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ +204 (*c* 0.18, acetone)) and **17b** (65 mg, more polar, crystallized from EtOAc/hexane; mp 230−233 °C; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ −169 (*c* 0.26, acetone)).

(+)-(*trans*)-9-(3-Bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (18a) and (−)-(*trans*)-9-(3-Bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (18b). The enantiomers of compound **18** (250 mg) were separated using a Chiralpak AS column, eluting with 3:7 EtOH/hexane to provide **18a** (less polar, crystallized from EtOAc/hexane, 25 mg; mp >260 °C; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ +282 (*c* 0.34, DMSO)) and **18b** (more polar, crystallized from EtOAc/hexane, 25 mg; mp >260 °C; Anal. ($C_{17}H_{13}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ −285 (*c* 0.21, DMSO)).

(*cis*)-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (20) and (*trans*)-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (21). Enamine **e8** (0.083 g, 0.52 mmol), pyran-3,5-dione[35] (0.050 g, 0.44 mmol), and 3-bromo-4-fluorobenzaldehyde (0.116 g, 0.57 mmol) via method A (0.17 g, 90%) and method D provided after chromatography (40:38:1:1, 30:38:1:1, and then 20:38:1:1 hexane/EtOAc/HCO_2H/H_2O) **21** as the less polar isomer (crystallized from CH_2Cl_2; mp 161−162 °C; ^{1}H NMR (DMSO-d_6) δ 0.84 (t, 3H), 1.54−1.70 (m, 1H), 1.92−2.06 (m, 1H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.74 (s, 1H), 5.21 (dd, 1H), 7.27−7.31 (m, 2H), 7.49 (m, 1H), 10.42 (bs, 1H); MS (ESI+) *m*/*z* 408 (M + H)$^+$, 425 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}NO_4FBr$) C, H, N) and **20** as the more polar isomer (crystallized from EtOAc/hexane; mp 246−248 °C; ^{1}H NMR (DMSO-d_6) δ 0.81 (t, 3H), 1.63−1.79 (m, 1H), 1.95−2.09 (m, 1H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.74 (s, 1H), 5.12 (m, 1H), 7.23 (ddd, 1H), 7.29 (t, 1H), 7.45 (dd, 1H), 10.43 (bs, 1H); MS (ESI+) *m*/*z* 408 (M + H)$^+$, 425 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}NO_4FBr$) C, H, N).

(+)-(*cis*)-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (20a) and (−)-(*cis*)-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (20b). The enantiomers of compound **20** (500 mg) were separated using a (*R*,*R*)-Whelk-O1 column, eluting with 9:4:2 hexane/MeOH/CH_2Cl_2 to provide **20b** (less polar, crystallized from EtOH; mp 131−136 °C (foams); Anal. ($C_{18}H_{15}NO_4FBr$ EtOH) C, H, N; $[\alpha]^{23}_D$ −163 (*c* 1.1, acetone)) and **20a** (more polar, crystallized from EtOH; mp 131−136 °C (foams); Anal. ($C_{18}H_{15}NO_4FBr$ EtOH) C, H, N; $[\alpha]^{23}_D$ +123 (*c* 0.61, acetone)).

(*R*)-(+)-(*trans*)-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (21a) and (*S*)-(−)-(*trans*)-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (21b). The enantiomers of compound **21** (500 mg) were separated using a Chiralpak AS column, eluting with 1:9 EtOH/hexane to provide **21a** (less polar; mp 249−251 °C; Anal. ($C_{18}H_{15}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ +229 (*c* 1.0, acetone)) and **21b** (more polar, crystallized from EtOH; mp 250−252 °C; Anal. ($C_{18}H_{15}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ −229 (*c* 0.43, acetone)).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (22) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (23).** Enamine **e9** (0.42 g, 2.6 mmol), 3-bromo-4-fluorobenzaldehyde (0.56 g, 2.9 mmol), and pyran-3,5-dione[35] **c1** (0.25 g, 2.2 mmol) via method A (0.71 g, 71%) and method D provided, after chromatography using hexane/EtOAc/HCO_2H/H_2O (40:38:1:1, 30:38:1:1, and then 20:38:1:1), **23** (58 mg, 5%) (less polar, rechromatographed using 2% MeOH in CH_2Cl_2, rechromatograhed using hexanes:acetone (3:1), recrystallized from acetone/hexanes; mp 206−208 °C; ^{1}H NMR

(DMSO-d_6) δ 0.92 (t, 3H), 1.28−1.42 (m, 2H), 1.47−1.61 (m, 1H), 1.86−1.98 (m, 1H), 4.05 (s, 2H), 4.54 (AB q, 2H), 4.73 (s, 1H), 5.23 (dd, 1H), 7.29 (m, 2H), 7.48 (dd, 1H), 10.42 (bs, 1H); MS (ESI+) *m/z* 422 $(M + H)^+$, 439 $(M + NH_4)^+$; MS (ESI−) *m/z* 420 $(M - H)^-$; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N) and **22** (46 mg, 4%, more polar, recrystallized from EtOAc/hexane; mp 219−220 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, 3H), 1.22−1.42 (m, 2H), 1.53−1.69 (m, 1H), 1.88−2.02 (m, 1H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.74 (s, 1H), 5.13 (dd, 1H), 7.22 (ddd, 1H), 7.29 (t, 1H), 7.44 (dd, 1H), 10.44 (bs, 1H); MS (ESI+) *m/z* 422 $(M + H)^+$, 439 $(M + NH_4)^+$; MS (ESI−) *m/z* 420 $(M - H)^-$; Anal. ($C_{19}H_{17}NO_4FBr\cdot 0.25\ C_6H_{14}$) C, H, N).

(+)-*cis*-9-(3-Bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (22a) (−)-*cis*-9-(3-Bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (22b). The enantiomers of compound **22** (620 mg) were separated using a (*R*,*R*)-Whelk-O1 column, eluting with 9:4:2 hexane/MeOH/CH_2Cl_2 to provide **22b** (less polar, recrystallized from EtOAc/hexane; mp 219−230 °C; Anal. ($C_{19}H_{17}NO_4FBr\cdot 0.3EtOAc\cdot 0.1$ hexane) C, H, N; $[\alpha]^{23}_D$ −108 (*c* 0.15, acetone)) and **22a** (more polar, recrystallized from EtOAc/hexane; mp 215−217 °C; Anal. ($C_{19}H_{17}NO_4FBr\cdot 0.3EtOAc\cdot 0.3$ hexane) C, H, N).

(+)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (23a). Compound **22a** (0.30 g, 0.71 mmol) was taken up in a solution of NH_3 in MeOH (10 mL), heated to 90 °C overnight in a sealed tube, cooled, concentrated, and chromatographed (2:1 hexane/acetone) to provide **23a** (80 mg, 27%) (less polar, recrystallized from acetone/hexane; mp 215−217 °C; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ +175 (*c* 0.03, acetone) and recovered **22a** (more polar).

(−)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*-furo[3,4-*b*]pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (23b). Compound **22b** (0.44 g) was taken up in a solution of NH_3 in MeOH (20 mL), heated to 90 °C ON in a sealed tube, cooled, concentrated, and chromatographed (2:1 hexane/acetone) to provide **23b** (0.20 g, 45%) (less polar, recrystallized from EtOAc/hexane; mp 216−217 °C; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ −196 (*c* 0.03, acetone)) and recovered **22b** (more polar).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-methoxymethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (24) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-methoxymethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (25).** Enamine **e10** (0.57 g, 3.6 mmol), 3-bromo-4-fluorobenzaldehyde (0.79 g, 3.9 mmol), pyran-3,5-dione[35] **c1** (0.34 g, 3.0 mmol) via method A (0.75 g, 57%) and via method C, eluting with 2%, 4%, and 6% EtOH in CH_2Cl_2, provided **25** (0.12 g 9%) (less polar, recrystallized from hexane/EtOAc; mp 213-215 °C; ^{1}H NMR (DMSO-d_6) δ 3.28 (s, 3H), 3.65 (dd, J = 11.53, 4.41 Hz, 1H), 3.78 (dd, J = 11.53, 2.71 Hz, 1H), 4.06 (ABq, 2H), 4.54 (ABq, 2H), 4.73 (s, 1H), 5.36 (dd, J = 4.24, 2.54 Hz, 1H), 7.25−7.32 (m, 2H), 7.47−7.51 (m, 1H), 10.44 (s, 1H); MS (ESI+) *m/z* 424 $(M + H)^+$; MS (ESI−) *m/z* 422 $(M - H)^-$; Anal. ($C_{18}H_{15}BrFNO_5$) C, H, N) and **24** (0.89 g, 70%) (more polar, recrystallized from hexane/EtOAc; mp 234−236 °C; ^{1}H NMR (DMSO-d_6) δ 3.35 (s, 3H), 3.76−3.86 (m, 2H), 4.05 (s, 2H), 4.52 (ABq, 2H), 4.77 (s, 1H), 5.26−5.30 (m, 1H), 7.24−7.35 (m, 2H), 7.46 (dd, J = 6.78, 2.03 Hz, 1H), 10.50 (s, 1H); MS (ESI+) *m/z* 424 $(M + H)^+$; MS (ESI−) *m/z* 422 $(M - H)^-$; Anal. ($C_{18}H_{15}BrFNO_5$) C, H, N).

(+)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-methoxymethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (25a) (−)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-methoxymethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (25b). The enantiomers of compound **25** (490 mg) were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **25a** (less polar, recrystallized from EtOH; mp 224−225 °C; Anal. ($C_{18}H_{15}BrFNO_5$) C, H, N; $[\alpha]^{23}_D$ +183 (*c* 0.27, acetone)) and **25b** (more polar, recrystallized from EtOH; mp 224−225 °C; Anal. ($C_{18}H_{15}BrFNO_5$) C, H, N; $[\alpha]^{23}_D$ −181 (*c* 0.28, acetone)).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-isopropyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (26) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-isopropyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (27).** Enamine **e11** (0.99 g, 6.3 mmol), 3-bromo-4-fluorobenzaldehyde (1.4 g, 6.8 mmol), and pyran-3,5-dione[35] **c1** (0.60 g, 5.3 mmol) via method A, chromatographing using 5:1, 3:1, and 2:1 hexane/acetone (1.7 g, 73%), and method C, chromatographing with 80:38:1:1, 40:38:1:1, 27:38:1:1, and 20:38:1:1 hexane/EtOAc/HCO_2H/H_2O, provided **27** (0.65 g, 50%, less polar; mp 230−232 °C; ^{1}H NMR (DMSO-d_6) δ 0.65 (d, J = 6.78 Hz, 3H), 1.08 (d, J = 7.12 Hz, 3H), 2.15−2.26 (m, 1H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.74 (s, 1H), 5.16 (d, J = 2.37 Hz, 1H), 7.25−7.33 (m, 2H), 7.46−7.51 (m, 1H), 10.35 (s, 1H); MS (ESI+) *m/z* 422 $(M + H)^+$; MS (ESI−) *m/z* 420 $(M - H)^-$; Anal. ($C_{19}H_{17}BrFNO_4$) C, H, N) and **26** (0.29 g, 22%, more polar; mp 169−171 °C; ^{1}H NMR (DMSO-d_6) δ 0.66 (d, J = 6.78 Hz, 3H), 1.06 (d, J = 7.12 Hz, 3H), 2.20−2.33 (m, 1H), 4.05 (s, 2H), 4.50 (d, J = 16.28 Hz, 1H), 4.60 (d, J = 16.28 Hz, 1H), 4.73 (s, 1H), 5.01−5.05 (m, 1H), 7.23 (ddd, J = 8.65, 5.26, 2.37 Hz, 1H), 7.29 (t, J = 8.48 Hz, 1H), 7.44 (dd, J = 6.61, 1.86 Hz, 1H), 10.37 (s, 1H); MS (ESI+) *m/z* 422 $(M + H)^+$; MS (ESI−) *m/z* 420 $(M - H)^-$; Anal. ($C_{19}H_{17}BrFNO_4\cdot 0.4H_2O$) C, H, N).

***cis*-(3-Bromo-4-fluorophenyl)-3-butyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (28) and *trans*-(3-Bromo-4-fluorophenyl)-3-butyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (29).** Enamine **e12** (0.54 g, 3.2 mmol), 3-bromo-4-fluorobenzaldehyde (0.70 g, 3.4 mmol), and pyran-3,5-dione[35] **c1** (0.30 g, 2.6 mmol) via method A (0.92 g, 78%) and method C, eluting with 40:38:1:1 and 20:38:1:1 hexane/EtOAc/HCO_2H/H_2O, provided **29** (0.27 g, 31%) (less polar, recrystallized from EtOAc/hexane; mp 228−230 °C; ^{1}H NMR (DMSO-d_6) δ 0.88 (t, J = 7.12 Hz, 3H), 1.23−1.37 (m, 4H), 1.48−1.60 (m, 1H), 1.89−2.02 (m, 1H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.73 (s, 1H), 5.21 (dd, J = 8.14, 3.05 Hz, 1H), 7.25−7.33 (m, 2H), 7.46−7.51 (m, 1H), 10.40 (s, 1H); MS (ESI+) *m/z* 436 $(M + H)^+$; MS (ESI−) *m/z* 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$ 0.1 hexane) C, H, N) and **28** (more polar, recrystallized from EtOAc/hexane; mp 192−194 °C; ^{1}H NMR (DMSO-d_6) δ 0.87 (t, J = 6.78 Hz, 3H), 1.16−1.36 (m, 4H), 1.58−1.73 (m, 1H), 1.90−2.06 (m, 1H), 4.05 (s, 2H), 4.55 (ABq, 2H), 4.73 (s, 1H), 5.10−5.16 (m, 1H), 7.24 (ddd, J = 8.31, 4.92, 1.70 Hz, 1H), 7.29 (t, J = 8.48 Hz, 1H), 7.42 (dd, J = 6.61, 1.86 Hz, 1H), 10.44 (s, 1H); MS (ESI+) *m/z* 436 $(M + H)^+$; MS (ESI−) *m/z* 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N).

(+)-*trans*-(3-Bromo-4-fluorophenyl)-3-butyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (29a) (−)-*trans*-(3-Bromo-4-fluorophenyl)-3-butyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (29b). The enantiomers of compound **29** were separated using a Chiralpak AS column, eluting with 1:4 EtOH:hexane to provide **29a** (less polar, rechromatographed using 2:1 hexane/acetone; MS (ESI−) *m/z* 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ +172 (*c* 0.56, acetone)) and **29b** (more polar, rechromatographed using 2:1 hexane/acetone; MS (ESI+) *m/z* 436 $(M + H)^+$, 453 $(M + NH_4)^+$; MS (ESI−) *m/z* 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ −159 (*c* 0.43, acetone)).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-isobutyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (30) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-isobutyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (31).** Enamine **e13** (0.54 g, 3.2 mmol), 3-bromo-4-fluorobenzaldehyde (0.70 g, 3.4 mmol), and pyran-3,5-dione[35] **c1** (0.30 g, 2.6 mmol) via method A (0.89 g, 76%) and method C provided **31** (less polar; mp 136−140 °C; ^{1}H NMR (DMSO-d_6) δ 0.93 (d, J = 6.44 Hz, 3H), 0.97 (d, J = 6.10 Hz, 3H), 1.32−1.46 (m, 1H), 1.72−1.86 (m, 2H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.73 (s, 1H), 5.23−5.29 (m, 1H), 7.26−7.32 (m, 2H), 7.46−7.50 (m, 1H), 10.40 (s, 1H); MS (ESI+) *m/z* 436 $(M + H)^+$, 453 $(M + NH_4)^+$; MS (ESI−) *m/z* 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N) and **30** (more polar; mp 141−153 °C; ^{1}H NMR (DMSO-d_6) δ 0.94 (d, J = 6.10 Hz, 6H), 1.34−

1.50 (m, 1H), 1.72−1.88 (m, 2H), 4.06 (s, 2H), 4.55 (ABq, 2H), 4.74 (s, 1H), 5.13 (d, J = 8.81 Hz, 1H), 7.21 (ddd, J = 8.48, 4.92, 2.20 Hz, 1H), 7.29 (t, J = 8.65 Hz, 1H), 7.45 (dd, J = 6.61, 2.20 Hz, 1H), 10.44 (s, 1H); MS (ESI+) m/z 436 $(M + H)^+$, 453 $(M + NH_4)^+$; MS (ESI−) m/z 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4 \cdot 0.5H_2O$) C, H, N).

(+)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-isobutyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (31a) (−)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-isobutyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (31b). The enantiomers of compound **31** were separated using a Chiralpak AD column, eluting with 1:9 EtOH/hexane to provide **31a** (less polar; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ +191 (*c* 1.0, acetone) and **31b** (more polar; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ − 180 (*c* 0.6, acetone)).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-pentyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (32) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-pentyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (33).** Enamine **e14** (0.59 g, 3.2 mmol), 3-bromo-4-fluorobenzaldehyde (0.70 g, 3.4 mmol), and pyran-3,5-dione[35] **c1** (0.30 g, 2.6 mmol) via method A (0.95 g, 78%) and method C, chromatographing with 40:38:1:1 and 20:38:1:1 hexane/EtOAc/HCOOH/H_2O, provided **33** (0.26 g, 30%) (less polar, recrystallized from EtOAc/hexane; mp 119−129 °C; ^{1}H NMR (DMSO-d_6) δ 0.87 (t, J = 6.44 Hz, 3H), 1.24−1.39 (m, 6H), 1.46−1.60 (m, 1H), 1.89−2.02 (m, 1H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.73 (s, 1H), 5.21 (dd, J = 8.14, 3.05 Hz, 1H), 7.25−7.32 (m, 2H), 7.46−7.50 (m, 1H), 10.36−10.43 (m, 1H); MS (ESI+) m/z 450 $(M + H)^+$, 467 $(M + NH_4)^+$; MS (ESI−) m/z 448 $(M - H)^-$; Anal. ($C_{21}H_{21}BrFNO_4$) C, H, N) and **32** (0.12 g, 14%, more polar, recrystallized from EtOAc/hexane; mp 220−223 °C; ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 6.78 Hz, 3H), 1.20−1.31 (m, 6H), 1.58−1.71 (m, 1H), 1.91−2.04 (m, 1H), 4.05 (s, 2H), 4.55 (ABq, 2H), 4.73 (s, 1H), 5.11−5.16 (m, 1H), 7.20−7.26 (m, 1H), 7.28 (t, J = 8.48 Hz, 1H), 7.42 (dd, J = 6.78, 2.03 Hz, 1H), 10.43 (s, 1H); MS (ESI+) m/z 450 $(M + H)^+$, 467 $(M + NH_4)^+$; MS (ESI−) m/z 448 $(M - H)^-$; Anal. ($C_{21}H_{21}BrFNO_4$) C, H, N).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-phenyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (34).** Enamine **e15** (0.87 g, 4.2 mmol), 3-bromo-4-fluorobenzaldehyde (0.93 g, 4.6 mmol), and pyran-3,5-dione[35] **c1** (0.40 g, 3.5 mmol) via method A (1.15 g, 68%) and method C, chromatographing with 2% MeOH in CH_2Cl_2, recrystallizing with EtOAc/hexane, rechromatographing with 2:1 hexane/acetone, recrystallizing with EtOAc/hexane, provided the title compound (75 mg, 5%; mp 167−170 °C; ^{1}H NMR (DMSO-d_6) δ 4.05 (s, 2H), 4.49 (ABq, 2H), 4.83 (s, 1H), 6.17 (d, J = 1.02 Hz, 1H), 7.25−7.39 (m, 4H), 7.45−7.52 (m, 4H), 10.39 (s, 1H); MS (ESI+) m/z 456 $(M + H)^+$, 473 $(M + NH_4)^+$; MS (ESI−) m/z 454 $(M - H)^-$; Anal. ($C_{22}H_{15}BrFNO_4$ 0.5 H_2O) C, H, N).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-7,7-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (35) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-7,7-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (36).** Enamine **e8** (1 g, 6.4 mmol), carbonyl **c3** (1.4 g, 10 mmol), and 3-bromo-4-fluorobenzaldehyde (1.7 g, 8.3 mmol) via method A (2.4 g, 81%) and method C provided, after crystallization from acetone, compound **35** (0.15 g, 5%) (more polar isomer by TLC, recrystallized from EtOAc; mp 274−277 °C; ^{1}H NMR (DMSO-d_6) δ 0.78 (t, J = 7.29 Hz, 3H), 1.15 (s, 3H), 1.25 (s, 3H), 1.63−1.74 (m, 1H), 1.95−2.06 (m, 1H), 4.57 (AB q, 2H), 4.67 (s, 1H), 5.06−5.12 (m, 1H), 7.19−7.26 (m, 1H), 7.28 (t, J = 8.48 Hz, 1H), 7.44 (dd, J = 6.78, 2.03 Hz, 1H), 10.35 (s, 1H); MS (ESI+) m/z 436 $(M + H)^+$; MS (ESI−) m/z 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N. The acetone filtrate was concentrated and chromatographed to provide **36** (0.60 g, 21%): less polar isomer, crystallized from EtOAc; mp 239−242 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 7.29 Hz, 3H), 1.15 (s, 3H), 1.25 (s, 3H), 1.56−1.68 (m, 1H), 1.95−2.04 (m, 1H), 4.57 (s, 2H), 4.67 (s, 1H), 5.16 (dd, J = 6.78, 3.39 Hz, 1H), 7.24−7.29 (m, 2H), 7.46 (dd, 1H), 10.32 (s, 1H); MS (ESI+) m/z 436 $(M + H)^+$; MS (ESI−) m/z 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N.

(+)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-7,7-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (36a) and (−)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-7,7-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (36b). The enantiomers of compound **36** (560 mg) were separated using a Chiralpak AS column, eluting with 14:86 EtOH/hexanes to provide **36a** (less polar, crystallized from EtOAc, 0.15 g; mp 257−259 °C; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ +243 (*c* 0.3, acetone)) and **36b** (more polar, crystallized from EtOAc, 0.16 g; mp 270−273 °C; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ − 248 (*c* 0.4, acetone)).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,5-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (37) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,5-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (38).** Enamine **e3** (0.60 g, 4.3 mmol), 3-bromo-4-fluorobenzaldehyde (1.7 g, 8.5 mmol), and ethyl butyrylacetate (1.1 g, 6.8 mmol) via method A (0.64 g of intermediate obtained after chromatography using 5:1 hexane/acetone) and method C provided, after chromatography using 4:1 and 1:1 hexane/acetone, compound **38** (0.19 g, 10%, less polar; ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 7.29 Hz, 3H), 1.51 (s, 3H), 1.58 (s, 3H), 1.64−1.75 (m, 1H), 2.03−2.13 (m, 1H), 3.98 (d, J = 16.61 Hz, 1H), 4.23 (d, J = 16.61 Hz, 1H), 4.75 (s, 1H), 5.19 (dd, J = 6.78, 3.05 Hz, 1H), 7.21 (ddd, J = 8.56, 5.00, 2.03 Hz, 1H), 7.29 (t, J = 8.48 Hz, 1H), 7.46 (dd, J = 6.61, 2.20 Hz, 1H), 9.76 (s, 1H); MS (ESI+) m/z 436 $(M + H)^+$; MS (ESI−) m/z 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N) and **37** (0.20 g, 11%) (more polar, crystallized from EtOAc/hexane; mp 239−246 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 7.29 Hz, 3H), 1.15 (s, 3H), 1.25 (s, 3H), 1.56−1.68 (m, 1H), 1.95−2.04 (m, 1H), 4.57 (s, 2H), 4.67 (s, 1H), 5.16 (dd, J = 6.78, 3.39 Hz, 1H), 7.24−7.29 (m, 2H), 7.46 (dd, 1H), 10.32 (s, 1H); MS (ESI+) m/z 436 $(M + H)^+$; MS (ESI−) m/z 434 $(M - H)^-$; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N).

(+)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,5-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (38a) and (−)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,5-dimethyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (38b). The enantiomers of compound **38** (163 mg) were separated using a Chiralpak AS column, eluting with 12:88 EtOH/hexanes to provide **38a** (less polar, rechromatographed 2:1 hexane/acetone, 70 mg; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ +198 (*c* 0.2, acetone)) and **38b** (more polar, rechromatographed 2:1 hexane/acetone, 60 mg; Anal. ($C_{20}H_{19}BrFNO_4$) C, H, N; $[\alpha]^{23}_D$ −206 (*c* 0.4, acetone)).

***trans*-9-(3-Chloro-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (39).** Enamine **e9** (1.1 g, 6.3 mmol), 3-chloro-4-fluorobenzaldehyde (1.1 g, 6.8 mmol), and pyran-3,5-dione[35] **c1** (0.60 g, 5.3 mmol) via method A, chromatographing with 1:1 hexane/EtOAc (1.9 g, 88%), and method C, chromatographing with 2% and 5% EtOH in CH_2Cl_2, provided **39** (0.63 g, 31%) as the less polar isomer: mp 199−201 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.12 Hz, 3H), 1.28−1.42 (m, 2H), 1.47−1.61 (m, 1H), 1.86−1.99 (m, 1H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.73 (s, 1H), 5.23 (dd, J = 7.97, 3.22 Hz, 1H), 7.24 (ddd, J = 8.56, 4.83, 2.20 Hz, 1H), 7.32 (t, J = 8.81 Hz, 1H), 7.36 (dd, J = 7.12, 2.37 Hz, 1H), 10.40 (s, 1H); MS (ESI+) m/z 378 $(M + H)^+$, 395 $(M + NH_4)^+$; MS (ESI−) m/z 376 $(M - H)^-$; Anal. ($C_{19}H_{17}ClFNO_4 \cdot 0.15CH_2Cl_2$) C, H, N.

(+)-*trans*-9-(3-Chloro-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (39a) and (−)-*trans*-9-(3-Chloro-4-fluorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (39b). The enantiomers of compound **39** were separated using a Chiralpak AS column, eluting with 12:88 EtOH/hexane to provide **39a** (less polar, recrystallized from EtOAc; mp 226−229 °C; Anal. ($C_{19}H_{17}ClFNO_4$) C, H, N; $[\alpha]^{23}_D$ +221 (*c* 0.58, acetone)) and **39b**

(more polar, recrystallized from EtOAc; mp 226−229 °C; Anal. ($C_{19}H_{17}ClFNO_4$) C, H, N; $[\alpha]^{23}_D$ − 219 (*c* 0.61, acetone)).

***cis*-9-(4-Fluoro-3-iodophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (40) and *trans*-9-(4-Fluoro-3-iodophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (41).** Enamine **e9** (1.1 g, 6.3 mmol), 3-iodo-4-methylbenzaldehyde[36] (1.7 g, 6.8 mmol), and pyran-3,5-dione[35] **c1** (0.60 g, 5.3 mmol) via method A, chromatographing with 4:1 and 2:1 hexane/acetone (2.0 g, 76%), and method C, chromatographing with 2% and 5% EtOH in CH_2Cl_2, provided **41** (0.81 g, 43%, less polar, recrystallized from EtOAc; mp 238−240 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.12 Hz, 3H), 1.27−1.41 (m, 2H), 1.47−1.61 (m, 1H), 1.86−1.99 (m, 1H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.70 (s, 1H), 5.23 (dd, J = 8.14, 3.05 Hz, 1H), 7.16 (t, J = 8.31 Hz, 1H), 7.26 (ddd, J = 8.56, 5.17, 2.20 Hz, 1H), 7.63 (dd, J = 6.10, 2.03 Hz, 1H), 10.38 (s, 1H); MS (ESI+) *m*/*z* 470 (M + H)$^+$, 487 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 468 (M − H)$^-$; Anal. ($C_{19}H_{17}FINO_4$) C, H, N) and **40** (more polar, recrystallized from EtOAc; mp 246−247 °C; ^{1}H NMR (DMSO-d_6) δ 0.92 (t, J = 7.46 Hz, 3H), 1.21−1.40 (m, 2H), 1.55−1.70 (m, 1H), 1.88−2.01 (m, 1H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.70 (s, 1H), 5.11−5.16 (m, 1H), 7.16 (t, J = 8.1 Hz, 1H), 7.22 (ddd, J = 8.48, 5.26, 2.20 Hz, 1H), 7.58 (dd, J = 6.10, 2.03 Hz, 1H), 10.42 (s, 1H); MS (ESI+) *m*/*z* 470 (M + H)$^+$, 487 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 468 (M − H)$^-$; Anal. ($C_{19}H_{17}FINO_4$·0.5EtOAc) C, H, N).

(+)-*cis*-9-(4-Fluoro-3-iodophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (40a) and (−)-*cis*-9-(4-Fluoro-3-iodophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (40b). The enantiomers of compound **40** were separated using a Chiralpak AS column, eluting with 1:1 EtOH/hexane to provide **40a** (less polar; Anal. ($C_{19}H_{17}FINO_4$) C, H, N; $[\alpha]^{23}_D$ +168 (*c* 0.29, acetone)) and **40b** (more polar; Anal. ($C_{19}H_{17}FINO_4$) C, H, N; $[\alpha]^{23}_D$ − 176 (*c* 0.33, acetone)).

(+)-*trans*-9-(4-Fluoro-3-iodophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (41a). Compound **40a** (200 mg) was taken up in 2 M NH_3 in EtOH (15 mL), heated to 80 °C ON, cooled, concentrated, and chromatographed (2% and 5% EtOH in CH_2Cl_2) to provide **41a** as the less polar isomer (Anal. ($C_{19}H_{17}FINO_4$) C, H, N; $[\alpha]^{23}_D$ +165 (*c* 0.27, acetone)) and recovered **40a** as the more polar isomer.

(−)-*trans*-9-(4-Fluoro-3-iodophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (41b). Compound **40b** (150 mg) was taken up in 2 M NH_3 in EtOH (10 mL), heated to 80 °C ON, concentrated, and chromatographed (2% and 5% EtOH in CH_2Cl_2) to provide **41b** as the less polar isomer (Anal. ($C_{19}H_{17}FINO_4$) C, H, N; $[\alpha]^{23}_D$ − 184 (*c* 0.53, acetone)) and recovered **40b** as the more polar isomer.

***trans*-9-(3,4-Dichlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (42).** Enamine **e9** (1.1 g, 6.3 mmol), 3,4-dichlorobenzaldehyde (1.2 g, 6.8 mmol), and pyran-3,5-dione[35] **c1** (0.60 g, 5.3 mmol) via method A, chromatographing with 4:1 and 2:1 hexane/acetone (1.6 g, 71%), and method C, chromatographing with 2% and 5% EtOH in CH_2Cl_2, provided **42** (0.58 g, 39%) as the less polar isomer, which was recrystallized from EtOAc: mp 227−230 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.12 Hz, 3H), 1.28−1.41 (m, 2H), 1.47−1.62 (m, 1H), 1.86−1.98 (m, 1H), 4.05 (s, 2H), 4.54 (d, J = 2.71 Hz, 2H), 4.74 (s, 1H), 5.22 (dd, J = 7.80, 3.05 Hz, 1H), 7.23 (dd, J = 8.48, 2.03 Hz, 1H), 7.43 (d, J = 2.03 Hz, 1H), 7.54 (d, J = 8.48 Hz, 1H), 10.42 (s, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{19}H_{17}Cl_2NO_4$) C, H, N.

(+)-*trans*-9-(3,4-Dichlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (42a) and (−)-*trans*-9-(3,4-Dichlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (42b). The enantiomers of compound **42** were separated using a Chiralpak AS column, eluting with 12:88 EtOH/hexane to provide **42a** (less polar, recrystallized from EtOAc; mp 253−255 °C; Anal. ($C_{19}H_{17}Cl_2NO_4$) C, H, N; $[\alpha]^{23}_D$ +198 (*c* 0.34, acetone)) and **42b** (more polar, recrystallized from EtOAc; mp 253−255 °C; Anal. ($C_{19}H_{17}Cl_2NO_4$·0.25H_2O) C, H, N; $[\alpha]^{23}_D$ − 208 (*c* 0.38, acetone)).

***trans*-9-(3-Bromo-4-chlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (43).** Enamine **e9** (1.1 g, 6.3 mmol), 3-bromo-4-chlorobenzaldehyde[37] (1.5 g, 6.8 mmol), and pyran-3,5-dione[35] **c1** (0.60 g, 5.3 mmol) via method A, chromatographing with 1:1 hexane/EtOAc (1.9 g, 76%), and method C, chromatographing with 2% and 5% EtOH in CH_2Cl_2, provided **43** (0.68 g, 38%) as the less polar isomer, which was recrystallized from EtOAc: mp 223−227 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.12 Hz, 3H), 1.27−1.42 (m, 2H), 1.47−1.62 (m, 1H), 1.85−1.98 (m, 1H), 4.05 (s, 2H), 4.54 (d, J = 2.71 Hz, 2H), 4.73 (s, 1H), 5.23 (dd, J = 7.97, 2.88 Hz, 1H), 7.26 (dd, J = 8.48, 2.03 Hz, 1H), 7.53 (d, J = 8.48 Hz, 1H), 7.56 (d, J = 2.03 Hz, 1H), 10.41 (s, 1H); MS (ESI+) *m*/*z* 438 (M + H)$^+$, 455 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 436 (M − H)$^-$; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N.

(+)-*trans*-9-(3-Bromo-4-chlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (43a) and (−)-*trans*-9-(3-Bromo-4-chlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (43b). The enantiomers of compound **43** were separated using a Chiralpak AS column, eluting with 1:1 EtOH/hexane to provide **43a** (less polar, recrystallized from EtOAc; mp 249−252 °C; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N; $[\alpha]^{23}_D$ +191 (*c* 0.51, acetone)) and **43b** (more polar, recrystallized from EtOAc; mp 255−256 °C; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N; $[\alpha]^{23}_D$ − 196 (*c* 0.36, acetone)).

***trans*-9-(4-Bromo-3-chlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (44).** Enamine **e9** (0.56 g, 3.3 mmol), 4-bromo-3-chlorobenzaldehyde[37] (0.60 g, 2.7 mmol), and pyran-3,5-dione[35] **c1** (0.32 g, 2.7 mmol) via method A, chromatographing with 4:1 and 2:1 hexane/acetone (0.84 g, 66%), and method C, chromatographing with 2% and 5% EtOH in CH_2Cl_2, provided **44** (0.33 g, 44%) as the less polar isomer, which was recrystallized from EtOAc: mp 243−245 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.12 Hz, 3H), 1.28−1.41 (m, 2H), 1.47−1.61 (m, 1H), 1.85−1.98 (m, 1H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.72 (s, 1H), 5.22 (dd, J = 7.97, 2.88 Hz, 1H), 7.15 (dd, J = 8.31, 2.20 Hz, 1H), 7.42 (d, J = 2.37 Hz, 1H), 7.67 (d, J = 8.48 Hz, 1H), 10.42 (s, 1H); MS (ESI+) *m*/*z* 438 (M + H)$^+$, 455 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 436 (M − H)$^-$; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N).

(+)-*trans*-9-(4-Bromo-3-chlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (44a) and (−)-*trans*-9-(4-Bromo-3-chlorophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (44b). The enantiomers of compound **44** were separated using a Chiralpak AS column, eluting with 15:85 EtOH/hexane to provide **44a** (less polar, recrystallized from EtOAc; mp 258−260 °C; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N; $[\alpha]^{23}_D$ +190 (*c* 0.28, acetone)) and **44b** (more polar, recrystallized from EtOAc; mp 258−260 °C; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N; $[\alpha]^{23}_D$ − 207 (*c* 0.26, acetone)).

***trans*-9-(3,4-Dibromophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (45).** Enamine **e9** (1.1 g, 6.3 mmol), 3,4-dibromobenzaldehyde (1.8 g, 6.8 mmol), and pyran-3,5-dione[35] **c1** (0.60 g, 5.3 mmol) via method A, chromatographing with 1:1 hexane/EtOAc (2.0 g, 74%), and method C, chromatographing with 2% and 5% EtOH in CH_2Cl_2, provided **45** (0.67 g, 36%) as the less polar isomer, which was recrystallized from EtOAc: mp 240−244 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.12 Hz, 3H), 1.28−1.41 (m, 2H), 1.47−1.60 (m, 1H), 1.85−1.98 (m, 1H), 4.05 (s, 2H), 4.54 (ABq, 2H), 4.71 (s, 1H), 5.23 (dd, J = 7.97, 2.88 Hz, 1H), 7.18 (dd, J = 8.48, 2.03 Hz, 1H), 7.55 (d, J = 2.37 Hz, 1H), 7.66 (d, J = 8.14 Hz, 1H), 10.41 (s, 1H); MS (ESI+) *m*/*z* 482 (M + H)$^+$, 499 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 480 (M − H)$^-$; Anal. ($C_{19}H_{17}Br_2NO_4$) C, H, N.

(+)-*trans*-9-(3,4-Dibromophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (45a) and (−)-*trans*-9-(3,4-Dibromophenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (45b). The

enantiomers of compound **45** were separated using a Chiralpak AS column, eluting with 12:88 EtOH/hexane to provide **45a** (less polar, recrystallized from EtOAc; mp 257−260 °C; Anal. ($C_{19}H_{17}Br_2NO_4$) C, H, N; $[\alpha]^{23}_D$ +175 (*c* 0.44, acetone)) and **45b** (more polar, recrystallized from EtOAc; mp 257−260 °C; Anal. ($C_{19}H_{17}Br_2NO_4$) C, H, N; $[\alpha]^{23}_D$ − 183 (*c* 0.42, acetone)).

***trans*-9-(3-Bromo-4-methylphenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (46).** Enamine **e9** (1.1 g, 6.3 mmol), 3-bromo-4-methylbenzaldehyde[38] (1.4 g, 6.8 mmol), and pyran-3,5-dione[35] **c1** (0.60 g, 5.3 mmol) via method A, chromatographing with 4:1 and 2:1 hexane/acetone (2.0 g, 84%), and method C, chromatographing with 2% and 5% EtOH in CH_2Cl_2, provided **46** as the less polar isomer, which was recrystallized from EtOAc: mp 223−234 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.12 Hz, 3H), 1.27−1.41 (m, 2H), 1.46−1.60 (m, 1H), 1.85−1.98 (m, 1H), 2.27 (s, 3H), 4.04 (s, 2H), 4.54 (ABq, 2H), 4.67 (s, 1H), 5.23 (dd, J = 8.14, 3.05 Hz, 1H), 7.13 (dd, J = 7.80, 2.03 Hz, 1H), 7.24 (d, J = 8.14 Hz, 1H), 7.37 (d, J = 2.03 Hz, 1H), 10.35 (s, 1H); MS (ESI+) *m*/*z* 418 (M + H)$^+$, 435 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 416 (M − H)$^-$; Anal. ($C_{20}H_{20}BrNO_4$) C, H, N.

(+)-*trans*-9-(3-Bromo-4-methylphenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (46a) and (−)-*trans*-9-(3-Bromo-4-methylphenyl)-3-propyl-5,9-dihydro-3*H*,4*H*-2,6-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (46b). The enantiomers of compound **46** were separated using a Chiralpak AS column, eluting with 1:9 EtOH/hexane to provide **46a** (less polar, recrystallized from EtOAc; mp 249−251 °C; Anal. ($C_{20}H_{20}BrNO_4$) C, H, N; $[\alpha]^{23}_D$ +211 (*c* 0.35, acetone)) and **46b** (more polar, recrystallized from EtOAc; mp 252−254 °C; Anal. ($C_{20}H_{20}BrNO_4$) C, H, N; $[\alpha]^{23}_D$ − 223 (*c* 0.54, acetone)).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,6,7,9-tetrahydro-3*H*,4*H*-furo[3,4-*b*]quinoline-1,8-dione (47) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,6,7,9-tetrahydro-3*H*,4*H*-furo[3,4-*b*]-quinoline-1,8-dione (48).** Enamine **e8** (1.7 g, 11 mmol), 3-bromo-4-fluorobenzaldehyde (2.4 g, 12 mmol), and 1,3-cyclohexanedione (**c8**) (1.0 g, 8.9 mmol) via method A (3.6 g, 93%) and method C, chromatographing with 13:38:1:1 hexane/EtOAc/HCO_2H/H_2O, provided **48** (0.22 g, 7%) (less polar, recrystallized from EtOAc; mp 230−232 °C; ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.29 Hz, 3H), 1.54−1.72 (m, 1H), 1.79−2.09 (m, 3H), 2.20−2.30 (m, 2H), 2.55−2.64 (m, 2H), 4.67 (s, 1H), 5.12 (dd, J = 6.78, 3.39 Hz, 1H), 7.19−7.29 (m, 2H), 7.41−7.47 (m, 1H), 10.11 (s, 1H); MS (ESI+) *m*/*z* 406 (M + H)$^+$, 423 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 404 (M − H)$^-$; Anal. ($C_{19}H_{17}BrFNO_3$) C, H, N) and **47** (0.66 g, 20%) (more polar, recrystallized from EtOAc; mp 245−247 °C; ^{1}H NMR (DMSO-d_6) δ 0.77 (t, J = 7.29 Hz, 3H), 1.62−1.77 (m, 1H), 1.81−2.09 (m, 3H), 2.21−2.31 (m, 2H), 2.53−2.69 (m, 2H), 4.66 (s, 1H), 5.03−5.10 (m, 1H), 7.18 (ddd, J = 8.56, 5.00, 2.37 Hz, 1H), 7.24 (t, J = 8.65 Hz, 1H), 7.41 (dd, J = 6.78, 2.03 Hz, 1H), 10.13 (s, 1H); MS (ESI+) *m*/*z* 406 (M + H)$^+$, 423 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 404 (M − H)$^-$; Anal. ($C_{19}H_{17}BrFNO_3$) C, H, N).

***cis*-8-(3-Bromo-4-fluorophenyl)-3-ethyl-5,8-dihydro-3*H*,4*H*-2,6-dioxa-4-aza-*s*-indacene-1,7-dione (49) and *trans*-8-(3-Bromo-4-fluorophenyl)-3-ethyl-5,8-dihydro-3*H*,4*H*-2,6-dioxa-4-aza-*s*-indacene-1,7-dione (50).** Methyl 3-aminocrotonate (**e5**) (6.3 g, 55 mmol), 3-bromo-4-fluorobenzaldehyde (14 g, 71 mmol), and ethyl butyrylacetate (**c12**) (10.4 g, 65 mmol) via method A, chromatographing with 2:1 hexane/EtOAc (9.6 g, 40%), and method D, using 2.1 equiv of NBS and chromatographing with 3% MeOH in CH_2Cl_2, provided **50** (0.49 g, 14%, less polar; ^{1}H NMR (DMSO-d_6) δ 0.88 (t, J = 7.29 Hz, 3H), 1.58−1.72 (m, 1H), 1.92−2.05 (m, 1H), 4.69 (s, 1H), 4.94 (dd, J = 16.28, 0.68 Hz, 1H), 5.04 (d, J = 16.62 Hz, 1H), 5.21 (dd, J = 6.61, 3.56 Hz, 1H), 7.29−7.35 (m, 2H), 7.54−7.58 (m, 1H), 10.74 (s, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{17}H_{13}BrFNO_4$) C, H, N) and **49** (0.49 g, 14%, more polar; mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 7.29 Hz, 3H), 1.66−1.77 (m, 1H), 1.95−2.05 (m, 1H), 4.69 (s, 1H), 4.94 (dd, J = 16.27, 0.68 Hz, 1H), 5.04 (d, J = 16.27 Hz, 1H), 5.16−5.20 (m, 1H), 7.25−7.36 (m, 2H), 7.53 (dd, J = 6.78, 2.03 Hz, 1H), 10.80 (s, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$, 411 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{17}H_{13}BrFNO_4$) C, H, N).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-4,5,6,9-tetrahydro-3*H*-2,7-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (51) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-4,5,6,9-tetrahydro-3*H*-2,7-dioxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (52).** Enamine **e17** (0.17 g, 1.4 mmol), 3-bromo-4-fluorobenzaldehyde (0.28 g, 1.4 mmol), and dihydro-2*H*-pyran-2,4(3H)-dione[39] (**c7**) (0.12 g, 1.1 mmol) via method A, heated to 80 °C for 60 h, and chromatographed with 2% and 5% EtOH in CH_2Cl_2 provided **52** (less polar, recrystallized from EtOH; mp 252−255 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 7.46 Hz, 3H), 1.56−1.71 (m, 1H), 1.95−2.08 (m, 1H), 2.61 (dt, J = 17.46, 3.6 Hz, 1H), 2.75−2.90 (m, 1H), 4.19−4.37 (m, 2H), 4.67 (s, 1H), 5.15 (dd, J = 6.78, 3.39 Hz, 1H), 7.23−7.33 (m, 2H), 7.48−7.53 (m, 1H), 10.26 (s, 1H); MS (ESI+) *m*/*z* 408 (M + H)$^+$, 425 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_4$) C, H, N) and **51** (more polar, recrystallized from EtOH; mp 226−229 °C; ^{1}H NMR (DMSO-d_6) δ 0.80 (t, J = 7.29 Hz, 3H), 1.61−1.77 (m, 1H), 1.94−2.08 (m, 1H), 2.63 (dt, J = 17.29, 3.90 Hz, 1H), 2.74−2.87 (m, 1H), 4.21−4.36 (m, 2H), 4.67 (s, 1H), 5.06−5.12 (m, 1H), 7.22−7.32 (m, 2H), 7.47 (dd, J = 6.78, 1.70 Hz, 1H), 10.32 (s, 1H); MS (ESI+) *m*/*z* 408 (M + H)$^+$, 425 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 406 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_4 \cdot 0.25H_2O$) C, H, N).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*,4*H*-2-oxa-6-thia-4-azacyclopenta[*b*]naphthalene-1,8-dione (53) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*,4*H*-2-oxa-6-thia-4-azacyclopenta[*b*]naphthalene-1,8-dione (54).** Enamine **e17** (0.19 g, 1.5 mmol), 3-bromo-4-fluorobenzaldehyde (0.40 g, 1.9 mmol), and thiopyran-3,5-dione[40] (**c9**) (0.24 g, 1.8 mmol) via method A, heated to 80 °C for 60 h, and chromatographed with 2% and 5% EtOH in CH_2Cl_2 provided **54** (0.15 g, 24%) (less polar, recrystallized from EtOH; mp 236−240 °C (dec); ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.12 Hz, 3H), 1.53−1.69 (m, 1H), 1.95−2.06 (m, 1H), 3.14 (dd, J = 15.93, 1.70 Hz, 1H), 3.50 (dd, J = 7.46, 2.03 Hz, 1H), 3.55 (dd, J = 8.31, 1.86 Hz, 1H), 3.87 (dd, J = 16.95, 1.36 Hz, 1H), 4.73 (s, 1H), 5.15 (dd, J = 6.95, 3.22 Hz, 1H), 7.23−7.32 (m, 2H), 7.44−7.48 (m, 1H), 10.30 (s, 1H); MS (ESI+) *m*/*z* 441 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 422 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_3S \cdot 0.2EtOH \cdot 0.1CH_2Cl_2$) C, H, N) and **53** (0.20 g, 31%) (more polar, recrystallized from EtOH; mp 251−254 °C (dec); ^{1}H NMR (DMSO-d_6) δ 0.76 (t, J = 7.29 Hz, 3H), 1.61−1.76 (m, 1H), 1.95−2.06 (m, 1H), 3.16 (dd, J = 15.94, 1.70 Hz, 1H), 3.48 (dd, J = 15.94, 1.36 Hz, 1H), 3.58 (dd, J = 16.95, 1.70 Hz, 1H), 3.82 (d, J = 16.28 Hz, 1H), 4.72 (s, 1H), 5.08 (dd, J = 5.76, 3.73 Hz, 1H), 7.18−7.24 (m, 1H), 7.27 (t, J = 8.48 Hz, 1H), 7.42 (dd, J = 6.78, 2.03 Hz, 1H), 10.32 (s, 1H); MS (ESI+) *m*/*z* 441 (M + NH$_4$)$^+$; MS (ESI−) *m*/*z* 422 (M − H)$^-$; Anal. ($C_{18}H_{15}BrFNO_3S$) C, H, N).

(−)-*trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3*H*,4*H*-2-oxa-6-thia-4-azacyclopenta[*b*]naphthalene-1,8-dione (54b). The enantiomers of compound **54** were separated using a Chiralpak AS column, eluting with 15:85 EtOH/hexane to provide **54b** as the less polar enantiomer, which was recrystallized from EtOAc: mp >260 °C; Anal. ($C_{18}H_{15}BrFNO_3S$) C, H, N; $[\alpha]^{23}_D$ −227 (*c* 0.43, DMSO).

***cis*-8-(3-Bromo-4-fluorophenyl)-5-methyl-1,1-dioxo-1,2,3,4,5,8-hexahydro-6-oxa-1λ^6-thia-4-aza-*s*-indacen-7-one (55) and *trans*-8-(3-Bromo-4-fluorophenyl)-5-methyl-1,1-dioxo-1,2,3,4,5,8-hexahydro-6-oxa-1λ^6-thia-4-aza-*s*-indacen-7-one (56).** Enamine **c6** (1.6 g, 12 mmol), 3-bromo-4-fluorobenzaldehyde (2.6 g, 13 mmol), and tetrahydrothiophene-3-oxo-1,1-dioxide[41] (**c10**) (1.3 g, 10 mmol) via method A (2.3 g, 53%) and method C, chromatographing with 1:1 hexane/acetone and rechromatographing with 10:38:1:1 hexane/EtOAc/HCO_2H/H_2O, provided **56** (0.16 g, 7%, less polar; mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.43 (d, J = 6.78 Hz, 3H), 2.82−2.97 (m, 1H), 3.00−3.14 (m, 1H), 3.35−3.46 (m, 2H), 4.81 (s, 1H), 5.20 (q, J = 6.78 Hz, 1H), 7.26−7.38 (m, 2H), 7.55 (dd, J = 6.78, 1.70 Hz, 1H), 10.39 (s, 1H); MS (ESI+) *m*/*z* 414 (M + H)$^+$; MS

(ESI−) *m*/*z* 412 (M − H)$^-$; Anal. ($C_{16}H_{13}BrFNO_4S$) C, H, N) and **55** (0.053 g, 2%, more polar; mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.44 (d, J = 6.78 Hz, 3H), 2.82−2.95 (m, 1H), 3.00−3.13 (m, 1H), 3.36−3.46 (m, 2H), 4.83 (s, 1H), 5.14 (q, J = 6.89 Hz, 1H), 7.27−7.36 (m, 2H), 7.50−7.57 (m, 1H), 10.44 (s, 1H); MS (ESI+) *m*/*z* 414 (M + H)$^+$; MS (ESI−) *m*/*z* 412 (M − H)$^-$; Anal. ($C_{16}H_{13}BrFNO_4S$) C, H, N).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-methyl-8,8-dioxo-4,5,6,7,8,9-hexahydro-3*H*-2-oxa-8λ^6-thia-4-azacyclopenta[*b*]naphthalen-1-one (57) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-methyl-8,8-dioxo-4,5,6,7,8,9-hexahydro-3*H*-2-oxa-8λ^6-thia-4-azacyclopenta-[*b*]naphthalen-1-one (58).** Enamine **e17** (0.53 g, 4.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.89 g, 4.4 mmol), and tetrahydrothiopyran-3-one 1,1-dioxide[41] (**c11**) (0.50 g, 3.4 mmol) via method A (0.94 g, 62%) and method C, chromatographing with 1:1 hexane/acetone and rechromatographing with hexane/EtOAc/HCO_2H/H_2O 10:38:1:1, provided **58** (0.035 g, 4%) (less polar, recrystallized from EtOAc; mp 257−259 °C; ^{1}H NMR (DMSO-d_6) δ 1.41 (d, J = 6.78 Hz, 3H), 2.16−2.28 (m, 2H), 2.52−2.69 (m, 2H), 3.17−3.26 (m, 2H), 4.85 (s, 1H), 5.16 (q, J = 6.78 Hz, 1H), 7.26−7.33 (m, 2H), 7.45−7.50 (m, 1H), 10.01 (s, 1H); MS (ESI+) *m*/*z* 428 (M + H)$^+$; MS (ESI−) *m*/*z* 426 (M − H)$^-$; Anal. ($C_{17}H_{15}BrFNO_4S\cdot0.4H_2O$) C, H, N) and **57** (0.034 g, 4%) (more polar, recrystallized from EtOAc; mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 1.40 (d, J = 6.78 Hz, 3H), 2.15−2.28 (m, 2H), 2.52−2.71 (m, 2H), 3.16−3.26 (m, 2H), 4.86 (s, 1H), 5.06 (q, J = 6.67 Hz, 1H), 7.24 (ddd, J = 8.48, 5.09, 2.37 Hz, 1H), 7.30 (t, J = 8.65 Hz, 1H), 7.44 (dd, J = 6.44, 2.03 Hz, 1H), 10.06 (s, 1H); MS (ESI+) *m*/*z* 428 (M + H)$^+$; MS (ESI−) *m*/*z* 426 (M − H)$^-$; Anal. ($C_{17}H_{15}BrFNO_4S\cdot0.25H_2O$) C, H, N).

***cis*-9-(3-Bromo-4-fluorophenyl)-2,3-dimethyl-2,3,5,9-tetrahydro-4*H*-6-oxa-2,4-diazacyclopenta[*b*]naphthalene-1,8-dione (59) and *trans*-9-(3-Bromo-4-fluorophenyl)-2,3-dimethyl-2,3,5,9-tetrahydro-4*H*-6-oxa-2,4-diazacyclopenta[*b*]naphthalene-1,8-dione (60).** The product from method A of compounds **17** and **18** was brominated as described in method C but, after concentration, was not heated. Instead, 0.90 g (1.8 mmol) of this brominated intermediate was treated with 2 M NH_3 in MeOH (20 mL), heated to 80 °C for 2 h, cooled, concentrated, and chromatographed (2%, 4%, 5%, 6%, 7%, and 10% EtOH in CH_2Cl_2) to provide **60** (0.038 g, 5%) (less polar, recrystallized from EtOAc; mp 248−252 °C; ^{1}H NMR (DMSO-d_6) δ 1.29 (d, J = 6.78 Hz, 3H), 2.75 (s, 3H), 4.02 (s, 2H), 4.23 (q, J = 6.78 Hz, 1H), 4.52 (d, J = 5.09 Hz, 2H), 4.75 (s, 1H), 7.21−7.30 (m, 2H), 7.43−7.48 (m, 1H), 10.05 (s, 1H); MS (ESI+) *m*/*z* 407 (M + H)$^+$; MS (ESI−) *m*/*z* 405 (M − H)$^-$; Anal. ($C_{18}H_{16}BrFN_2O_3$) C, H, N) and **59** (0.045 g, 6%) (more polar, recrystallized from EtOAc; mp 242−244 °C; ^{1}H NMR (DMSO-d_6) δ 1.33 (d, J = 6.78 Hz, 3H), 2.75 (s, 3H), 4.03 (s, 2H), 4.11 (q, J = 6.67 Hz, 1H), 4.51 (ABq, 2H), 4.75 (s, 1H), 7.18 (ddd, J = 8.48, 5.09, 2.37 Hz, 1H), 7.26 (t, J = 8.65 Hz, 1H), 7.43 (dd, J = 6.78, 2.03 Hz, 1H), 10.08 (s, 1H); MS (ESI+) *m*/*z* 407 (M + H)$^+$; MS (ESI−) *m*/*z* 405 (M − H)$^-$; Anal. ($C_{18}H_{16}BrFN_2O_3$) C, H, N).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-2-methyl-2,3,5,9-tetrahydro-4*H*-6-oxa-2,4-diazacyclopenta[*b*]naphthalene-1,8-dione (61) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-2-methyl-2,3,5,9-tetrahydro-4*H*-6-oxa-2,4-diazacyclopenta[*b*]naphthalene-1,8-dione (62).** The product from method A of compounds **20** and **21** was treated as described in the procedure for compounds **59** and **60** to provide **62** (less polar; ^{1}H NMR (DMSO-d_6) δ 0.51 (t, J = 7.29 Hz, 3H), 1.78−2.00 (m, 2H), 2.73 (s, 3H), 4.03 (s, 2H), 4.32 (t, J = 3.73 Hz, 1H), 4.52 (ABq, 2H), 4.76 (s, 1H), 7.22−7.29 (m, 2H), 7.44−7.49 (m, 1H), 9.98 (s, 1H); MS (ESI+) *m*/*z* 421 (M + H)$^+$; MS (ESI−) *m*/*z* 419 (M − H)$^-$. Anal. Calcd for $C_{19}H_{18}BrFN_2O_3$: C, 54.17; H, 4.31; N, 6.65. Found: C, 53.75; H, 5.35; N, 7.28) and **61** (more polar; ^{1}H NMR (DMSO-d_6) δ 0.56 (t, J = 7.29 Hz, 3H), 1.84−1.98 (m, 2H), 2.72 (s, 3H), 4.02 (s, 2H), 4.20 (t, J = 3.22 Hz, 1H), 4.52 (ABq, 2H), 4.73 (s, 1H), 7.17−7.29 (m, 2H), 7.37−7.46 (m, 1H), 10.00 (s, 1H); MS (ESI+) *m*/*z* 421 (M + H)$^+$; MS (ESI−) *m*/*z* 419 (M − H)$^-$; Anal. ($C_{19}H_{18}BrFN_2O_3$) C, H, N).

***cis*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-2,3,5,9-tetrahydro-4*H*-6-oxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (63) and *trans*-9-(3-Bromo-4-fluorophenyl)-3-ethyl-2,3,5,9-tetrahydro-4*H*-6-oxa-4-azacyclopenta[*b*]naphthalene-1,8-dione (64).** Enamine **e16** (0.50 g, 4.0 mmol), 3-bromo-4-fluorobenzaldehyde (1.1 g, 5.2 mmol), and pyran-3,5-dione[35] **c1** (0.55 g, 4.8 mmol) via method A, chromatographing with 1:1 hexane/EtOAc (2.7 g, 65%), and method C, chromatographing with 2%, 4%, 8%, and 10% EtOH in CH_2Cl_2, provided **64** (0.47 g, 13%) (less polar; mp 251−253 °C; ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.29 Hz, 3H), 1.29−1.44 (m, 1H), 1.79−1.92 (m, 1H), 1.99 (dd, J = 17.97, 2.03 Hz, 1H), 2.42−2.50 (m, 1H), 2.91−3.01 (m, 1H), 4.03 (s, 2H), 4.55 (ABq, 2H), 4.69 (s, 1H), 7.17−7.28 (m, 2H), 7.43 (dd, J = 6.78, 1.70 Hz, 1H), 10.17 (s, 1H); MS (ESI+) *m*/*z* 406 (M + H)$^+$; MS (ESI−) *m*/*z* 404 (M − H)$^-$; Anal. ($C_{19}H_{17}BrFNO_3$) C, H, N) and **63** (0. 57 g, 16%) (more polar; mp 218−226 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 7.29 Hz, 3H), 1.39−1.53 (m, 1H), 1.80−1.90 (m, 1H), 2.02 (dd, J = 17.97, 2.03 Hz, 1H), 2.40−2.49 (m, 1H), 2.86−2.94 (m, 1H), 4.03 (s, 2H), 4.54 (ABq, 2H), 4.70 (s, 1H), 7.17 (ddd, J = 8.48, 4.92, 2.20 Hz, 1H), 7.25 (t, J = 8.48 Hz, 1H), 7.39 (dd, J = 6.78, 2.03 Hz, 1H), 10.23 (s, 1H); MS (ESI+) *m*/*z* 406 (M + H)$^+$; MS (ESI−) *m*/*z* 404 (M − H)$^-$; Anal. ($C_{19}H_{17}BrFNO_3$) C, H, N).

10-(3-Bromo-4-fluorophenyl)-3,3-dimethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (66). 5-Amino-6*H*-pyran-3-one[35] (**e1**) (1.6 g, 12 mmol), 3-bromo-4-fluorobenzaldehyde (2.6 g, 13 mmol), and carbonyl **c3** (1 g, 8.8 mmol) via method A, chromatographing with 5% MeOH in CH_2Cl_2 and then recrystallizing from MeOH, provided the title compound (0.22 g, 47%): mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (s, 3H), 1.25 (s, 3H), 4.04 (s, 2H), 4.50 (m, 4H), 4.89 (s, 1H), 7.24 (m, 2H), 7.40 (dd, 1H), 10.02 (s, 1H); MS (APCI+) *m*/*z* 422 (M + H)$^+$; Anal. ($C_{19}H_{17}NO_4BrF\cdot0.25H_2O$) C, H, N.

10-(3-Bromo-4-fluorophenyl)-3,3,6,6-tetramethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (67). Carbonyl **c3** was substituted for carbonyl **c2** in the procedure for enamine **e2**, and the resulting major isomer, 5-ethoxy-2,2-dimethyl-6*H*-pyran-3-one, was treated with NH_3-saturated EtOH to provide 5-amino-2,2-dimethyl-6*H*-pyran-3-one: ^{1}H NMR (DMSO-d_6) δ 1.18 (s, 6H), 4.20 (s, 2H), 4.87 (s, 1H), 6.83 (bs, 2H). 5-Amino-2,2-dimethyl-6*H*-pyran-3-one (0.20 g, 1.4 mmol), 3-bromo-4-fluorobenzaldehyde (0.30 g, 1.4 mmol), and carbonyl **c3** (0.20 g, 1.4 mmol) via method A provided the title compound (0.20 g, 32%): mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.15 (s, 6H), 1.25 (s, 6H), 4.49 (s, 4H), 4.81 (s, 1H), 7.24 (m, 2H), 7.39 (m, 1H), 9.94 (s, 1H); MS (APCI+) *m*/*z* 450 (M + H)$^+$; Anal. ($C_{21}H_{21}BrFNO_4$) C, H, N.

Spiro[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-3,1′-cyclopentane] (68). 5-Amino-6*H*-pyran-3-one[35] (**e1**) (0.11 g, 1.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.25 g, 1.2 mmol), and carbonyl **c6** (0.17 g, 1.0 mmol) via method A, chromatographing with 5% MeOH in CH_2Cl_2 and recrystallized from CH_2Cl_2, provided the title compound (0.16 g, 36%): mp >260 °C; ^{1}H NMR (DMSO) δ 1.40−1.53 (m, 1H), 1.53−1.71 (m, 5H), 1.87−1.98 (m, 1H), 2.04−2.14 (m, 1H), 4.04 (s, 2H), 4.48 (AB q, 2H), 4.51 (s, 2H), 4.90 (s, 1H), 7.18−7.24 (m, 1H), 7.27 (t, 1H), 7.41 (dd, 1H), 10.06 (bs, 1H); MS (ESI+) *m*/*z* 448 (M + H)$^+$, 465 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 446 (M − H)$^-$; Anal. ($C_{21}H_{19}NO_4FBr\cdot0.1CH_2Cl_2$) C, H, N.

10-(3-Bromo-4-fluorophenyl)-3,3-diethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (69). 5-Amino-6*H*-pyran-3-one[35] (**e1**) (0.11 g, 1.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.25 g, 1.2 mmol), and carbonyl **c5** (0.17 g, 1.0 mmol) via method A, chromatographing with 5% MeOH in CH_2Cl_2 and recrystallized from CH_2Cl_2, provided the title compound (0.14 g, 31%): mp 260−262 °C; ^{1}H NMR (DMSO) δ 0.54 (t, 3H), 0.81 (t, 3H), 1.39−1.54 (m, 2H), 1.60−1.84 (m, 2H), 4.04 (s, 2H), 4.44−4.56 (m, 4H), 4.94 (s, 1H), 7.18−7.24 (m, 1H), 7.25 (t, 1H), 7.41 (dd, 1H), 10.01 (bs, 1H); MS (ESI+) *m*/*z* 450 (M + H)$^+$, 467 (M + NH_4)$^+$; MS (ESI−) *m*/*z* 448 (M − H)$^-$; Anal. ($C_{21}H_{21}NO_4FBr\cdot0.5CH_2Cl_2$) C, H, N.

(+)-*cis*-10-(3-Bromo-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (70a) and (−)-*cis*-10-(3-Bromo-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (70b). The enantiomers of compound **70** (from method B) were separated using a Chiralcel OD column, eluting with 15:85 EtOH/hexane to provide **70b** (less polar, rechromatographed with 4:1, 3:1, and 2:1 hexane/acetone; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ −21 (*c* 0.33, acetone)) and **70a** (more polar, rechromatographed with 4:1, 3:1, and 2:1 hexane/acetone; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ +16 (*c* 0.45, acetone)).

(+)-*trans*-10-(3-Bromo-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (71a) and (−)-*trans*-10-(3-Bromo-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (71b). The enantiomers of compound **71** (from method B) were separated using a Chiralpak AS column, eluting with 3:7 EtOH/hexane to provide **71b** (less polar, rechromatographed with 2:1 hexane/acetone; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ − 38 (*c* 0.25, acetone)) and **71a** (more polar, rechromatographed with 2:1 hexane/acetone; Anal. ($C_{19}H_{17}NO_4FBr$) C, H, N; $[\alpha]^{23}_D$ +50.6 (*c* 0.49, acetone)).

***trans*-10-(3-Chloro-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (72).** 3-Chloro-4-fluorobenzaldehyde (0.88 g, 5.5 mmol) via method B provided **72** (0.47 g, 29%) as the less polar isomer: ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J = 7.29 Hz, 3H), 1.59−1.74 (m, 1H), 1.91−2.04 (m, 1H), 3.93 (d, J = 16.61 Hz, 1H), 4.04 (s, 2H), 4.21 (d, J = 16.61 Hz, 1H), 4.37−4.46 (m, 1H), 4.50 (ABq, 2H), 4.93 (s, 1H), 7.18 (ddd, J = 8.48, 4.75, 2.03 Hz, 1H), 7.25−7.33 (m, 2H), 9.96 (s, 1H); MS (ESI+) *m*/*z* 378 (M + H)$^+$; MS (ESI−) *m*/*z* 376 (M − H)$^-$; Anal. ($C_{19}H_{17}ClFNO_4$) C, H, N.

(+)-*trans*-10-(3-Chloro-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (72a) and (−)-*trans*-10-(3-Chloro-4-fluorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (72b). The enantiomers of compound **72** were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **72b** (less polar, rechromatographed with 2:1 hexane/acetone; Anal. ($C_{19}H_{17}ClFNO_4$) C, H, N; $[\alpha]^{23}_D$ − 54 (*c* 0.34, acetone)) and **72a** (more polar, rechromatographed with 2:1 hexane/acetone; Anal. ($C_{19}H_{17}ClFNO_4$) C, H, N; $[\alpha]^{23}_D$ +54 (*c* 0.33, acetone)).

***trans*-1-Ethyl-10-(4-fluoro-3-iodophenyl)-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (73).** 4-Fluoro-3-iodobenzaldehyde[36] (1.4 g, 5.5 mmol) via method B provided **73** (0.70 g, 35%) as the less polar isomer, which was recrystallized from EtOAc: mp 233−235 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J = 7.29 Hz, 3H), 1.61−1.72 (m, 1H), 1.90−2.05 (m, 1H), 3.93 (d, J = 16.62 Hz, 1H), 4.03 (s, 2H), 4.20 (d, J = 16.95 Hz, 1H), 4.37−4.45 (m, 1H), 4.50 (ABq, 2H), 4.90 (s, 1H), 7.14 (t, J = 8.31 Hz, 1H), 7.17−7.24 (m, 1H), 7.58 (dd, J = 6.10, 2.03 Hz, 1H), 9.94 (s, 1H); MS (ESI+) *m*/*z* 470 (M + H)$^+$; MS (ESI−) *m*/*z* 468 (M − H)$^-$; Anal. ($C_{19}H_{17}FINO_4$) C, H, N.

(+)-*trans*-1-Ethyl-10-(4-fluoro-3-iodophenyl)-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (73a) and (−)-*trans*-1-Ethyl-10-(4-fluoro-3-iodophenyl)-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (73b). The enantiomers of compound **73** were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **73b** (less polar, recrystallized from EtOAc; mp 212−216 °C; Anal. ($C_{19}H_{17}FINO_4$·0.5EtOAc·0.25H_2O) C, H, N; $[\alpha]^{23}_D$ −40 (*c* 0.28, acetone)) and **73a** (more polar, recrystallized from EtOAc; mp 234−235 °C; Anal. ($C_{19}H_{17}FINO_4$) C, H, N; $[\alpha]^{23}_D$ +46 (*c* 0.32, acetone)).

***trans*-10-(3,4-Dichlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (74).** 3,4-Dichlorobenzaldehyde (0.97 g, 5.5 mmol) via method B provided **74** (0.62 g, 37%) as the less polar isomer, which was recrystallized from EtOAc: mp 249−252 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J = 7.29 Hz, 3H), 1.61−1.76 (m, 1H), 1.92−2.04 (m, 1H), 3.93 (d, J = 16.61 Hz, 1H), 4.04 (s, 2H), 4.21 (d, J = 16.61 Hz, 1H), 4.38−4.45 (m, 1H), 4.50 (ABq, 2H), 4.92 (s, 1H), 7.18 (dd, J = 8.31, 2.20 Hz, 1H), 7.35 (d, J = 2.03 Hz, 1H), 7.52 (d, J = 8.14 Hz, 1H), 9.97 (s, 1H); MS (ESI+) *m*/*z* 394 (M + H)$^+$; MS (ESI−) *m*/*z* 392 (M − H)$^-$; Anal. ($C_{19}H_{17}Cl_2NO_4$) C, H, N.

(+)-*trans*-10-(3,4-Dichlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (74a) and (−)-*trans*-10-(3,4-Dichlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (74b). The enantiomers of compound **74** were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **74b** (less polar, recrystallized from EtOAc; mp 243−245 °C; Anal. ($C_{19}H_{17}Cl_2NO_4$) C, H, N; $[\alpha]^{23}_D$ −52 (*c* 0.27, acetone)) and **74a** (more polar, recrystallized from EtOAc; mp 245−247 °C; Anal. ($C_{19}H_{17}Cl_2NO_4$) C, H, N; $[\alpha]^{23}_D$ +52 (*c* 0.34, acetone)).

***trans*-10-(3-Bromo-4-chlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (75).** 3-Bromo-4-chlorobenzaldehyde[37] (1.2 g, 5.5 mmol) via method B provided **75** (0.72 g, 38%) as the less polar isomer: mp 246−249 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J = 7.29 Hz, 3H), 1.59−1.75 (m, 1H), 1.90−2.04 (m, 1H), 3.93 (d, J = 16.95 Hz, 1H), 4.04 (s, 2H), 4.21 (d, J = 16.95 Hz, 1H), 4.38−4.45 (m, 1H), 4.50 (ABq, 2H), 4.91 (s, 1H), 7.21 (dd, J = 8.31, 2.20 Hz, 1H), 7.47−7.54 (m, 2H), 9.97 (s, 1H); MS (ESI+) *m*/*z* 438 (M + H)$^+$; MS (ESI−) *m*/*z* 436 (M − H)$^-$; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N.

(*R*)-(+)-*trans*-10-(3-Bromo-4-chlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (75a) and (*S*)-(−)-*trans*-10-(3-Bromo-4-chlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (75b). The enantiomers of compound **75** were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **75b** (less polar, recrystallized from EtOAc; mp 249−250 °C; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N; $[\alpha]^{23}_D$ −50 (*c* 0.45, acetone)) and **75a** (more polar, recrystallized from EtOAc; mp 255−256 °C; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N; $[\alpha]^{23}_D$ +50 (*c* 0.31, acetone)).

***trans*-10-(4-Bromo-3-chlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (76).** 4-Bromo-3-chlorobenzaldehyde[37] (0.60 g, 2.7 mmol) via method B provided **76** (0.36 g, 30%) as the less polar isomer, which was recrystallized from EtOAc: mp 251−254 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J = 7.29 Hz, 3H), 1.61−1.74 (m, 1H), 1.90−2.04 (m, 1H), 3.93 (d, J = 16.95 Hz, 1H), 4.04 (s, 2H), 4.21 (d, J = 16.62 Hz, 1H), 4.41 (dd, J = 10.68, 2.88 Hz, 1H), 4.50 (ABq, 2H), 4.91 (s, 1H), 7.10 (dd, J = 8.14, 2.03 Hz, 1H), 7.35 (d, J = 2.03 Hz, 1H), 7.65 (d, J = 8.48 Hz, 1H), 9.97 (s, 1H); MS (ESI+) *m*/*z* 438 (M + H)$^+$; MS (ESI−) *m*/*z* 436 (M − H)$^-$; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N.

(+)-*trans*-10-(4-Bromo-3-chlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (76a) and (−)-*trans*-10-(4-Bromo-3-chlorophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (76b). The enantiomers of compound **76** were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **76b** (less polar, recrystallized from EtOAc; mp 251−253 °C; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N; $[\alpha]^{23}_D$ −49 (*c* 0.48, acetone)) and **76a** (more polar, recrystallized from EtOAc; mp 251−255 °C; Anal. ($C_{19}H_{17}BrClNO_4$) C, H, N; $[\alpha]^{23}_D$ +49 (*c* 0.4, acetone)).

***trans*-10-(3,4-Dibromophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (77).** 3,4-Dibromobenzaldehyde (1.5 g, 5.5 mmol) via method B provided **77** (0.75 g, 36%) as the less polar isomer, which was recrystallized from EtOAc: mp 251−254 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J = 7.29 Hz, 3H), 1.59−1.75 (m, 1H), 1.91−2.05 (m, 1H), 3.93 (d, J = 16.61 Hz, 1H), 4.04 (s, 2H), 4.21 (d, J = 16.95 Hz, 1H), 4.38−4.45 (m, 1H), 4.50 (ABq, 2H), 4.89 (s, 1H), 7.13 (dd, J = 8.31, 2.20 Hz, 1H), 7.49 (d, J = 2.03 Hz, 1H), 7.64 (d, J = 8.48 Hz, 1H), 9.97 (s, 1H); MS (ESI+) *m*/*z* 482 (M + H)$^+$; MS (ESI−) *m*/*z* 480 (M − H)$^-$; Anal. ($C_{19}H_{17}Br_2NO_4$) C, H, N.

(+)-*trans*-10-(3,4-Dibromophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (77a) and (−)-*trans*-10-(3,4-Dibromophenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (77b). The enantiomers of compound **77** were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **77b** (less polar, recrystallized from EtOAc; mp 255−256 °C (dec); Anal. ($C_{19}H_{17}Br_2NO_4$) C, H, N; $[\alpha]^{23}_D$ −42 (*c*

0.3, acetone)) and **77a** (more polar, recrystallized from EtOAc; mp 256−258 °C (dec); Anal. ($C_{19}H_{17}Br_2NO_4$) C, H, N; $[\alpha]^{23}_D$ +44 (*c* 0.35, acetone)).

***trans*-10-(3-Bromo-4-methylphenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (78).** 3-Bromo-4-methylbenzaldehyde[38] (1.1 g, 5.5 mmol) via method B provided **78** (0.69 g, 38%) as the less polar isomer, which was recrystallized from EtOAc: mp 237−238 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J = 7.12 Hz, 3H), 1.60−1.74 (m, 1H), 1.89−2.06 (m, 1H), 2.25 (s, 3H), 3.92 (d, J = 16.95 Hz, 1H), 4.03 (s, 2H), 4.20 (d, J = 16.61 Hz, 1H), 4.38−4.44 (m, 1H), 4.50 (ABq, 2H), 4.89 (s, 1H), 7.08 (dd, J = 7.80, 1.70 Hz, 1H), 7.22 (d, J = 7.80 Hz, 1H), 7.32 (d, J = 1.70 Hz, 1H), 9.91 (s, 1H); MS (ESI+) m/z 418 $(M + H)^+$; MS (ESI−) m/z 416 $(M - H)^-$; Anal. ($C_{20}H_{20}BrNO_4$) C, H, N.

(+)-*trans*-10-(3-Bromo-4-methylphenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (78a) and (−)-*trans*-10-(3-Bromo-4-methylphenyl)-1-ethyl-9,10-dihydro-1*H*,8*H*-2,7-dioxa-9-azaanthracene-4,5-dione (78b). The enantiomers of compound **78** were separated using a Chiralpak AS column, eluting with 1:4 EtOH/hexane to provide **78b** (less polar, recrystallized from EtOAc; mp 248−250 °C (dec); Anal. ($C_{20}H_{20}BrNO_4$) C, H, N; $[\alpha]^{23}_D$ −51 (*c* 0.3, acetone)) and **78a** (more polar, recrystallized from EtOAc; mp 250−251 °C (dec); Anal. ($C_{20}H_{20}BrNO_4$) C, H, N; $[\alpha]^{23}_D$ +52 (*c* 0.4, acetone)).

Supporting Information Available: X-ray crystallographic data on compounds **7**, **12**, **17**, **21a**, **75b**, and the 3-fluoro-4-iodo derivative of **17b**; results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Abrams, P. Describing bladder storage function: overactive bladder syndrome and detrusor overactivity. *Urology* **2003**, *62* (Suppl. 5B), 28−37.

(2) Brading, A. F. A myogenic basis for the overactive bladder. *Urology* **1997**, *50* (Suppl. 6A), 57−67.

(3) De Groat, W. C. A Neurologic basis for the overactive bladder. *Urology* **1997**, *50* (Suppl. 6A), 36−52.

(4) Quayle, J. M.; Nelson, M. T.; Standen, N. B. ATP-sensitive and inwardly rectifying potassium channels in smooth muscle. *Physiol. Rev.* **1997**, *77*, 1165−1232.

(5) Ashcroft, F. M.; Gribble, F. M. Correlating structure and function in ATP-sensitive K+ channels. *Trends Neurosci.* **1998**, *21*, 288−294.

(6) Coghlan, M. J.; Carroll, W. A.; Gopalakrishnan, M. Recent developments in the biology and medicinal chemistry of potassium channel modulators: Update from a decade of progress. *J. Med. Chem.* **2001**, *44*, 1627−1653.

(7) Andersson, K. E.; Appell, R.; Cardozo, L. D.; Chapple, C.; Drutz, H. P.; Finkbeiner, A. E.; Haab, F.; Vela Navarrete, R. The pharmacological treatment of urinary incontinence. *BJU Int.* **1999**, *84*, 923−947.

(8) Foster, C. D.; Speakman, M. J.; Fujii, K.; Brading, A. F. The effects of cromakalim on the detrusor muscle of human and pig urinary bladder. *Br. J. Urol.* **1989**, *63*, 284−94.

(9) Howe, B. B.; Halterman, T. J.; Yochim, C. L.; Do, M. L.; Pettinger, S. J.; Stow, R. B.; Ohnmacht, C. J.; Russell, K.; Empfield, J. R.; Trainor, D. A.; Brown, F. J.; Kau, S. T. ZENECA ZD6169: a novel KATP channel opener with in vivo selectivity for urinary bladder. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 884−890.

(10) Nurse, D. E.; Restorick, J. M.; Mundy, A. R. The effect of cromakalim on the normal and hyperreflexic human detrusor muscle. *Br. J. Urol.* **1991**, *68*, 27−31.

(11) Wein, A. J. Pharmacological agents for the treatment of urinary incontinence due to overactive bladder. *Expert Opin. Invest. Drugs* **2001**, *10*, 65−83.

(12) Butera, J. A.; Antane, M. M.; Antane, S. A.; Argentieri, T. M.; Freeden, C.; Graceffa, R. F.; Hirth, B. H.; Jenkins, D.; Lennox, J. R.; Matelan, E.; Norton, N. W.; Quagliato, D.; Sheldon, J. H.; Spinelli, W.; Warga, D.; Wojdan, A.; Woods, M. Design and SAR of novel potassium channel openers targeted for urge urinary incontinence. I. *N*-Cyanoguanidine bioisosteres possessing in vivo bladder selectivity. *J. Med. Chem.* **2000**, *43*, 1187−1202.

(13) (a) Gopalakrishnan, M.; Buckner, S. A.; Whiteaker, K. L.; Shieh, C. C.; Molinari, E. J.; Milicic, I.; Daza, A. V.; Davis-Taber, R.; Scott, V. E.; Sellers, D.; Chess-Williams, R.; Chapple, C. R.; Liu, Y.; Liu, D.; Brioni, J. D.; Sullivan, J. P.; Williams, M.; Carroll, W. A.; Coghlan, M. J. (−)-(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 novel ATP-sensitive potassium channel opener efficacious in suppressing urinary bladder contractions. I. In vitro characterization. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 379−386. (b) Brune, M. E.; Fey, T. A.; Brioni, J. D.; Sullivan, J. P.; Williams, M.; Carroll, W. A.; Coghlan, M. J.; Gopalakrishnan, M. (−)-(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 novel ATP-sensitive potassium channel opener efficacious in suppressing urinary bladder contractions. II. In vivo characterization. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 387−394.

(14) Drizin, I.; Holladay, M. W.; Yi, L.; Zhang, H. Q.; Gopalakrishnan, S.; Gopalakrishnan, M.; Whiteaker, K. L.; Buckner, S. A.; Sullivan J. P.; Carroll, W. A. Structure−activity studies for a novel series of tricyclic dihydropyrimidines as KATP channel openers (KCOs). *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1481−1484.

(15) Drizin, I.; Altenbach, R. J.; Buckner, S. A.; Whiteaker, K. L.; Scott, V. E.; Darbyshire, J. F.; Jayanti, V.; Henry, R. F.; Coghlan, M. J.; Gopalakrishnan, M.; Carroll, W. A. Structure−activity studies for a novel series of tricyclic dihydropyridopyrazolones and dihydropyridoisoxazolones as KATP channel openers. *Bioorg. Med. Chem.* **2004**, *12*, 1895−1904.

(16) Carroll, W. A.; Altenbach, R. J.; Bai, H.; Brioni, J. D.; Brune, M. E.; Buckner, S. A.; Cassidy, C.; Chen, Y.; Coghlan, M. J.; Daza, A. V.; Drizin, I.; Fey, T. A.; Fitzgerald, M.; Gopalakrishnan, M.; Gregg, R. J.; Henry, R. F.; Holladay, M. W.; King, L. L.; Kort, M. E.; Kym, P. R.; Milicic, I.; Tang, R.; Turner, S. C.; Whiteaker, K. L.; Yi, L.; Zhang, H.; Sullivan J. P. 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 KATP 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 KATP opener that selectively inhibits spontaneous bladder contractions. *J. Med. Chem.* **2004**, *47*, 3163−3179.

(17) Carroll, W. A.; Agrios, K. A.; Altenbach, R. J.; Buckner, S. A.; Chen, Y.; Coghlan, M. J.; Daza, A. V.; Drizin, I.; Gopalakrishnan, M.; Henry, R. F.; Kort, M. E.; Kym, P. R.; Milicic, I.; Smith, J. C.; Tang, R.; Turner, S. C.; Whiteaker, K. L.; Zhang, H.; Sullivan, J. P. Synthesis and structure−activity relationships of a novel series of tricyclic dihydropyridine-based KATP openers that potently inhibit bladder contractions in vitro. *J. Med. Chem.* **2004**, *47*, 3180−3192.

(18) Morgan, M. A.; Van Heyningen, E. 2*H*-Pyran-3,5(4*H*,6*H*)-diones. *J. Am. Chem. Soc.* **1958**, *79*, 422−424.

(19) Curran, D. P.; Kuo, S.-C. The tandem radical cyclization approach to angular triquinanes: model studies and the total synthesis of (±)-silphiperfolene and (±)-9-episilphiperfolene. *Tetrahedron* **1987**, *43*, 5653−5661.

(20) An alternative synthesis of enamine **e17** can be found in the following reference: Hiyama, T.; Oishi, H.; Suetsugu, Y.; Nishide, K.; Saimoto, H. Synthesis of 4-amino-2(5*H*)-furanones through intra- and intermolecular nitrile addition of ester enolates. Construction of carbon framework of an antitumor antibiotic basidalin. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2139−2150.

(21) Although an X-ray was not taken on compound **17b**, the (−)-enantiomer of the analogous 3-fluoro-4-iodo derivative was confirmed by X-ray to possess (*S*)-stereochemistry.

(22) Scott, V. E.; Davis-Taber, R. A.; Silvia, C.; Hoogenboom, L.; Choi, W.; Kroeger, P.; Whiteaker, K. L.; Gopalakrishnan, M. Characterization of human urinary bladder KATP channels containing SUR2B splice variants expressed in L-cells. *Eur. J. Pharmacol.* **2004**, *483*, 195−205.

(23) Quast, U.; Bray, K. M.; Andres, H.; Manley, P. W.; Baumlin, Y.; Dosogne, J. Binding of the K+ channel opener [^{3}H]P1075 in rat isolated aorta: relationship to functional effects of openers and blockers. *Mol. Pharmacol.* **1993**, *43*, 474−481.

(24) Babenko, A. P.; Aguilar-Bryan, L.; Bryan, J. A view of SUR/KIR6.X, KATP channels. *Annu. Rev. Physiol.* **1998**, *60*, 667−687.

(25) Buckner, S. A.; Milicic, I.; Daza, A.; Davis-Taber, R.; Scott, V. E. S.; Sullivan, J. P.; Brioni, J. D. Pharmacological and molecular analysis of ATP-sensitive K^+ channels in the pig and human detrusor. *Eur. J. Pharmacol.* **2000**, *400*, 287−295.

(26) Buckner, S. A.; Milicic, I.; Daza, A. V.; Coghlan, M. J.; Gopalakrishnan, M. Spontaneous phasic activity of the pig urinary bladder smooth muscle: characteristics and sensitivity to potassium channel modulators. *Br. J. Pharmacol.* **2002**, *135*, 639−648.

(27) (a) Fryer, R. M.; Rakestraw, P. A.; Preusser, L. C.; Brune, M. E.; Carroll, W. A.; Buckner, S. A.; Shieh, C.-C.; King, L. L.; Marsh, K. C.; Gopalakrishnan, M.; Cox, B. F.; Reinhart, G. A. Pharmacological characterization of the novel dihydropyridine potassium channel opener, (9*R*)-9-(3-iodo-4-methylphenyl)-5,9-dihydro-3*H*-furo[3,4-*b*]-pyrano[4,3-*e*]pyridine-1,8(4*H*,7*H*)-dione (A-325100), and the regulation of cardiovascular function in conscious and anesthetized beagle

dogs. *J. Cardiovasc. Pharmacol.* **2005**, *46*, 232−240. (b) Davis-Taber, R.; Molinari, E. J.; Altenbach, R. J.; Whiteaker, K. L.; Shieh, C.-C.; Rotert, G.; Buckner, S. A.; Malysz, J.; Milicic, I.; McDermott, J. S.; Gintant, G. A.; Coghlan, M. J.; Carroll, W. A.; Scott, V. E.; Gopalakrishnan, M. [125I]A-312110, a novel high-affinity 1,4-dihydropyridine ATP-sensitive K^+ channel opener: characterization and pharmacology of binding. *Mol. Pharmacol.* **2003**, *64*, 143−153.

(28) Compounds that were <60% efficacious and had $pEC_{50} > 6$ in FLIPR were considered partial agonists. Since the highest concentration that was tested in FLIPR was 10 μM, compounds that had $pEC_{50} < 6$ and were <60% efficacious were not considered as partial agonists because these agents may have not yet reached maximum efficacy.

(29) Plots were generated using the Prism software and analyzed using linear regression. Compounds without activity in FLIPR were excluded from the analysis.

(30) Fabiyi, A. C.; Gopalakrishnan, M.; Lynch, J. J.; Brioni, J. D.; Coghlan, M. J.; Brune, M. E. In vivo evaluation of the potency and bladder−vascular selectivity of the ATP-sensitive potassium channel openers (−)-cromakalim, ZD6169 and WAY-133537 in rats. *BJU Int.* **2003**, *91*, 284−290.

(31) Domon, K.; Mori, K. Pheromone synthesis. CXCIII. Simple synthesis of (±)-stigmolone (8-hydroxy-2,5,8-trimethyl-4-nonanone), the pheromone of *Stigmatella aurantiaca*. *Eur. J. Org. Chem.* **1999**, *5*, 979−980.

(32) Kuwahara, S.; Moriguchi, M,; Miyagawa, K.; Konno, M.; Kodama, O. Synthesis of (−)-syringolides 1 and 2. *Tetrahedron* **1995**, *51*, 8809−8814.

(33) Taber, D. F.; Ruckle, R. E. Cyclopentane construction by dirhodium tetraacetate-mediated intramolecular C−H insertion: steric and electronic effects. *J. Am. Chem. Soc.* **1986**, *108*, 7686−7693.

(34) Capozzi, G.; Roelens, S.; Talami, S. A protocol for the efficient synthesis of enantiopure β-substituted β-lactones. *J. Org. Chem.* **1993**, *58*, 7932−7936.

(35) Altenbach, R. J.; Agrios, K.; Drizin, I.; Carroll, W. A. 5-Amino-2*H*-pyran-3(6*H*)-one, **1**, a convenient intermediate in the synthesis of pyran containing 1,4-dihydropyridines. *Synth. Commun.* **2004**, *34*, 557−565.

(36) Liu, G.; Xin, Z.; Pei, Z.; Hajduk, P. J.; Abad-Zapatero, C.; Hutchins, C. W.; Zhao, H.; Lubben, T. H.; Ballaron, S. J.; Haasch, D. L.; Kaszubska, W.; Rondinone, C. M.; Trevillyan, J. M.; Jirousek, M. R. Fragment screening and assembly: a highly efficient approach to a selective and cell active protein tyrosine phosphatase 1B inhibitor. *J. Med. Chem.* **2003**, *46*, 4232−4235.

(37) Carroll, W. A.; Agrios, K. A.; Basha, F. Z.; Chen, Y.; Kort, M. E.; Kym, P. R.; Tang, R.; Turner, S. C.; Yi, L. Synthesis of tricyclic fused dihydropyridine derivatives as potassium channel openers. PCT Int. Appl. WO 0183480, 2001.

(38) Pearson, D. E.; Pope, H. W.; Hargrove, W. W. 3-Bromoacetophenone. *Org. Synth., Collect. Vol.* **1973**, *V*, 117−121.

(39) Carroll, W. A.; Agrios, K. A.; Basha, F. Z.; Chen, Y.; Kort, M. E.; Kym, P. R.; Tang, R.; Turner, S. C.; Yi, L. Synthesis of tricyclic fused dihydropyridine derivatives as potassium channel openers. PCT Int. Appl. WO 0183480, 2001.

(40) Fehnel, E. A.; Paul, A. P. Thiapyran derivatives. V. The monosulfinyl and monosulfonyl analogs of phloroglucinol. *J. Am. Chem. Soc.* **1956**, *77*, 4241−4244.

(41) Altenbach, R. J.; Kalvoda, L.; Carroll, W. A. A convenient multigram scale synthesis of tetrahydrothiophene-3-one-1,1-dioxide. *Synth. Commun.* **2004**, *34*, 567−570.

JM060549U