Thiophene Systems. 14. Synthesis and Antihypertensive Activity of Novel 7-(Cyclic amido)-6-hydroxythieno[3,2-*b*]pyrans and Related Compounds as New Potassium Channel Activators[1]

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The synthesis and antihypertensive activity of novel 7-(cyclic amido)-6-hydroxy-5,5-dimethylthieno[3,2-*b*]pyrans and related compounds are described. The compounds were tested for oral antihypertensive activity in spontaneously hypertensive rats (SHR) and selected compounds were evaluated in vitro for increases in ^{86}Rb efflux in rabbit isolated mesenteric arteries. The effects on activity in SHR of lactam ring size, the presence of heteroatoms in the lactam ring, the relative stereochemistry at C-6 and C-7, and the substituents on the thiophene ring are examined. The best racemic compound in this series is **32**, *trans*-5,6-dihydro-6-hydroxy-5,5-dimethyl-2-nitro-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran, which is 10-fold more potent than cromakalim with an ED_{30} = 0.015 mg/kg in SHR. Compound **32** could be resolved and the antihypertensive activity determined to reside primarily in the (6*S*,7*S*)-(−)-enantiomer **41**. Surprisingly, the elimination of water to give the enamides **50–52**, thiophene isosteres of bimakalim, diminishes activity significantly.

Introduction

Potassium (K^+) channels have an important physiological role as modulators of cardiac, neuronal, smooth muscle and endocrine function. A wide variety of K^+ channel subtypes have been identified and characterized.[2] An ATP-dependent K^+ channel (K_{ATP}) has been found in vascular tissue and has profound effects on the cardiovascular system.[3] Selective stimulation of K^+ efflux from vascular smooth muscle represents a new approach to the regulation of vascular tone. K^+ efflux in smooth muscle causes transmembrane hyperpolarization, a reduction in calcium entry through voltage and receptor operated channels, and, hence, vascular smooth muscle relaxation, as well as diminished responsiveness to vasoconstrictors. The functional antagonism caused by blockade of both receptor and voltage operated channels could be superior to that of traditional calcium channel blockers.[4] A new class of drugs, the K^+ channel activators, of which the prototype is cromakalim (1, BRL 34915),[5-9] affect this channel.[10] Since the mechanism of action of 1 has been elucidated, other compounds including nicorandil,[11] pinacidil,[12] and minoxidil sulfate[13] have been shown to possess similar properties.

As the archetype of the benzopyran family of K^+ channel activators, compound 1 has stimulated a widespread synthetic effort in the search for better agents.[14-16] The (−)-enantiomer of 1, lemakalim, is approximately 100–200 times more potent than the (+)-enantiomer as a K^+ channel activator.[7,17] Lemakalim is currently in Phase II clinical trials as a potential long-term antihypertensive agent.[18]

Homologation and aromatization of the pyrrolidinone ring as well as dehydration led to the synthesis of the chromene derivative bimakalim (2, EMD 52692).[19] Com-

(1) For previous paper in this series, see: McNally, J. J.; Sanfilippo, P. J.; Fitzpatrick, L.; Press, J. B. Thiophene Systems. 13. The Synthesis of Novel Thienopyranones. *J. Heterocycl. Chem.* **1992**, *29*, 247–250.

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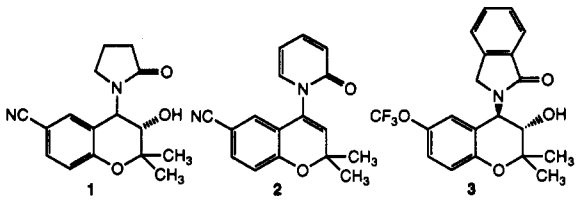


pound 2 is 10-fold more potent than cromakalim in reducing blood pressure in spontaneously hypertensive rats (SHR) and is currently in Phase II clinical trials as a potential selective coronary vasodilator. Of note, compound 2 does not possess the asymmetry typical of most compounds in this class.

Replacement of the C-6 cyano with a trifluoromethoxy moiety and substituting a bulky isoindolone group for the C-4 lactam gives celikalim (3, WAY-120,491) which in addition to being 10-fold more potent than 1 has a slower onset and longer duration of action.[20,21] One of the most common structural feature of all benzopyran K^+ channel activators is an electron-withdrawing substituent at C-6 of the ring system, which is a key determinant of potency.

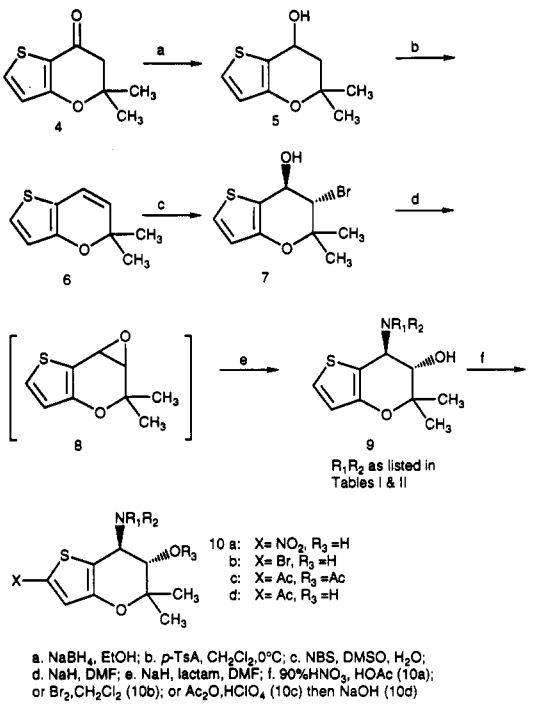
Our research in biologically active thiophene derivatives[1,22-24] prompted a synthetic program in thiophene isosteres of 1. We have previously reported the preparation of the parent thienopyranone system.[1] We now report the synthesis and antihypertensive activity of novel 7-(cyclic amido)-6-hydroxythieno[3,2-*b*]pyrans and related compounds as a new chemical series of potent K^+ channel activators.

Chemistry

The preparation of the 7-(cyclic amido)-6-hydroxythieno[3,2-*b*]pyrans is outlined in Scheme I. Sodium borohydride reduction of pyranone 4[1] gives alcohol 5. Dehydration of 5 is achieved using catalytic *p*-toluenesulfonic acid and ground molecular sieves under relatively dilute conditions to give 5,5-dimethyl-5*H*-thieno[3,2-*b*]-pyran (6) in 99% yield. When the reaction conditions are more concentrated, an ether "dimeric" product forms in substantial yield and interferes with purification. Reaction of 6 with *N*-bromosuccinimide and water in DMSO gives bromohydrin 7, which is thermally unstable and decomposes upon standing even at 0 °C overnight. However, 7 can be stored in a methylene chloride solution containing sodium bicarbonate under a nitrogen atmosphere at 0 °C for several days.

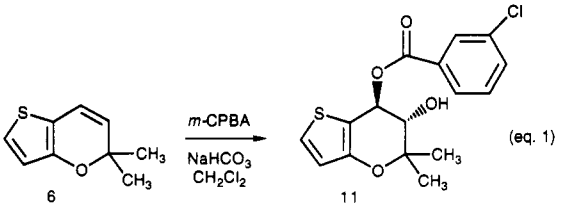
Treatment of bromohydrin 7 with 1 equiv of NaH in DMF generates epoxide 8, which is also extremely unstable and is not isolated. Its formation may be monitored by the disappearance of 7 by TLC and is complete within minutes. Subsequent addition of a lactam and an additional equivalent of NaH gives the *trans*-7-(cyclic amido)-6-hydroxythieno[3,2-*b*]pyrans 9 listed in Tables I and II.

Scheme I



a. $NaBH_4$, EtOH; b. *p*-TsA, CH_2Cl_2,0°C; c. NBS, DMSO, H_2O; d. NaH, DMF; e. NaH, lactam, DMF; f. 90%HNO_3, HOAc (10a); or Br_2,CH_2Cl_2 (10b); or Ac_2O,$HClO_4$ (10c) then NaOH (10d)

Attempts to form the epoxide 8 directly from the olefin 6 using *m*-CPBA were unsuccessful. The only product isolated is the ester 11 (eq 1) presumably via expected



epoxidation followed by ring opening of the epoxide 8 with the byproduct *m*-chlorobenzoic acid. Attempts to use less nucleophilic peracids also fail. Interestingly, this epoxidation reaction succeeds in 59% yield in the cyanobenzopyran series.[19]

The 7-(cyclic amido)-6-hydroxythieno[3,2-*b*]pyran 9 can undergo a variety of electrophilic substitution reactions to give the 2-substituted thiophene derivatives 10 (Scheme I). Nitration of 9 with 90% nitric acid in acetic acid gives a moderate yield of **10a**. Bromination of 9 occurs either with bromine or NBS to give **10b**. Acylation with either acetyl chloride or acetic anhydride in the presence of a Lewis or protic acid catalyst gives the acetyl acetate **10c**. Saponification of **10c** with methanolic sodium hydroxide yields the 2-acetyl-6-hydroxythieno[3,2-*b*]pyran derivative **10d**.

Cyano substitution on thiophene was required for a direct comparison of our novel series to cromakalim. The synthetic route employed utilizes the carboalkoxylation of aromatic halides through palladium catalysis.[25] As outlined in Scheme II, the hydroxy group of **33** is protected as the benzyl ether **33a**. Carboalkoxylation of **33a** using catalytic bis(triphenylphosphine)palladium chloride in MeOH in the presence of CO and triethylamine yields the

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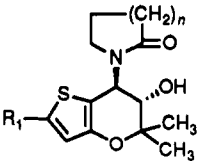
Table I. Substituted 7-(Cyclic amido)-5,6-dihydro-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyrans

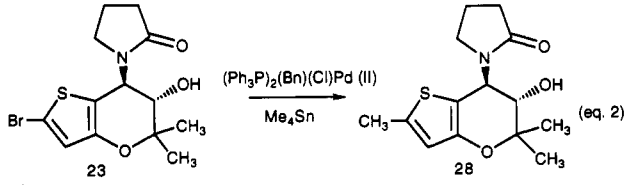


no.	R_1	*n*	% yield[a]	mp, °C	formula	anal.[b]	% change MAP[c]	ED_{30}, mg/kg, po[d]
18 (desoxy)	H	1	66	85–89	$C_{13}H_{19}NO_2S$	C,H,N,S	−14	
19	H	1	55	154–155	$C_{13}H_{17}NO_3S$	C,H,N,S	−55	5.03 (3.64–7.03)
20	$C(O)CH_3$	1	83	102–106	$C_{15}H_{19}NO_4S$	C,H,N	−62	0.2 (0.10–0.32)
21	C(O)Ph	1	53	198–200	$C_{20}H_{21}NO_4S$	C,H,N	−50, −4[e]	
22	$C(O)CF_3$	1	45	111–113	$C_{15}H_{16}F_3NO_4S$	C,H,N	−68, −55[e]	
23	Br	1	22	162–165	$C_{13}H_{16}BrNO_3S$	C,H,N	−43, −3[e]	
24	NO_2	1	42	214–217	$C_{13}H_{16}N_2O_5S$	C,H,N,S	−60	0.19 (0.10–0.33)
25	CO_2CH_3	1	58	167–168	$C_{15}H_{19}NO_5S$	C,H,N	−31	
26	CO_2Bn	1	16	146–151	$C_{21}H_{23}NO_5S$	C,H,N,S	−14	
27	CN	1	100	244–247	$C_{14}H_{16}N_2O_3S$	C,H,N	−67	0.07 (0.052–0.095)
28	CH_3	1	79	175–176	$C_{14}H_{19}NO_3S$	C,H,N	−28	
29 (desoxy)	H	2	64	68–70	$C_{14}H_{21}NO_2S$	C,H,N,S	−6	
30	H	2	43	151–152	$C_{14}H_{19}NO_3S$	C,H,N,S	−53	
31	$C(O)CH_3$	2	22	124–126	$C_{16}H_{21}NO_4S$	C,H,N	−67	0.09 (0.03–0.17)
32	NO_2	2	48	210–211	$C_{14}H_{18}N_2O_5S$	C,H,N,S	−65	0.015 (0.003–0.021)
33	Br	2	78	200–202	$C_{14}H_{18}BrNO_3S$	C,H,N	−64	
34	CO_2CH_3	2	65	104–106	$C_{16}H_{21}NO_5S$	C,H,N,S	−37	
35	$CONH_2$	2	61	287–288	$C_{15}H_{20}N_2O_4S$	C,H,N,S	−68	0.20 (0.10–0.31)
36	CN	2	93	212–214	$C_{15}H_{18}N_2O_3S$	C,H,N,S	−66	0.03 (0.026–0.041)
37	CO_2H	2	88	268–270	$C_{15}H_{19}NO_5S$	C,H,N,S	−9	
38	CONHMe	2	77	179–181	$C_{16}H_{22}N_2O_4S \cdot {}^1/_4H_2O$	C,H,N	−29	
39	$CONMe_2$	2	50	*f*	$C_{17}H_{24}N_2O_4S$	C,H,N	−63, −7[g]	
40[h]	$(+)NO_2$	2	59	158–160	$C_{14}H_{18}N_2O_5S$	C,H,N	−19[g]	1.9 (1.4–2.9)
41[i]	$(-)NO_2$	2	57	160–162	$C_{14}H_{18}N_2O_5S$	C,H,N	−63[g]	0.013 (0.010–0.016)
42[j]	NO_2	2	12	186–189	$C_{14}H_{18}N_2O_5S$	C,H,N	−24	
43	H	3	48	153–154	$C_{15}H_{21}NO_3S$	C,H,N,S	−12	
44	NO_2	3	71	218–219	$C_{15}H_{20}N_2O_5S$	C,H,N	−34	
1								0.19 (0.14–0.23)
2[19]								0.010

[a] Percentage yield of last step. [b] Analyses for the elements indicated were within ±0.4% of the theoretical values. [c] Maximal change in mean arterial blood pressure (MAP) comparing MAP immediately before and up to 240 min after oral administration of 20 mg/kg of the test substance, except where noted ($N \geq$ six rats). [d] Dose to produce 30% reduction in MAP. 95% confidence limits in parentheses. [e] Test substance dose of 1 mg/kg. [f] Semisolid. [g] Test substance dose of 0.1 mg/kg. [h] (+) enantiomer of **32**. [i] (−) enantiomer of **32**. [j] Cis 6,7-isomer of **32**.

methyl ester **34a**. Reaction of **34a** with ammonium hydroxide in MeOH gives the amide **35a**. Dehydration of **35a** with trifluoroacetic anhydride, and subsequent removal of the benzyl ether with boron tribromide, produces the nitrile **36**.

Alkyl substitution on thiophene is achieved using a palladium-catalyzed organotin coupling (eq 2).[26,27] Thus, treatment of **23** with catalytic *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) and tetramethyltin in HMPA or DMF gives **28** in 79% yield.



23 28

An alternative method to introduce C-7 nitrogen substitution utilizes the reaction of epoxide **8** with sodium azide (Scheme III). This reaction gives a greater than 9:1 mixture of the desired trans azido alcohol **12** to cis azido alcohol **13**. Interestingly, none of the cis isomer is observed when the epoxide is reacted with amide anions. Reduction of **12** with LAH gives amine **14**, which, upon treatment with 5-chlorovaleryl chloride and triethylamine then NaH, provides an alternate route to **30**. Amine **14** may also be converted to an isoindoline derivative in two steps: reductive amination with 2-carbomethoxybenzaldehyde followed by thermolytic ring closure. Nitration then provides **49**. Likewise, treatment of **13** with LAH gives the cis amino alcohol **15**. Acylation of **15** with 5-chlorovaleryl chloride followed by ring closure produces the piperidinone which gives the cis isomer **42** upon nitration.

Compound **1** was resolved into its enantiomers via separation of the diastereomeric α-methylbenzyl carbamates.[7] Using this methodology, the diastereomeric α-methylbenzyl carbamates of **32** were prepared and easily separated by silica gel chromatography. However, attempts to hydrolyze the carbamates with trichlorosilane–triethylamine or other conditions resulted in decomposition. Apparently, the nitro group of **32** causes unanticipated instability of the thienopyran system to the alkaline conditions required for cleavage of the carbamate. Ultimately, resolution was achieved by preparing the diastereomeric α-methylbenzyl carbamates of **30**, separating the diastereomers by fractional recrystallization, saponifying with sodium ethoxide, and subsequently nitrating to give the enantiomers **40** and **41**.

As previously reported for the benzopyran system,[7,19] the elimination of water to form the chromene may be achieved by treatment with NaH or NaOH in refluxing THF or dioxane. Unfortunately, these reaction conditions decompose **32** due to its instability in base (vide supra). In our case, it is necessary to first activate **30** to the mesylate

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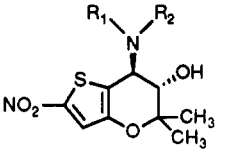
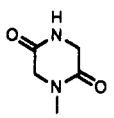
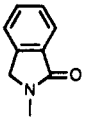
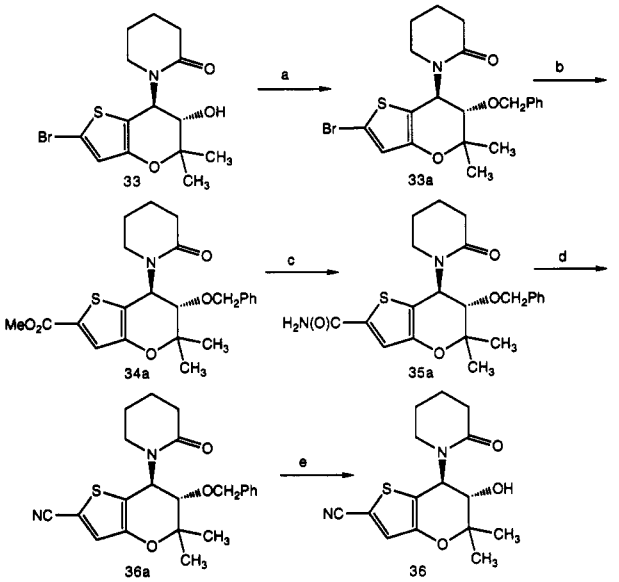
Table II. Substituted 7-(Heterocyclic)-5,6-dihydro-6-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyrans



no.	NR_1R_2	% yield[a]	mp, °C	formula	anal.[b]	% change MAP[c]
45		48	156–158	$C_{12}H_{15}N_3O_5S$	C,H,N	−3
46		45	211–212	$C_{13}H_{18}N_2O_3S$	C,H,N	−7
47		36	132–133	$C_{13}H_{16}N_2O_4S$	C,H,N	−4
48		52	113–114	$C_{14}H_{14}N_2O_5S$	C,H,N	−57, −10[d]
49		57	134–136	$C_{17}H_{16}N_2O_5S \cdot {}^1/_2H_2O$	C,H,N	−61, −58[d] ED_{30} = 0.22 mg/kg (0.18–0.26)[e]

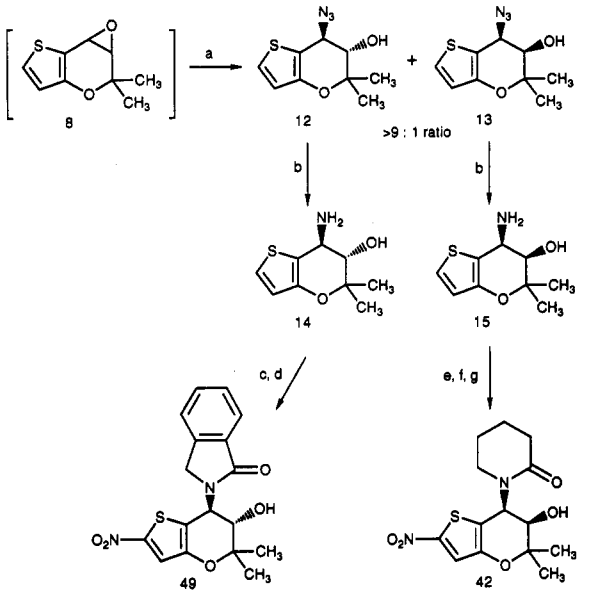
[a] Percentage yield of last step. [b] Analyses for the elements indicated were within ±0.4% of the theoretical values. [c] Maximal change in mean arterial blood pressure (MAP) comparing (MAP) immediately before and up to 240 min after oral administration of 20 mg/kg of the test substance, except where noted ($N \geq$ six rats). [d] Test substance dose of 1 mg/kg. [e] Dose to produce 30% reduction in MAP. 95% confidence limits in parentheses.

Scheme II



a. BnBr, NaH, DMF; b. $(Ph_3P)_2PdCl_2$, CO(160 psi), MeOH, 100°C, Et_3N; c. NH_4OH, MeOH; d. TFAA, pyr, CH_2Cl_2, 0°C; e. BBr_3, CH_2Cl_2

Scheme III



a. NaN_3, DMF; b. $LiAlH_4$, Et_2O; c. 2-carbomethoxybenzaldehyde, $NaCNBH_3$, MeOH, 40°C; d. 100°C, $PhCH_3$; e. Et_3N, $Cl(CH_2)_4COCl$; CH_2Cl_2; f. NaH, DMF g. 90%HNO_3, HOAc

16 and then nitrate to give 17 (Scheme IV). Treatment of 17 with NaH produces the desired enamide derivative 51.

Results and Discussion

The compounds in this study were evaluated for oral antihypertensive activity in the spontaneously hypertensive rat (SHR) (Tables I–III). Selected compounds were further evaluated for their effects on K^+ efflux in the rabbit mesenteric artery using $^{86}Rb^+$ as a surrogate marker for potassium (Table IV).

Most benzopyran K^+ channel activators commonly have an electron-withdrawing substituent at C-6 of the ring to achieve adequate potency. Thiophene is known to be electronically and sterically similar to benzene,[28] albeit electron rich. Therefore we anticipated electron-withdrawing substituents on thiophene to be essential for adequate antihypertensive activity. However, even the unsubstituted thiophene derivative 19 displays substantial antihypertensive activity at the oral screening dose of 20 mg/kg (Table I). Compound 19 is 30 times less potent

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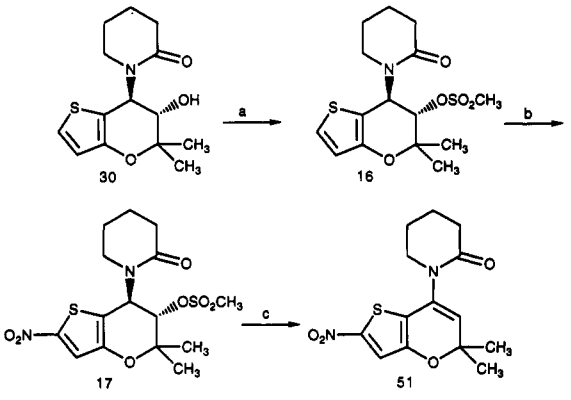
Scheme IV



a. MsCl, Et_3N, CH_2Cl_2; b. HNO_3, HOAc; c. NaH, rt, 2 days

than 1 indicating the surprising potency of these derivatives. As noted,[7] the carbonyl of the lactam enhances potency in the benzopyrans and this is also demonstrated by the lack of activity of 18 and 29 in the thieno[3,2-*b*]-pyran series. Increasing the lactam ring size at C-7 to a piperidinone moiety (30) maintains potency while the homopiperidine 43 has diminished activity.

Substituent effects on thiophene were then studied with either pyrrolidinone, piperidinone, or homopiperidinone groups at the 7-position. In the 2-pyrrolidinone series, powerful electron-withdrawing groups such as an acetyl (20), trifluoroacetyl (22), or nitro (24) significantly increase activity. Compounds 20 and 24 are equipotent to compound 1. Cyano substitution (27), the direct isostere of 1, enhances potency 3-fold. Substitution with other electron-withdrawing groups such as benzoyl (21), bromo (23), methoxycarbonyl (25), and benzyloxycarbonyl (26) significantly diminishes activity as compared to the unsubstituted thiophene 19. The electron-donating methyl group (28) also diminishes activity, indicating the SAR in the thienopyran series is different than the benzopyran.[29]

In the 2-piperidinone series, introduction of electron-withdrawing groups on thiophene significantly increases potency as compared to the 2-pyrrolidinone series. The acetyl compound 31 and cyano compound 36 are twice as potent as their pyrrolidinone counterparts 20 and 27. The nitro moiety (32) enhances potency to 10-fold more than either 14 or 1. Compound 32 is approximately equipotent to the reported values for compound 2.[19] Interestingly, whereas an amido substitution (35) is equipotent to 1, the monomethyl amido compound 38 is not effective at the screening dose. On the other hand, disubstitution of the amide (39) maintains good activity at the screening dose which is greatly diminished when tested at a lower doses. The methyl ester 34 is equipotent to its 2-pyrrolidinone analog 25. However, the carboxylic acid 37 is much less active at the screening dose. The most potent racemic compound in the 2-piperidinone series is 32. Although nitro substitution significantly enhances potency for the pyrrolidinone and piperidinone series, homopiperidinone 44 is only marginally effective at the screening dose.

The effects of other cyclic amides at the C-7 position were also examined while maintaining nitro substitution at the C-2 position of thiophene (Table II). An additional nitrogen in the ring to give the cyclic imidate 45 or 46 eliminates activity. Glycine anhydride 47 also has little activity at the screening dose. Aromatization of the piperidinone gives 48, which has good activity at the screening dose but diminished activity at a lower dose. An isoindolone group (49), a structural feature of 3, reduces potency 10-fold as compared to 32, making 49 equipotent to 1.

In the benzopyran series, elimination of water gives the chromene 2, which is reported to be 10-fold more potent than 1.[19] Interestingly, in the thienopyran series dehydration results in a marked loss of activity as observed for 50–52 (Table III).

The trans configuration between C-6 and C-7 is a crucial determinant of activity since the cis isomer 42 lacks activity. Resolution of 32 gives enantiomers 40 and 41 (Table I). The (−)-enantiomer 41 is 100 times more potent than the (+)-enantiomer 40, confirming that, similar to the other K^+ channel activators, activity resides mainly in one enantiomer. As noted in literature, pharmacological activity may depend on the exact relative orientation of both ring systems.[30] Evans et al. found an orthogonal arrangement of the pyrrolidinone with respect to the benzopyran for 1.[31] The same spatial arrangement between the piperidinone and the thienopyran exists in 41 as determined by X-ray structure (Figure 1).[32]

The mode of action of these novel thienopyrans was investigated by studying the increase in the basal efflux rate of $^{86}Rb^+$, a K^+ surrogate,[33,34] in rabbit mesenteric artery (Table IV). The more potent effectors of mean arterial pressure (MAP) in SHR exhibit the greatest increase of $^{86}Rb^+$ efflux. Although an exact correlation between these data and the in vivo SHR data was not observed, other factors such as absorption or intrinsic activity may be the cause. Compound 32 has potency similar to that of compound 1. The (−)-enantiomer 41 causes greater $^{86}Rb^+$ efflux activity whereas the (+)-enantiomer 40 is devoid of this activity. These data show that these novel thienopyrans enhance K^+ efflux from vascular smooth muscle tissue which, at least in part, may be presumed to be the cause of their pharmacological activity.

Compound 41 is an extremely potent antihypertensive agent and has potential in the treatment of vasospastic disorders and hypertension. Compound 41 is a potential development candidate with anti-anginal and anti-ischemic indications with properties possibly superior to calcium channel blockers, nitrates, or beta blockers. Further studies in this area are the subject of future reports from this laboratory.[36]

Experimental Section

Melting point determinations were done on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared

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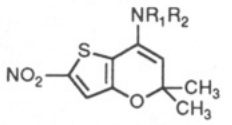
Table III. Substituted 7-(Heterocyclic)-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyrans



no.	NR_1R_2	% yield[a]	mp, °C	formula	anal.[b]	% change MAP[c]
50	piperidin-1-yl	35	122–124	$C_{14}H_{18}N_2O_3S$	C,H,N,S	−17
51	2-oxopiperidin-1-yl	47	148–151	$C_{14}H_{16}N_2O_4S$	C,H,N	−5
52	2-oxopyridin-1-yl	69	176–177	$C_{14}H_{12}N_2O_4S$	C,H,N	−14

[a] Percentage yield of last step. [b] Analyses for the elements indicated were within ±0.4% of the theoretical values. [c] Maximal change in mean arterial blood pressure (MAP) comparing MAP immediately before and up to 240 min after oral administration of 20 mg/kg of the test substance ($N \geq$ six rats).

Table IV. Increase in $^{86}Rb^+$ Efflux in Rabbit Isolated Mesenteric Artery[a] for Selected Thienopyran Derivatives

compd	concn,[b] μM	increase in ^{86}Rb efflux over basal rate, %[c]	compd	concn,[b] μM	increase in ^{86}Rb efflux over basal rate, %[c]
18	100	0	**33**	30	42
19	100	25	**34**	100	63
	30	8		30	51
	10	0	**35**	100	92
20	100	57		30	75
	30	40		10	73
	10	37	**36**	100	0
21	100	58		30	11
	30	33	**38**	100	25
	10	0	**39**	100	32
23	100	90	**40**	100	19
	30	64		30	11
	10	65		10	19
24	100	114		1	2
	30	110	**41**	100	53
	10	67		30	91
	1	48		10	80
29	100	0		3	66
30	100	40		1	26
	30	26	**43**	100	0
	10	7	**44**	30	25
31	100	26	**47**	100	0
	30	38	**48**	30	0
	10	13	**1**[d]	100	104 (50–108)
32	30	60		30	73 (61–85)
	10	56		10	46 (40–52)
	3	41		3	41 (28–54)

[a] Isolated rabbit aorta. [b] Concentration of test compound in buffer. [c] Percentage change of ^{86}Rb efflux from background control. [d] 95% confidence limits in parentheses.

Figure 1. X-ray structure of compound **41** (ORTEP drawing).

(IR) spectra were obtained on a Perkin-Elmer IR8 and are reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance (^1H NMR) spectra were recorded on a General Electric QE300 (300 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield relative to tetramethylsilane as standard. Microanalyses were performed on a Perkin-Elmer Model 240c elemental analyzer, and mass spectra were determined on a Finnigan INCOS 50, single stage quadrupole, using desorption chemical ionization techniques. Silica gel 60, 230–400 mesh, was used for both flash chromatography and medium-pressure chromatography (MPLC). Compounds in the tables are prepared according to the general procedures described. Physical properties of the compounds are summarized in Tables I–III.

5,6-Dihydro-7-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (5). Sodium borohydride (0.97 g, 25.5 mmol) was added to a solution of **4**[1] (3.1 g, 17.0 mmol) in ethanol (50 mL) and stirred at room temperature for 2 h. An additional 0.97 g of sodium borohydride was added and the mixture was stirred 16 h. The mixture was poured into H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O (5×) and dried over magnesium sulfate. The solvent was evaporated in vacuo to give the product, 2.96 g (95%), as a brown oil: IR (neat): 3373, 2976, 1561, 1400 cm^{-1}; MS *m/z* 185 (MH^+); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.45 (s, 3H), 1.87 (m, 1H), 1.94 (d, J = 7.0 Hz, 1H, exchanges with D_2O), 2.16 (m, 1H), 4.88 (m, 1H), 6.57 (d, J = 5.4 Hz, 1H), 7.13 (d, J = 5.4 Hz, 1H). This oil was used without further purification in the next step.

5,5-Dimethyl-5*H*-thieno[3,2-*b*]pyran (6). A mixture of **5** (1.3 g, 7.06 mmol), *p*-toluenesulfonic acid (0.11 g, 0.58 mmol), and ground molecular sieves (1.3 g) in CH_2Cl_2 (100 mL) was stirred at 0 °C for 1.5 h. The mixture was washed with 1.0 N aqueous sodium hydroxide and dried over magnesium sulfate. The solvent was evaporated in vacuo to give the product, 1.17 g (99%), as a red oil: IR (neat) 2976, 1504, 1531 cm^{-1}; MS *m/z* 167 (MH^+); ^1H NMR ($CDCl_3$) δ 1.45 (s, 6H), 5.27 (d, J = 9.8 Hz, 1H), 6.30 (d, J = 9.8 Hz, 1H), 6.60 (d, J = 5.3 Hz, 1H), and 6.99 (d, J = 5.3 Hz, 1H).

***trans*-6-Bromo-7-hydroxy-5,6-dihydro-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (7).** To compound **6** (10.9 g, 65.9 mmol) in DMSO (110 mL) and H_2O (1.6 mL, 88.9 mmol) was added NBS

(12.9 g, 72.5 mmol). After stirring at room temperature for 16 h, the mixture was poured into ice H_2O (400 mL) and extracted into CH_2Cl_2. The organic layer was washed with H_2O (5×), dried, and evaporated. The residue was purified by flash chromatography (CH_2Cl_2) to give 7, 11.5 g (66%), as a brown oil: ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H), 1.60 (s, 3H), 2.56 (d, J = 4 Hz, 1H, exchanges with D_2O), 4.10 (d, J = 7 Hz, 1H), 4.98 (dd, J = 4 Hz, J = 7 Hz, 1H), 6.56 (d, J = 5 Hz, 1H), 7.16 (d, J = 5 Hz, 1H).

***trans*-5,6-Dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (30).** A 0 °C solution of 60% NaH (1.7 g, 41.8 mmol) in DMF (115 mL) was treated with 7 (11.0 g, 41.8 mmol). After stirring at room temperature for 2 h, δ-valerolactam (6.2 g, 62.7 mmol) was added followed by 60% NaH (1.7 g, 41.8 mmol). The solution was stirred at room temperature overnight, poured into ice H_2O (500 mL), and extracted with CH_2Cl_2. The organic layer was washed with H_2O (5×), dried, and evaporated. The solid was triturated in Et_2O to give 5.1 g (43%) of **30**: mp 151–152 °C; IR (KBr) 3195, 1610, 1563 cm^{-1}; MS m/z 282 (MH^+); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.49 (s, 3H), 1.81 (m, 4H), 2.53 (t, J = 6.5 Hz, 2H), 3.15 (m, 1H), 3.24 (m, 1H), 3.68 (d, J = 5.0 Hz, 1H, exchanges with D_2O), 3.79 (dd, J = 5.0 Hz, J = 9.1 Hz, 1H, simplifies to d, J = 9.1 Hz with D_2O), 5.84 (d, J = 9.1 Hz, 1H), 6.57 (d, J = 5.4 Hz, 1H), 7.11 (d, J = 5.4 Hz, 1H). Anal. ($C_{14}H_{19}NO_3S$) C, H, N, S.

***trans*-5,6-Dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopyrrolidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (19)**: IR (KBr) 3263, 1665, 1562 cm^{-1}; MS m/z 268 (MH^+); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.50 (s, 3H), 2.07 (m, 2H), 2.52 (m, 2H), 3.00 (d, J = 5.5 Hz, 1H, exchanges with D_2O), 3.35 (m, 2H), 3.78 (dd, J = 5.5 Hz, J = 9.0 Hz, 1H, simplifies to d, J = 9.0 Hz, with D_2O), 5.28 (d, J = 9.0 Hz, 1H), 6.57 (d, 5.4 Hz, 1H), 7.11 (d, J = 5.4 Hz, 1H). Anal. ($C_{13}H_{17}NO_3S$) C, H, N, S.

***trans*-6-Hydroxy-5,5-dimethyl-7-(2-oxohexamethyleneimino)-5*H*-thieno[3,2-*b*]pyran (43)**: IR (KBr) 3200, 1615, 1523 cm^{-1}; MS m/z 296 (MH^+); ^1H NMR ($CDCl_3$) δ 7.13 (d, J = 5.4 Hz, 1H), 6.58 (d, J = 5.4 Hz, 1H), 5.75 (d, J = 9.2 Hz, 1H), 3.69 (m, 1H), 3.36 (d, J = 4.9 Hz, 1H), 3.23 (m, 2H), 2.64 (m, 2H), 1.86 (m, 6H), 1.47 (s, 3H), 1.29 (s, 3H). Anal. ($C_{15}H_{21}NO_3S$) C, H, N, S.

General Procedure for Bromination. *trans*-2-Bromo-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (33). Bromine (0.27 mL, 5.2 mmol) was added slowly to a solution of **30** (1.4 g, 5.0 mmol) in CH_2Cl_2 (30 mL). After stirring at room temperature for 2 h, the resulting precipitate was collected by filtration and purified by flash chromatography (1% MeOH/CH_2Cl_2). Recrystallization from CH_2Cl_2/hexanes gave 3.87 g (78%) of **33**, as a colorless solid: IR (KBr) 3442, 2942, 1616, 1571, 1488 cm^{-1}; MS m/z 360 (MH^+): ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.46 (s, 3H), 1.82 (m, 4H), 2.51 (m, 2H), 3.12 (m, 1H), 3.27 (m, 1H), 3.46 (d, J = 5.0 Hz, 1H, exchanges with D_2O), 3.78 (d of d, J = 9.0 Hz, J = 5.0 Hz, 1H, simplifies to d, J = 9.0 Hz, with D_2O), 5.74 (d, J = 9.0 Hz, 1H), 7.58 (s, 1H). Anal. ($C_{14}H_{18}BrNO_3S$) C, H, N.

***trans*-2-Bromo-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopyrrolidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (23).** IR (KBr) 3287, 1666, 1570 cm^{-1}; MS m/z 346 (MH^+); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.47 (s, 3H), 2.06 (m, 2H), 7.50 (m, 2H), 3.23 (br s, 1H, exchanges with D_2O), 3.34 (m, 2H), 3.76 (d, J = 9.1 Hz, 1H), 5.16 (d, J = 9.1 Hz, 1H), 6.56 (s, 1H). Anal. ($C_{13}H_{16}BrNO_3S$) C, H, N.

General Procedure for Nitration. *trans*-5,6-Dihydro-6-hydroxy-5,5-dimethyl-2-nitro-7-(2-oxopyrrolidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (24). Nitric acid (90%, 1.2 mL, 26.9 mmol) was added to an 18 °C solution of **19** (1.0 g, 3.7 mmol) in HOAc (30 mL). After stirring at room temperature for 1.5 h, the reaction mixture was poured into ice H_2O (200 mL). Within 10 min a yellow solid crystallized which was collected by filtration, washed with H_2O, and triturated with Et_2O to give 0.49 g (42%) of **24**: mp 214–217 °C; IR (KBr) 3216, 1655, 1512 cm^{-1}; MS m/z 313 (MH^+); ^1H NMR (DMSO-d_6) δ 1.23 (s, 3H), 1.43 (s, 3H), 2.00 (m, 2H), 2.36 (m, 2H), 3.16 (m, 1H), 3.20 (m, 1H), 3.80 (d, J = 9.5 Hz, 1H), 4.98 (d, J = 9.5 Hz, 1H), 5.92 (bs, 1H, exchanges with D_2O), 7.75 (s, 1H). Anal. ($C_{13}H_{16}N_2O_5S$), C, H, N, S.

***trans*-5,6-Dihydro-6-hydroxy-5,5-dimethyl-2-nitro-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (32)**: IR (KBr) 3231, 1613, 1515, 1492 cm^{-1}; MS m/z 327 (MH^+); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.51 (s, 3H), 1.84 (m, 4H), 2.55 (m, 2H), 3.20 (m, 2H), 3.84 (d, J = 9.5 Hz, 1H), 4.78 (br s, 1H, exchanges with D_2O), 5.86 (d, J = 9.5 Hz, 1H), 7.40 (s, 1H). Anal. ($C_{14}H_{18}N_2O_5S$) C, H, N, S.

General Procedure for Acetylation. *trans*-2-Acetyl-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopyrrolidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (20). A solution of **19** (1.76 g, 6.58 mmol) in acetic anhydride (15 mL) was treated with perchloric acid (70%, 10 drops). After stirring at 60 °C for 2 h, the solution was poured into ice H_2O (100 mL). The product was extracted into CH_2Cl_2, washed with H_2O (4×), dried, and evaporated. The resultant oil was purified by MPLC (1% MeOH/CH_2Cl_2) to give 0.85 g (37%) of *trans*-6-acetoxy-2-acetyl-5,6-dihydro-5,5-dimethyl-5-(2-oxopyrrolidin-1-yl)-5*H*-thieno[3,2-*b*]pyran: mp 170–172 °C; IR (KBr) 1755, 1690, 1666, 1564 cm^{-1}; MS m/z 352 (MH^+); ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.39 (s, 3H), 1.98 (m, 2H), 2.10 (s, 3H), 2.37 (m, 2H), 2.49 (s, 3H), 3.23 (m, 1H), 3.38 (m, 1H), 5.14 (d, J = 9.3 Hz, 1H), 5.47 (d, J = 9.3 Hz, 1H), 7.16 (s, 1H). Sodium hydroxide (50%, 0.15 g, 1.87 mmol) was added to a solution of the above compound (0.45 g, 1.3 mmol) in MeOH (20 mL). After stirring at room temperature for 1 h, the solution was poured into H_2O (100 mL) and extracted into CH_2Cl_2. The organic layer solution was washed with H_2O (3×), dried, and evaporated. The resultant oil was crystallized from Et_2O/hexanes to give 0.33 g (83%) of **20**, as a colorless solid: mp 102–106 °C; IR (KBr) 1665, 1561 cm^{-1}; MS m/z 310 (MH^+); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.51 (s, 3H), 2.07 (m, 2H), 2.48 (s, 3H), 2.51 (m, 2H), 3.34 (m, 2H), 3.45 (d, J = 6.2 Hz, 1H, exchanges with D_2O), 3.80 (dd, J = 6.2 Hz and J = 9.4 Hz, 1H, simplifies to d, J = 9.4 Hz, with D_2O), 5.29 (d, J = 9.4 Hz, 1H), 7.14 (s, 1H). Anal. ($C_{15}H_{19}NO_4S$) C, H, N.

***trans*-5,6-Dihydro-6-hydroxy-2,5,5-trimethyl-7-(2-oxopyrrolidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (28).** A solution of **23** (0.5 g, 1.44 mmol), tetramethyltin (0.22 mL, 1.58 mmol), and *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) (11 mg, 0.014 mmol) in hexamethylphosphoramide (20 mL) was heated to 65 °C for 4 days. The solution was poured into H_2O, and the product was extracted into CH_2Cl_2. The organic solution was washed several times with H_2O, and the solvent was evaporated. Purification by MPLC (2% MeOH/CH_2Cl_2) gave 0.317 g (78%) of **28**, as a colorless solid: mp 175–176 °C; IR (KBr) 1665, 1582 cm^{-1}; MS m/z 282 (MH^+); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.47 (s, 3H), 2.02–2.10 (m, 2H), 2.37 (s, 3H), 2.49–2.54 (m, 2H), 3.01 (d, J = 5.5 Hz, 1H, exchanges with D_2O), 3.28–3.44 (m, 2H), 3.74 (d of d, J = 5.5 and 9.0 Hz, 1H), 3.77 (d of d, J = 4.7 and 8.9 Hz, 1H, simplifies to d with D_2O), 5.20 (d, J = 9.0 Hz, 1H), 6.26 (s, 1H). Anal. ($C_{14}H_{19}NO_3S$) C, H, N.

***trans*-6-(Benzyloxy)-2-bromo-5,6-dihydro-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (33a).** A 0 °C solution of 60% NaH (0.47 g, 11.7 mmol) in DMF (50 mL) was treated with **33** (4.0 g, 11.1 mmol) and stirred at room temperature for 30 min. Benzyl bromide (1.45 mL, 12.2 mmol) was added, stirred an additional 2 h, and then poured into H_2O (200 mL) and extracted into CH_2Cl_2. The organic phase was washed several times with H_2O, dried, and evaporated. The residue was purified by flash chromatography (2% MeOH/CH_2Cl_2) and recrystallized from CH_2Cl_2/hexane to give 3.87 g (77%) of **33a**: mp 146–147 °C; IR (KBr) 1634, 1570 cm^{-1}; MS m/z 450 (MH^+); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.50 (s, 3H), 1.53–1.77 (m, 4H), 2.37–2.45 (m, 2H), 2.87 (m, 1H), 3.08 (m, 1H), 3.69 (d, J = 8.6 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.73 (d, J = 11.8 Hz, 1H), 5.90 (br s, 1H), 6.54 (s, 1H), 7.26–7.37 (m, 5H). Anal. ($C_{21}H_{24}BrNO_3S$) C, H, N.

***trans*-6-(Benzyloxy)-2-carbomethoxy-5,6-dihydro-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (34a).** A solution of **33a** (1.8 g, 4.0 mmol), triethylamine (0.87 mL, 6.25 mmol), and bis(triphenylphosphine)palladium(II) chloride (80 mg, 0.11 mmol) in MeOH (120 mL) was heated in a stainless steel Parr pressure reactor pressurized with CO (160 psi) at 100 °C for 4 days. The resultant solution was poured into H_2O, extracted with CH_2Cl_2, dried, and evaporated. Recrystallization from CH_2Cl_2/hexanes gave 1.25 g (73%) of **34a**: mp 144–145 °C; IR (KBr) 1717, 1646, 1569, 1472 cm^{-1}; MS m/z 430 (MH^+); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.53 (s, 3H), 1.61–1.82 (m, 4H), 2.38–2.55 (m, 2H), 2.90 (m, 1H), 3.08 (m, 1H), 3.80 (br s, 1H), 3.84 (s, 3H), 4.62 (d, J = 11.8 Hz, 1H), 4.76 (d, J = 11.8 Hz, 1H), 6.02 (br s, 1H), 7.22 (s, 1H), 7.27–7.38 (m, 5H). Anal. ($C_{23}H_{27}NO_6S$) C, H, N, S.

***trans*-6-(Benzyloxy)-2-carbamoyl-5,6-dihydro-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (35a).** A solution of **34a** (4.0 g, 9.31 mmol) in ammonium hydroxide (30 mL) and MeOH (20 mL) was stirred at room temperature for 5 days. The solution was poured into H_2O (60 mL), and the resulting precipitate was collected by filtration, washed with H_2O, and air-dried. Trituration with Et_2O gave 2.69 g (70%) of **35a**: mp 228–233 °C; IR (KBr) 1667, 1658, 1638, 1613, 1600, 1568, 1476 cm^{-1}; MS *m/z* 415 (MH^+); ^1H NMR (DMSO-d_6) δ 1.21 (s, 3H), 1.49 (s, 3H), 1.49–1.70 (m, 4H), 2.24–2.35 (m, 2H), 2.93–3.00 (m, 1H), 3.00–3.25 (m, 1H), 3.92 (d, *J* = 9.1 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.75 (d, *J* = 11.9 Hz, 1H), 5.76 (br s, 1H), 7.26–7.39 (m, 6H), 7.42 (br s, 1H), 7.90 (br s, 1H). Anal. ($C_{22}H_{26}N_2O_4S\cdot^1/_4H_2O$) C, H, N, S.

***trans*-6-(Benzyloxy)-2-cyano-5,6-dihydro-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (36a).** To a 0 °C solution of **35a** (2.3 g, 5.55 mmol) and pyridine (0.49 mL, 6.10 mmol) in CH_2Cl_2 (50 mL) was added slowly trifluoroacetic anhydride (1.65 mL, 11.7 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with ice H_2O. The organic layer was washed with 1 N hydrochloric acid and then 1 N sodium hydroxide, dried, and evaporated. The residue was purified by flash chromatography (2% MeOH/CH_2Cl_2). Recrystallization from CH_2Cl_2/hexanes gave 1.85 g (84%) of **36a**: mp 174–178 °C; IR (KBr) 2211, 1653, 1644, 1556, 1483 cm^{-1}; MS *m/z* 397 (MH^+); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.53 (s, 3H), 1.60–1.84 (m, 4H), 2.34–2.56 (m, 2H), 2.84–3.10 (m, 2H), 3.82 (br s, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 5.92 (br s, 1H), 7.04 (s, 1H), 7.29–7.38 (m, 5H).

***trans*-2-Cyano-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (36).** To a 0 °C solution of **36a** (1.4 g, 3.5 mmol) in CH_2Cl_2 (40 mL) was added dropwise boron tribromide (1.0 M in CH_2Cl_2, 17.6 mL, 17.6 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with ice H_2O. The organic layer was washed with H_2O, dried, and evaporated. The residue was purified by flash chromatography (3% MeOH/CH_2Cl_2). Recrystallization from CH_2Cl_2/hexanes gave 1.0 g (93%) of **36**: mp 212–214 °C; IR (KBr) 2210, 1624, 1558, 1486 cm^{-1}; MS *m/z* 307 (MH^+); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.50 (s, 3H), 1.77–1.90 (m, 4H), 2.53 (m, 2H), 3.17 (m, 2H), 3.66 (d, *J* = 5.9 Hz, 1H), 3.80 (dd, *J* = 5.9 Hz and *J* = 9.4 hz, 1H), 5.85 (d, *J* = 9.4 Hz, 1H), 5.92 (br s, 1H), 7.07 (s, 1H). Anal. ($C_{15}H_{18}N_2O_3S$) C, H, N, S.

Resolution of *trans*-5,6-Dihydro-6-hydroxy-5,5-dimethyl-2-nitro-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (32). A solution of **30** (2.5 g, 8.9 mmol), (−)-α-methylbenzyl isocyanate (1.5 mL, 10.7 mmol) in dry toluene (50 mL), and catalytic (2-(*N*,*N*-dimethylamino)ethanol was heated to reflux for 42 h and concentrated in vacuum to give a semisolid. Fractional crystallization from EtOAc/pentane afforded 1.03 g (27%) of the (−)-diastereomer carbamate derivative of **30**: mp 162–164 °C; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.44 (s, 3H), 1.46 (d, *J* = 2.3 Hz, 3H), 1.63–1.50 (m, 4H), 2.07 (m, 1H), 2.31 (m, 1H), 3.01 (m, 1H), 3.10 (m, 1H), 4.77 (m, 1H), 5.02 (d, *J* = 3.1 Hz, 1H), 5.25 (d, *J* = 2.6 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 6.55 (d, *J* = 1.8 Hz, 1H), 7.09–7.07 (dd, *J* = 1.8 Hz, 1H), 7.37–7.22 (m, 5H).

MPLC chromatography (5% *tert*-butyl methyl ether/CH_2Cl_2) of the mother liquor gave an additional 0.85 g (22.5%) of the (−)-diastereomer carbamate derivative and 1.4 g (37%) of the (+)-diastereomer carbamate derivative of **30**: mp 162–164 °C; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.37 (s, 3H), 1.48 (d, *J* = 2.3 Hz, 3H), 1.80 (m, 4H), 2.47 (m, 2H), 3.15 (m, 1H), 3.32 (m, 1H), 4.80 (m, 1H), 5.05 (d, *J* = 3.1 Hz, 1H), 5.18 (d, *J* = 2.4 Hz, 1H), 6.09 (d, *J* = 3.1 Hz, 1H), 6.56 (d, *J* = 1.8 Hz, 1H), 7.12–7.10 (dd, *J* = 1.8 Hz, 1H), 7.26–7.38 (m, 5H).

The foregoing carbamates (0.3 g, 0.7 mmol) were hydrolyzed to the parent alcohols by treatment with ethanolic NaOEt (0.2 g of Na in 20 mL of EtOH) at reflux for 30 min. Recrystallization from EtOAc/hexanes gave 160 mg (81%) of the (−)-enantiomer of **30**: mp 175–177 °C; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.49 (s, 3H), 1.87–1.81 (m, 4H), 2.55–2.05 (m, 2H), 3.13–3.07 (m, 1H), 3.30–3.24 (m, 1H), 3.68 (d, *J* = 1.7 Hz, 1H), 3.83–3.70 (d d, *J* = 3.0 Hz, 1H), 5.83 (d, *J* = 3 Hz, 1H), 6.57 (d, *J* = 5.4 Hz, 1H), 7.11 (d, *J* = 5.4 Hz, 1H); MS *m/z* 282 (MH^+). Anal. ($C_{14}H_{18}N_2O_5S$) C, H, N.

Similarly, 155 mg (79%) of the (+)-enantiomer of **30**: mp 175–177 °C; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.49 (s, 3H), 1.87–1.76 (m, 4H), 2.52 (m, 2H), 3.14–3.08 (m, 1H), 3.29–3.25 (m, 1H), 3.78 (m, 2H), 5.84 (d, *J* = 2.7 Hz, 1H), 6.56 (d, *J* = 5.4 Hz, 1H), 7.11 (d, *J* = 5.4 Hz, 1H); MS *m/z* 282 (MH^+).

Each enantiomeric alcohol (0.12 g, 0.42 mmol) was treated with nitric acid (0.2 mL, 90 wt % soln) in acetic acid (5 mL). Recrystallization from MeOH/Et_2O gave 67 mg (57%) of the (−)-enantiomer **41**: mp 160–162 °C; $[\alpha]^{25}_D$ ($CHCl_3$) = −80.1° (18.1 mg in 1.81 mL); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.51 (s, 3H), 1.89 (m, 4H), 2.52 (m, 2H), 3.21 (m, 2H), 3.86–3.81 (dd, *J* = 3.2 Hz, 1H), 3.98 (d, *J* = 2.1 Hz, 1H), 5.86 (d, *J* = 3.2 Hz, 1H), 7.39 (s, 1H); MS *m/z* 327 (MH^+). Anal. ($C_{14}H_{18}N_2O_5S$) C, H, N.

Similarly, 81 mg (59%) of the (+)-enantiomer **40** was obtained: mp 158–160 °C; $[\alpha]^{25}_D$ ($CHCl_3$) = +81.6° (19.2 mg in 1.92 mL); ^1H NMR ($CDCl_3$) δ 1.32 (m, 3H), 1.52 (s, 3H), 1.93–1.75 (m, 4H), 2.52 (m, 2H), 3.21 (m, 2H), 3.84 (d, *J* = 9.5 Hz, 1 H), 4.11 (d, *J* = 2.2 Hz, 1H), 5.86 (d, *J* = 9.5 Hz, 1H), 7.39 (s, 1H); MS *m/z* 327 (MH^+). Anal. ($C_{14}H_{18}N_2O_5S$) C, H, N.

Enantiomeric purity of **40** and **41** was found to be greater than 99.8%, as determined by HPLC analysis on a commercially available β-cyclodextrin column using a simple isocratic method without derivatization.

The X-ray structure[32] of **41** consisted of the following properties: (1) monoclinic cell with dimensions: *a* = 13.439 (1) Å, *b* = 6.625 (4) Å, *c* = 18.327 (1) Å, *V* = 1572.7 (8) $Å^3$, β = 105.451 (5)°; (2) $C_{14}H_{18}N_2O_5S$, FW = 326.37; (3) calculated density = 1.378 g/cm^3; (4) $P2_1$, *Z* = 4; (5) μ = 20.12 cm^{-1}; (6) structure was solved by direct methods (*J. Appl. Crystallogr.* **1984**, *17*, 42–46); (7) R_{value} = 0.030.

***trans*-7-Azido-5,6-dihydro-6-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (12) and *cis*-7-Azido-5,6-dihydro-6-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (13).** To a 0 °C solution of **7** (22.4 g, 85.1 mmol) in DMF (220 mL) was added NaH (60% in oil, 3.58 g, 89.4 mmol). The mixture was stirred at room temperature for 1.5 h to generate **8**. An aqueous solution of sodium azide (11.1 g, 0.17 mol) was added dropwise. The reaction was stirred at room temperature for 16 h and then poured into ice H_2O (1 L) and extracted into Et_2O. The Et_2O solution was washed with H_2O (5×), dried, and evaporated. The residue was purified by flash chromatography (15% hexanes/CH_2Cl_2) to give 11.82 g (62%) of **12** as a tan solid: mp 48–50 °C; IR (KBr) 3471, 2104, 1568, 1402 cm^{-1}; MS *m/z* 226 (MH^+); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.47 (s, 3H), 2.29 (d, *J* = 5.8 Hz, 1H, exchanges with D_2O), 3.78 (m, 1H, simplifies to d, *J* = 7.0 Hz, with D_2O), 4.44 (d, *J* = 7.0 Hz, 1H), 6.58 (d, *J* = 5.4 Hz, 1H), 7.18 (d, *J* = 5.4 Hz, 1H). Anal. ($C_9H_{11}N_3O_2S$) C, H, N.

Crude fractions containing the cis isomer were combined, and the solvent was evaporated. The combined fractions which contained the cis isomer were purified by flash chromatography (13% Et_2O/5% CH_2Cl_2/pentanes) to give **13** as a gray solid: mp 104–105 °C; IR (KBr) 3381, 2099, 1558 cm^{-1}; MS *m/z* 198 [(MH − N_2)$^+$]; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.46 (s, 3H), 2.12 (d, *J* = 9 Hz, 1H, exchanges with D_2O), 3.88 (d of d, *J* = 9 and 4.4 Hz, 1H, simplifies to d, *J* = 4.4 Hz with D_2O exchange), 4.57 (d, *J* = 4.4 Hz, 1H), 6.63 (d, *J* = 5.5 Hz, 1H), 7.21 (d, *J* = 5.5 Hz, 1H). Anal. ($C_9H_{11}N_3O_2S$) C, H, N.

***trans*-7-Amino-5,6-dihydro-6-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (14).** To a suspension of $LiAlH_4$ (0.67 g, 17.8 mmol) in Et_2O (40 mL) was carefully added in small portions of **12** (2.0 g, 8.88 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched by sequential dropwise addition of H_2O (0.7 mL), 15% aqueous sodium hydroxide (0.7 mL), and H_2O (2.0 mL). The aluminum salts were removed by filtration. The Et_2O solution was dried and then evaporated to give 1.64 g (93%) of **14** as a beige solid: mp 111–116 °C; IR (KBr) 3110, 2971, 1565, 1403 cm^{-1}; MS *m/z* 200 (MH^+); ^1H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.48 (s, 3H), 1.85 (br s, 3H, exchanges with D_2O), 3.38 (d, *J* = 8.6 Hz, 1H), 3.70 (d, *J* = 8.6 Hz, 1H), 6.55 (d, *J* = 5.4 Hz, 1H), 7.07 (d, *J* = 5.4 Hz, 1H). Anal. ($C_9H_{13}NO_2S$) C, H, N, S.

***cis*-7-Amino-5,6-dihydro-6-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (15).** Using the procedure described above, **13** (3.14 g, 13.9 mmol) was converted to 2.39 g (86%) of **15** as a colorless solid: mp 122–123 °C; IR (KBr) 3382, 3300–3000, 1558 cm^{-1}; MS *m/z* 200 (MH^+); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.32 (s, 3H), 1.60–2.20 (br s, 3H, exchanges with D_2O), 3.50 (d, *J* = 4.5 Hz, 1H), 4.14 (d, *J* = 4.5 Hz, 1H), 6.60 (d, *J* = 5.4 Hz, 1H), and 7.10 (d, *J* = 5.4 Hz, 1H). Anal. ($C_9H_{13}NO_2S$) C, H, N.

***cis*-5,6-Dihydro-6-hydroxy-5,5-dimethyl-2-nitro-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran (42).** To a 0 °C solution of **15** (2.27 g, 11.4 mmol) and triethylamine (4.8 mL, 34.1 mmol) in CH_2Cl_2 (50 mL) was added 5-chlorovaleryl chloride (1.55 mL, 12.0 mmol). The resultant solution was stirred at 0 °C for 1 h and the solvent was evaporated. The product was purified by flash chromatography to give 2.95 g (81%) of *cis*-7-(5-chloropentanamido)-5,6-dihydro-6-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran as an oil: IR (KBr) 3395, 3328, 1675, 1645, 1629, 1563 cm^{-1}; MS *m/z* 318 (MH^+); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.48 (s, 3H), 1.85–1.88 (m, 4H), 1.95 (d, J = 10.0 Hz, 1H, exchanges with D_2O), 2.30–2.34 (m, 2H), 3.55–3.59 (m, 2H), 3.65 (dd, J = 4.1 and 10.0 Hz, 1H, simplifies to d with D_2O), 5.30 (m, 1H), 6.31 (br d, 1H, exchanges with D_2O), 6.58 (d, J = 5.4 Hz, 1H), 7.10 (d, J = 5.4 Hz, 1H).

To a 0 °C solution of the above compound (2.83 g, 8.9 mmol) in DMF (40 mL) was added NaH (60%, 0.374 g, 9.34 mmol). The resultant solution was stirred at ambient temperature for 1 h. The solution was poured into H_2O, and the product was extracted into CH_2Cl_2. The organic solution was washed several times with H_2O, dried, and evaporated. The product was purified by flash chromatography (2% MeOH/CH_2Cl_2) to give 1.63 g (65%) of *cis*-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-5*H*-thieno[3,2-*b*]pyran as a colorless solid: mp 108–110 °C; IR (KBr) 3500–3100, 1615, 1561 cm^{-1}; MS *m/z* 282 (MH^+); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.44 s, 3H), 1.70–1.90 (m, 4H), 2.37 (br d, 1H, exchanges with D_2O), 2.48–2.53 (m, 2H), 3.25–3.35 (m, 2H), 3.44–3.49 (m, 1H), 5.91 (d, J = 4.0 Hz, 1H), 6.64 (d, J = 5.4 Hz, 1H), 7.15 (d, J = 5.4 Hz, 1H).

Nitration using nitric acid and recrystallization from Et_2O gave 0.18 g (11%) of **42** as a yellow solid: mp 186–189 °C; IR (KBr) 3400–3200, 1621, 1505 cm^{-1}; MS *m/z* 327 (MH^+); ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.48 (s, 3H), 1.82–1.91 (m, 4H), 2.51–2.55 (m, 2H), 2.75 (br s, 1H, exchanges with D_2O), 3.48–3.53 (m, 2H), 3.95 (dd, J = 4.2 and 7.9 Hz, 1H), 5.8 (br s, 1H), 7.47 (s, 1H). Anal. ($C_{14}H_{18}N_2O_5S$) C, H, N.

***trans*-5,6-Dihydro-6-hydroxy-7-(2-oxoisoindol-1-yl)-5,5-dimethyl-2-nitro-5*H*-thieno[3,2-*b*]pyran (49).** A solution of **14** (1.3 g, 6.5 mmol) in MeOH (5 mL) was slowly added to a solution of 2-carbomethoxybenzaldehyde (5.4 g, 32.7 mmol) in MeOH (20 mL) followed by catalytic zinc chloride. The mixture was stirred at room temperature for 2 h. Sodium cyanoborohydride (0.75 g, 12.2 mmol) was added, and the mixture was heated to 40 °C overnight. The reaction was poured into ice H_2O, extracted twice with CH_2Cl_2, and then concentrated. The oil was dissolved in toluene (20 mL) and heated to 100 °C for 5 h. The mixture was concentrated, and the resulting oil was purified by flash chromatography (10% acetone/CH_2Cl_2) to give 1.8 g (88%) of *trans*-5,6-dihydro-6-hydroxy-7-(2-oxoisoindol-1-yl)-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran: mp 211–212 °C. Nitration using nitric acid and recrystallization from Et_2O gave 1.4 g (67%) of **49**: mp 134–136 °C; MS *m/z* 361 (MH^+); ^1H NMR ($CDCl_3$) δ 1.21 (s, 3H), 1.57 (s, 3H), 3.62 (m, 2H), 3.99 (dd, J = 3.1 Hz, 1H), 4.46 (d, J = 6.0 Hz, 1H), 5.56 (d, J = 9.2 Hz, 1H), 7.49 (s, 1H), 7.23–7.64 (m, 4H).

5,5-Dimethyl-2-nitro-7-(2-oxopiperidin-1-yl)-5*H*-thieno-[3,2-*b*]pyran (51). To a 0 °C solution of **30** (3.0 g, 10.67 mmol) and triethylamine (5.0 mL, 35.9 mmol) in CH_2Cl_2 (50 mL) was added dropwise methanesulfonyl chloride (0.9 mL, 11.6 mmol). The resultant solution was stirred for 2 h at 0 °C and then washed successively with saturated aqueous sodium bicarbonate and 1 N hydrochloric acid. The organic layer was dried and then evaporated to give 2.15 g (56%) of **16**: mp 137–138 °C; IR (KBr) 1637 cm^{-1}; MS *m/z* 360 (MH^+); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.54 (s, 3H), 1.64–1.90 (m, 4H), 2.48–2.52 (m, 2H), 3.09 (s, 3H), 3.07–3.12 (m, 1H), 3.22–3.29 (m, 1H), 4.89 (d, J = 8.8 Hz, 1H), 6.23 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 5.3 Hz, 1H), 7.14 (d, J = 5.3 Hz, 1H). Anal. ($C_{15}H_{21}NO_5S_2$) C, H, N.

Nitration using nitric acid and recrystallization from Et_2O gave 1.56 g (64%) of **17** as a yellow solid: mp 181–182 °C; IR (KBr) 1642 cm^{-1}; MS *m/z* 405 (MH^+); ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.56 (s, 3H) 1.70–1.97 (m, 4H), 2.50–2.54 (m, 2H), 3.09 (s, 3H), 3.08–3.11 (m, 1H), 3.32–3.35 (m, 1H), 4.92 (d, J = 9.0 Hz, 1H), 6.25 (br d, 1H), 7.42 (s, 1H). Anal. ($C_{15}H_{20}N_2O_7S_2 \cdot H_2O$) C, H, N.

To a 0 °C solution of **17** (1.35 g, 3.34 mmol) in DMF (15 mL) was added NaH (60%, 0.147 g, 3.67 mmol). The resultant mixture was stirred at room temperature for 2 days and then poured into ice H_2O (100 mL). The product was extracted into CH_2Cl_2 and washed several times with H_2O. The product was purified by flash chromatography (1% MeOH/CH_2Cl_2). Recrystallization from CH_2Cl_2/hexane gave **51** as an orange solid: mp 148–151 °C; IR (KBr) 1652, 1499, 1413, 1306 cm^{-1}; MS *m/z* 309 (MH^+); ^1H NMR ($CDCl_3$) δ 1.53 (s, 6H), 1.90–1.94 (m, 4H), 2.53 (m, 2H), 3.55 (m, 2H), 5.49 (s, 1H), 7.40 (s, 1H). Anal. ($C_{14}H_{16}N_2O_4S$) C, H, N.

Antihypertensive Activity. Antihypertensive activity was assessed using a direct measurement of arterial blood pressure in adult spontaneously hypertensive rats (SHR).[35] Mean arterial pressure and heart rate were derived from the measurements. On the day of the experiment, a catheter was implanted into the left carotid artery of SHR under light ether anesthesia. The catheter was exteriorized at the nape of the neck and secured with an adhesive wrap. Rats were then placed in Bollman restraint cages in a quiet room for a 60-min postsurgical recovery period. Rats with mean arterial pressures >150 mmHg were used for further evaluation. Recordings of arterial pressure were obtained using a Statham pressure transducer connected to a Gould 2800 chart recorder. Groups of four to six SHR received a single oral dose of drug or vehicle, administered by gavage at doses of 0.003–20 mg/kg and were monitored continuously for 4 h postdosing. Compounds were solubilized in distilled H_2O. Data were expressed as the percentage change from mean predrug values for each rat. Differences from predrug values were analyzed using regression analysis over the linear portion of the dose–response curves. Oral ED_{30}s (dose that produces a 30% reduction in mean arterial pressure) were calculated for several of the more potent drugs.

Rb^{86} Efflux from Smooth Muscle.[33,34] Rabbit aorta (or other suitable vascular preparations) were removed from freshly sacrificed animals. The vessels were cleaned and cut into small circular rings. The rings were place onto stainless steel wires and immersed in a physiological buffer (37 °C, bubbled with 95% O_2/5% CO_2). ^{86}Rb (4–5 μCi/mL) was added to the 40–50 mL buffer containing all of the aortic rings. This loads each ring with an approximately equal amount of ^{86}Rb. After 3–4 h, each set of two rings was moved through a series of tubes containing 4 mL of buffer. The rings were moved through the tubes according to a set time protocol (10 min). A background efflux rate was determined over a 30–40-min period. Test compound was added to a number of the vials (usually five), and finally, the rings were placed into the vials containing no test compound for a period of 10–20 min. At the completion of the experiment, the tissues were digested overnight in Protosol before being placed into scintillation cocktail to determine the total amount of radioactivity remaining within the tissues. An aliquot was removed from each of the efflux vials and quantitated in a liquid scintillation spectrometer. An efflux rate (or percent change from predrug rates) was determined and followed with time in the presence and absence of test compounds.

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Supplementary Material Available: Tables listing the crystallographic data (33 pages). Ordering information is given on any current masthead page.