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Novel Thieno[2,3-*b*]- and [3,4-*b*]Pyrans as Potassium Channel Openers. Thiophene Systems—XVII[1]

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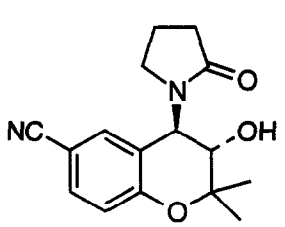
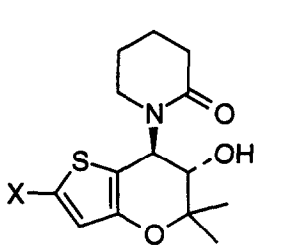
Abstract—The syntheses and antihypertensive activity of the thieno[3,4-*b*]pyran and thieno[2,3-*b*]pyran isosteres of the potassium channel opener (PCO) RWJ 26629 (± **2a**) are reported. While the unsubstituted thiophene derivatives were active at 20 mg/kg, introduction of a strong electron withdrawing group in the 2-position of the thieno[3,2-*b*] series increased potency. Similar substitution on the thieno[3,4-*b*] series significantly lowered potency. Compounds **26** and **30** are approximately 5-fold more potent than the prototypic PCO cromakalim (± **1**).

Introduction

The role of potassium channels in regulating membrane potential has been elucidated by the discovery of cromakalim (±1), the prototypic selective and potent benzopyran potassium channel opener (PCO).[2] The efflux of potassium from vascular smooth muscle, effected by agents such as **1**, causes a hyperpolarization of the cell membrane which, in turn, results in reduction of calcium influx through both voltage (VOC) and receptor operated (ROC) calcium channels.[3] The profound antihypertensive effect of **1** can be attributed to this functional antagonism of both VOC and ROC and may thus provide a new type of therapy for treating high blood pressure as well as a variety of other smooth muscle disorders. The interest in PCOs has led to the synthesis of a variety of other benzopyrans and derivatives.[4] We recently reported[5] the synthesis and antihypertensive activity of a series of thieno[3,2-*b*]pyran isosteres of **1**. While other aromatic heterocyclic isosteres of **1** have been reported, they are significantly less potent than the benzopyran system.[6] In contrast, the thieno[3,2-*b*]pyrans are considerably more potent than the corresponding benzopyrans. The 2-nitro derivative **2a** (RWJ 26629) is 10-fold more potent than **1** in spontaneously hypertensive rats (SHR).[5] Typical of other PCOs, **2a** stimulates the efflux of ^{86}Rb, a radioactive surrogate for potassium,[7] from rabbit aorta. Furthermore, at low doses, **2a** selectively dilates coronary vasculature, thus making it a potential antianginal agent.[8]



1
cromakalim



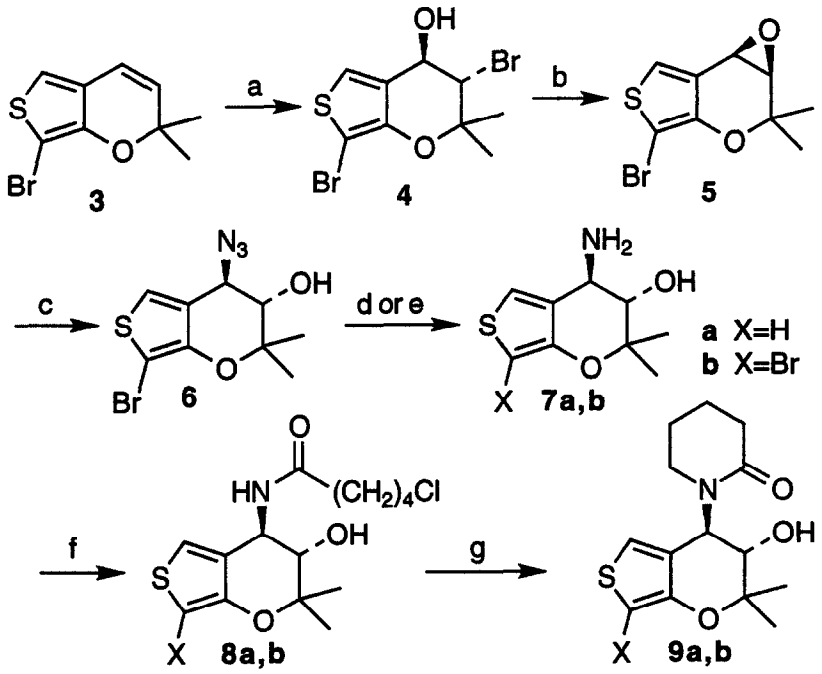
2a, X = NO_2, RWJ 26629
2b, X = CN

During our on-going research investigating thiophene isosteres of biologically active compounds, we have frequently shown that there can be significant differences in biological activity among thiophene regioisomers.[9,10] With these differences in mind, and given the remarkable potency of **2a**, we wish to report the synthesis of the thieno[3,4-*b*]- and -[2,3-*b*]pyran regioisomers of **2a** and their biological activity.

Chemistry

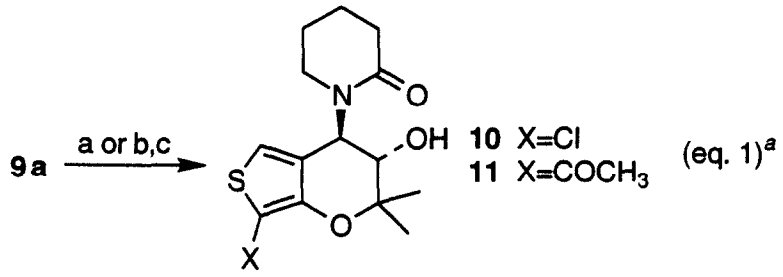
The synthesis of the 7-(2-oxopiperidin-1-yl)-6-hydroxythieno[3,4-*b*]pyrans (**9a**) is outlined in Scheme I. We have previously described the formation of 3-bromo-5,5-dimethyl-5*H*-thieno[3,4-*b*]pyran (**3**)[1] from 5,5-dimethyl-5*H*-thieno[3,4-*b*]pyran-7-one.[11] Treatment of **3** with hypobromous acid (formed *in situ* from *N*-bromosuccinimide and water) gives bromohydrin **4** which is converted to epoxide **5** by the action of sodium hydride. Unlike the isomeric intermediate epoxide in the thieno[3,2-*b*]pyran system, **5** is quite stable since it can be purified by chromatography and stored for several weeks at room temperature without noticeable changes in appearance or reactivity. The enhanced stability of **5** is also reflected in its reduced reactivity for ring opening with weak nucleophiles. Reaction of the sodium salt of the appropriate lactam, which works well in the [3,2-*b*] system,[5] fails in this case. However, sodium azide, a stronger nucleophile, reacts readily with **5** to give *trans*-azidoalcohol **6**. Intermediates **3**–**6** are more stable than the corresponding intermediates in the thieno[3,2-*b*]- series which is probably reflective of electronic differences recently described for these systems.[1] The overall conversion of **3** to **6** occurs in 57% yield.

Reduction of the azide **6** is achieved in high yield either by the action of triphenylphosphine[12] to give amine **7b** or by treatment with lithium aluminum hydride which simultaneously debrominates thiophene to form **7a**. Acylation of amines **7a** or **7b** with 5-chlorovaleryl chloride and subsequent cyclization of **8a** or **8b** with sodium hydride produces the 7-(2-oxopiperidin-1-yl)-6-hydroxy-thieno[3,4-*b*]pyrans **9a** and **b** in high yields.

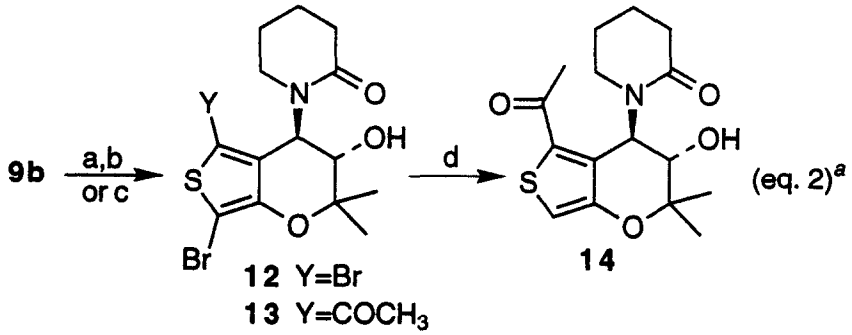


Scheme I. [a](a) NBS, H_2O; (b) NaH; (c) NaN_3, H_2O; (d) $LiAlH_4$; (e) $P(C_6H_5)_3$; (f) $Cl(CH_2)_4COCl$, NEt_3; (g) NaH.

Sulfuryl chloride regiospecifically chlorinates thiophene in the 3-position of **9a**, which is doubly activated as a result of being α to sulfur and *ortho* to the ether linkage, to give **10** exclusively (Equation 1). Reaction of **9a** with acetic anhydride occurs both on the 6-hydroxyl group as well as the 3-position to give the 6-acetoxy-3-acetylthieno[3,4-*b*]pyran derivative. The 6-hydroxyl can be easily regenerated with methanolic potassium carbonate to give **11**. Bromine reacts at the 1-position of bromo derivative **9b** to give the dibromo product **12** (Equation 2). Acetylation of **9b** and regeneration of the hydroxy group gives the 1-acetyl-3-bromo derivative **13**. Hydrogenation of **13** over palladium catalyst removes the 3-bromine substituent to give the 1-acetyl derivative **14**. Treatment of **9a** or **9b** with a variety of nitrating agents (even under forcing conditions) fails to give the desired nitro derivatives as a consequence of extensive decomposition.



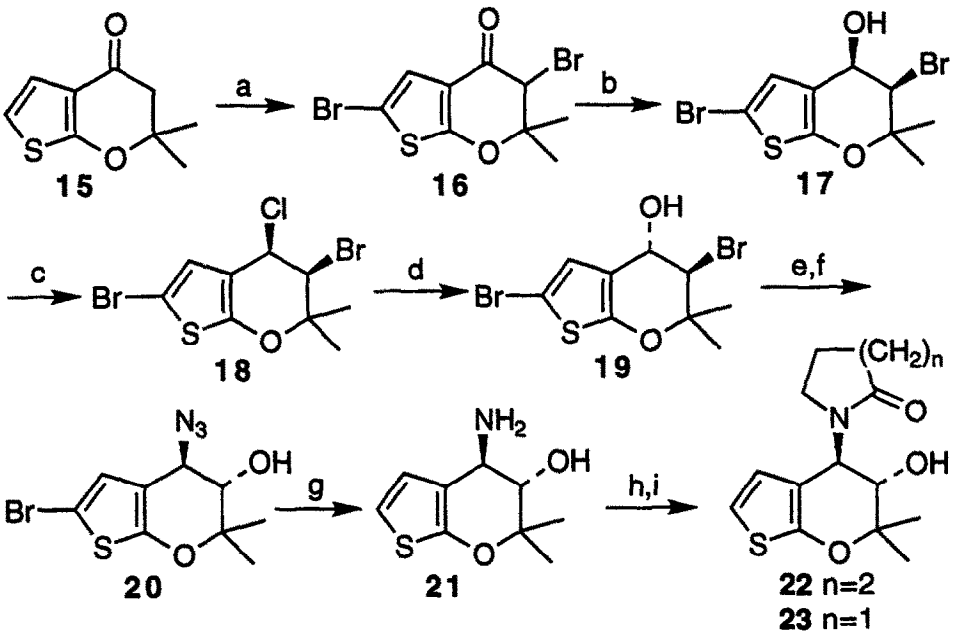
Equation 1. [a](a) SO_2Cl_2; (b) Ac_2O, $HClO_4$; (c) K_2CO_3, MeOH.



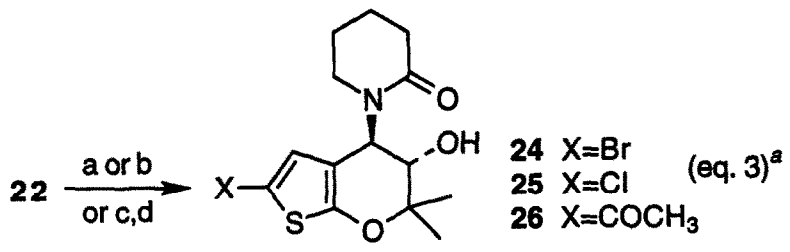
Equation 2. [a](a) Ac_2O, $HClO_4$; (b) K_2CO_3, MeOH; (c) Br_2; (d) Pd, H_2.

Unlike the synthesis for the [3,4-*b*] series which utilizes olefin **3**, the corresponding olefin in the [2,3-*b*] series was unavailable, presumably due to the inherent instability of the thieno[2,3-*b*]pyran system.[1] All attempts to prepare the olefin from ketone **15** failed. Although reduction of **15** proceeds as expected to the corresponding alcohol, attempts to dehydrate the alcohol gave only ring opened products.[1] Therefore, synthesis of the thieno[2,3-*b*]pyrans required an alternative approach (Scheme II).

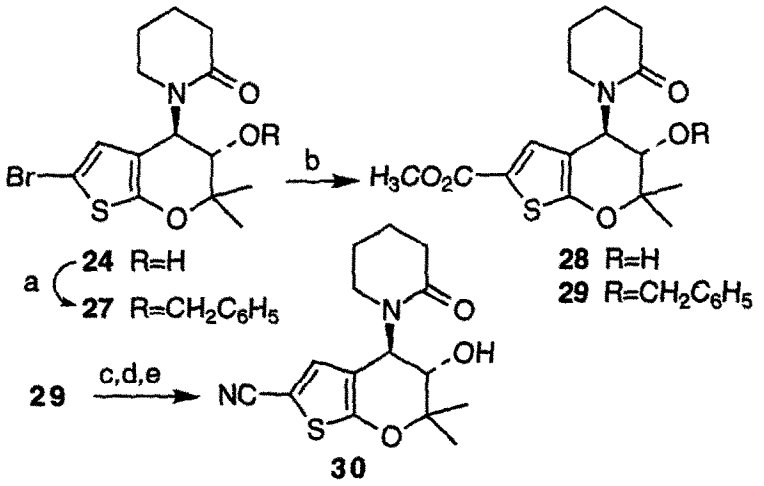
Two equivalents of bromine react with **15** to give the dibromoketone **16**. Reduction of **16** with sodium borohydride proceeds in high yield to give only the *cis*-bromohydrin **17**. Several attempts to reduce the bromoketone directly to the requisite *trans*-bromohydrin using either hindered reducing agents such as diisobutylaluminum hydride or thermodynamic reducing conditions such as aluminum isopropoxide gave only trace amounts of the required *trans*-bromohydrin isomer **19**. However, reaction of **17** with thionyl chloride gives the *cis*-trihalo derivative **18** with expected retention of configuration. Treatment of **18** with silica gel causes displacement of the chloride with inversion to give the desired *trans*-bromohydrin **19** in an excellent conversion. Up to 20 g of alcohol **17** has been isomerized in high yield by this procedure and **19** requires no additional purification for use in subsequent reactions. Treatment of **19** with sodium hydride produces an epoxide *in situ*, which is too unstable to isolate, but reacts with sodium azide to give the *trans*-azidoalcohol **20**. Subsequent reduction with lithium aluminum hydride produces the amine **21**. Acylation with 5-chlorovaleryl chloride and cyclization with sodium hydride gives the desired product **22**. This same scheme, utilizing 4-chlorobutyryl chloride as the acylating agent, gives the pyrrolidinone **23**. Bromine, sulfuryl chloride and acetic anhydride react readily with **22** to substitute on the position α to sulfur to give **24**, **25** and **26** (after hydrolysis of the O acetyl group) in high yields (Equation 3). However, treatment of **22** with a variety of nitrating agents fails to give the desired 2-nitro derivative and results only in decomposition of the starting material. The failure of both the thieno[2,3-*b*]- and -[3,4-*b*]pyrans to give the corresponding nitrated products is in sharp contrast to what we observed in the thieno[3,2-*b*]pyran series, which readily nitrates[5] to give **2a** in good yield.



Scheme II. [a](a) Br_2; (b) $NaBH_4$; (c) $SOCl_2$; (d) silica gel; (e) NaH; (f) NaN_3, H_2O; (g) $LiAlH_4$; (h) $Cl(CH_2)_{n+2}COCl$, NEt_3; (i) NaH.



Equation 3. [a](a)Br_2; (b) SO_2Cl_2; (c) Ac_2O, $HClO_4$; (d) K_2CO_3, MeOH.



Scheme III. [a](a) NaH, $C_6H_5CH_2Br$; (b) $(PPh_3)_2Pd(II)Cl_2$, CO, NEt_3, MeOH; (c) NH_4OH; (d) TFAA; (e) BBr_3.

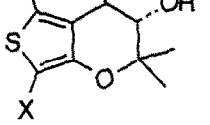
Palladium-catalyzed carboalkoxylation[13] of the bromo derivatives **24** and **27** provides a convenient route to other substitution products (**28** and **29**) not accessible via electrophilic chemistry (Scheme III). Further conversion of ester **29** with ammonium hydroxide gives the corresponding amide which is easily dehydrated to the nitrile by the action of trifluoroacetic anhydride. Deprotection of the alcohol ultimately gives the cyanothieno[2,3-*b*]pyran **30**, the direct isostere of the cyanobenzopyran cromakalim (± **1**).

Attempts to extend the palladium-catalyzed carboalkoxylation to the thieno[3,4-*b*]pyran series failed. Even at temperatures of up to 180 °C and reaction times of greater than 2 weeks, **9b** and **12** fail to react, and only starting material is recovered. This lack of reactivity in the [3,4-*b*]-series may be due to the steric congestion at the reaction site as well as in differences in the electronic nature as compared to the [3,2-*b*] or [2,3-*b*] systems.

Results and Discussion

The various thieno[3,4-*b*]- and -[2,3-*b*]pyrans were evaluated for antihypertensive activity at an oral screening dose of 20 mg/kg in the spontaneously hypertensive rat (SHR).[14] Results for cromakalim (**1**) and RWJ 26629 (**2a**) are included for comparison. Blood pressure was monitored for 4 h after dosing, and the maximal percent changes in mean arterial blood pressure (MAP) are reported in Tables 1 and 2. Biochemical evaluation of all of these compounds was not performed, however, RWJ 26629[5] and other closely related thieno[3,2-*b*]pyrans[15] cause $^{86}Rb^+$ efflux from rabbit aorta which is typical of potassium channel openers.

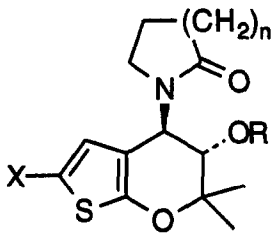
Table 1. Substituted *trans*-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7*H*-thieno[3,4-*b*]pyrans



no.	X	Y	R	%[a]	mp,°C	formula	anal.[b]	ΔMAP[c]
9a	H	H	H	69	171-172	$C_{14}H_{19}NO_3S$	C,H,N	-49
9b	Br	H	H	84	207-208	$C_{14}H_{18}BrNO_3S$	C,H,N	-2
10	Cl	H	H	75	207-209	$C_{14}H_{18}ClNO_3S$	C,H,N	-14
11	$COCH_3$	H	H	87	278-279	$C_{16}H_{21}NO_4S$	C,H,N	-7
12	Br	Br	H	93	192-194	$C_{14}H_{17}Br_2NO_3S$	C,H,N	-5
13	Br	$COCH_3$	H	50	175-176	$C_{16}H_{21}BrNO_4S$	C,H,N	-13
14	H	$COCH_3$	H	75	191-192	$C_{16}H_{21}NO_4S$[d]	C,H,N[d]	-20
31	$COCH_3$	H	Ac	60	161-163	$C_{18}H_{23}NO_5S$	C,H,N	-1

[a]Percent yield of isolated product in last step.
[b]Analyses for the elements indicated were within ± 0.4% of the theoretical values.
[c]%Change in Mean Arterial blood Pressure (ΔMAP) was measured directly before and up to 3 h after oral administration of 20 mg/kg of the test substance ($N \geq 6$).
[d]C calc'd, 59.42; found, 58.82.

Table 2. Substituted *trans*-4-(lactam-1-yl)-5,6-dihydro-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyrans



no.	X	R	n	%[a]	mp,°C	formula	anal.[b]	ΔMAP[c]	ED_{30}[d]
22	H	H	2	71	160-161	$C_{14}H_{19}NO_3S$	C,H,N	-43	
23	H	H	1	73	172-173	$C_{13}H_{17}NO_3S$	C,H,N	-46	
24	Br	H	2	66	167-169	$C_{14}H_{18}BrNO_3S$	C,H,N	-67	0.32 (0.22-0.51)
25	Cl	H	2	75	195-196	$C_{14}H_{18}ClNO_3S$	C,H,N	-67	0.47 (0.19-0.78)
26	$COCH_3$	H	2	65	166-172	$C_{16}H_{21}NO_4S$	C,H,N	-61	0.03 (0.014-0.040)
28	CO_2CH_3	H	2	63	195-197	$C_{16}H_{21}NO_5S$	C,H,N	-68	0.17 (0.07-0.27)
30	CN	H	2	76	200-201	$C_{15}H_{18}N_2O_3S$	C,H,N	-66[e]	0.042 (0.029-0.057)
32	$COCH_3$	Ac	2	88	180-181	$C_{18}H_{23}NO_5S$	C,H,N	-67	0.12 (0.08-0.16)
33	Br	H	1	22	166-168	$C_{13}H_{16}BrNO_3S$	C,H,N	-45	
34	Cl	H	1	35	190-191	$C_{13}H_{16}ClNO_3S$	C,H,N	-57, -19[f]	
35	$COCH_3$	H	1	60	277-280	$C_{15}H_{19}NO_4S$	C,H,N	-64	0.21 (0.13-0.30)
36	CO_2CH_3	H	1	87	184-185	$C_{15}H_{19}NO_5S$	C,H,N	-60, -35[f]	
1	cromakalim								0.19 (0.14-0.23)
2a[g]	NO_2 ([3,2-*b*]-series, RWJ 26629)							-65	0.015 (0.003-0.021)
2b[g]	CN ([3,2-*b*]-series)							-66	0.03 (0.026-0.041)

[a]Percent yield of isolated product in last step.
[b]Analyses for the elements indicated were within ± 0.4% of the theoretical values.
[c]%Change in Mean Arterial blood Pressure (ΔMAP) was measured directly before and up to 3 h after oral administration of 20 mg/kg of the test substance ($N \geq 6$).
[d]Effective Dose (mg/kg) at which MAP drops by 30% (95% confidence). Determined by dose response curve.
[e]Test substance dose of 0.3 mg/kg.
[f]Test substance dose of 1 mg/kg.
[g]See Ref. 5.

The unsubstituted thieno[3,4-*b*]- (**9a**) and -[2,3-*b*]pyrans (**22**, **23**) have good activity at 20 mg/kg (-49, -43 and -46% respectively), similar to what was previously observed for the unsubstituted derivatives in the thieno[3,2-*b*]pyran series.[5] However, introduction of substituents onto the thiophene of the thieno[3,4-*b*]pyrans attenuates the antihypertensive effects. Larger electron-withdrawing substituents, such as bromine or acetyl (**9b**, **11**) in the 3-position essentially eliminate activity while the smaller chlorine group (**10**) maintains only low activity. Acetyl substitution in the 1-position (**13**,**14**) also gives only weak activity.

Substitutions on the thiophene of the 4-(2-oxopiperidin-1-yl)-thieno[2,3-*b*]pyran series have a considerably more positive effect on activity. Either weak electron-withdrawing substituents, such as bromine (**24**) or chlorine (**25**), or strong electron-withdrawing groups, such as acetyl (**26**), carbomethoxy (**28**) or cyano (**30**), reduces MAP by more than 60% at 20 mg/kg (Table 2). Selected compounds were evaluated at lower doses, and the effective doses which produce a 30% drop in MAP (ED_{30}) were determined from the dose–response curves (Table 2). Derivatives with the weak electron-withdrawing groups bromo- (**24**) or chloro- (**25**) are about half as potent as cromakalim (**1**). Stronger electron-withdrawing groups improve potency even more dramatically; the carbomethoxy derivative **28** is equipotent to **1** while the cyano (**30**) and acetyl (**26**) derivatives are approximately five-fold more potent than **1**. The best compounds in the thieno-[2,3-*b*]- series are **26** (ED_{30} = 0.03 mg/kg) and **30** (ED_{30} = 0.042 mg/kg) which are about half as potent as **2a** (ED_{30} = 0.015 mg/kg), the best compound in the thieno[3,2-*b*]pyran series. While the 2-nitro derivative in the thieno[2,3-*b*]pyran series would have been extremely interesting for direct comparison to **2a**, we were unable to nitrate **22** as previously noted (*vide supra*).

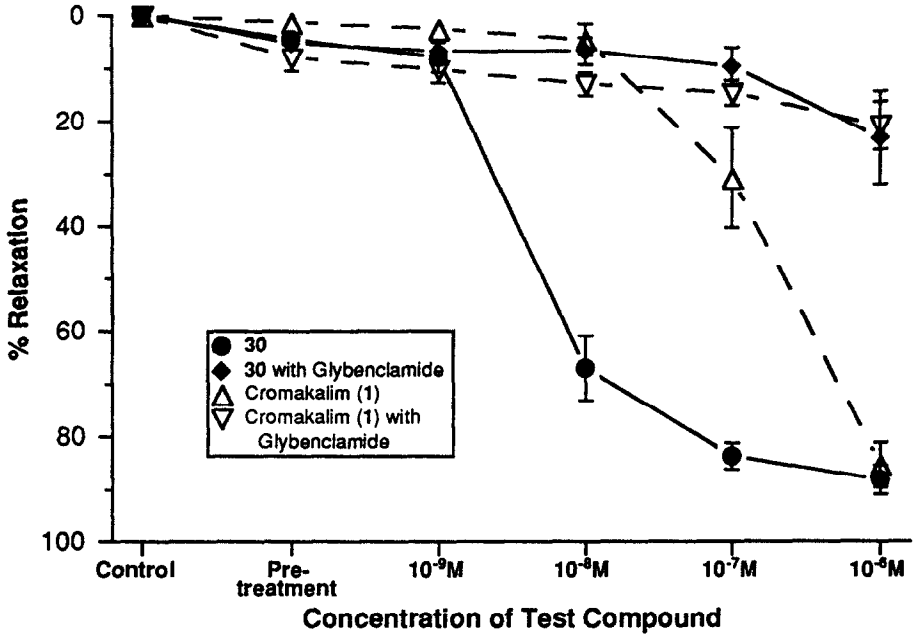
The 4-(2-oxopyrrolidin-1-yl) derivatives were also evaluated for their antihypertensive effects. The unsubstituted (**23**) and the 2-bromo (**33**) derivatives are moderately active at 20 mg/kg, while other compounds with strong electron-withdrawing substituents reduce MAP more than 60% at this dose. The chloro (**34**) and ester (**36**) derivatives are substantially less active at 1.0 mg/kg than their corresponding 4-(2-oxopiperidin-1-yl) derivatives, **25** and **28** respectively. Only **35**, the 2-acetyl derivative, remains equipotent to **1**, but is substantially less potent than **26** its piperidinone counterpart.

To test for the potential potassium channel opening mechanism of smooth muscle relaxation, compound **30** was evaluated in aortic smooth muscle for antagonism by ATP-dependent potassium channel antagonist glybenclamide (Table 3, Figure 1).[16] Compound **30** relaxed phenylephrine-contracted aortic rings in a concentration-dependent manner with 67.1 ± 6.1% relaxation occurring at 10^{-8} M. In the presence of 10 μM glybenclamide, the relaxant activity of **30** was attentuated with only 6.9 ± 2.5% relaxation observed at 10^{-8} M. Cromakalim (**1**) elicited a similar pattern of relaxation as **30** but the concentration–response was shifted to the right indicating that cromakalim was less potent than **30** by more than 10-fold. Cromakalim at 10^{-6} M, relaxed tissues by 85.3 ± 4.3%, whereas in the presence of glybenclamide only 21.0 ± 4.5% relaxation was observed. Nitroglycerine produced relaxation of all tissues to the same maximal extent, regardless of the pretreatment regimen, indicating that the antagonism exerted by glybenclamide was specific for compound **30** and cromakalim. It can be inferred from this glybenclamide-sensitive antagonism, that compound **30** is a potassium channel activator.

Table 3. Effect of glybenclamide on rat aortic ring relaxation by test compounds[a]

	Concentration[b]			
Cmpd.	[10^{-9}]	[10^{-8}]	[10^{-7}]	[10^{-6}]
30	8.0±2.8	67.1±6.1	83.6±2.5	88.1±2.8
30 + glybenclamide	6.9±1.0	6.9±2.5	9.8±3.6	23.3±8.8
1 (cromakalim)	2.7±1.5	4.7±2.9	30.9±9.5	85.3±4.3
1 + glybenclamide	10.3±2.5	13.1±2.2	14.8±2.4	21.0±4.5

[a]Data are reported as percent of maximal relaxation of rat aortic rings. Shown are relaxation at concentrations for **30** + gly, **30** alone, cromakalim (**1**) + gly, and cromakalim (**1**) alone, $n = 5$ or 6 for all experiments.
[b]Concentrations in [M]; ± SEM.



Rat aortic rings were suspended in Krebs bicarbonate buffer at 37 °C under a resting tension of 2 g and contracted with 0.1 μM phenylephrine to produce an average tension of 2.4 g, $n = 23$. Tissues received either glybenclamide (gly), 10 μM or vehicle (10% DMSO) as pretreatment followed by a cumulative concentration response to **30** or cromakalim and a final dose of nitroglycerine (100 mg) to induce maximal relaxation. Data are reported as percent of maximal relaxation. Shown are the concentration response curves for **30** + gly, **30** alone, cromakalim (**1**) + gly and cromakalim (**1**) alone; $n = 5$ or 6 for all experiments.

Figure 1. Effect of pre-treatment with glybenclamide on relaxation of rat aortic rings with test compounds

The enhanced potency of the substituted thieno[3,2-*b*]-[5] and -[2,3-*b*]pyran series, in which the aromatic substituents have a similar orientation, and the poor activity of the substituted thieno[3,4-*b*]pyran series which has a dramatically different orientation, led us to speculate that the position of substituents on the thiophene ring is at least as important as their electron-withdrawing properties for good activity in these series. With this in mind, we generated the electropotential maps[17] of selected derivatives in the -[2,3-*b*]-, -[3,4-*b*]- and -[3,2-*b*]- series. We felt comparison of electropotential maps vs biological effects could provide some insights into differences among these derivatives. For quantitative purposes, a comparison of this type would be best made using biochemical data such as $^{86}Rb^+$ efflux as a surrogate for K^+; however, the nature of the $^{86}Rb^+$ efflux assay is not a measure suitable for quantitative comparisons.[18] On the other hand, assuming similar bioavailabilities, the dramatic differences of activity in SHR might at least be qualitatively rationalized by comparison of electropotential maps. Compound **30** (Figure 2) has an electropotential map typical of the most potent -[2,3-*b*]- and -[3,2-*b*]-derivatives with a large region of negative electropotential area (light grey) perpendicular to the ring system in left-hand quadrants. A similar map of **2b** (the [3,2-*b*] isomer of **30**) has this region shifted toward the lower left quadrant while that of the nitro derivative **2a** has a significantly expanded region of electronegativity in the left quadrants which encompasses the electronegative areas of both **30** and **2b**. Electropotential maps for the relatively inactive thieno[3,4-*b*]-series have a dramatic shift in location of the region of electronegative potential around the substituted thiophene (as might be expected from differences in the substituent geometry). These differences in electropotential maps may provide insight into the differences in biological potency measured between the series of thieno[2,3-*b*]-, -[3,4-*b*]- and -[3,2-*b*]pyran derivatives as well as other related benzopyrans.

These series of thienopyrans are among the most potent potassium channel openers synthesized to date. While **2a** remains the most interesting derivative in our studies, **26** and **30** are similar in potency to **2a**. Differences in the electropotential maps of **26** or **30** vis-à-vis **2a** may be predictive of differences in biological activity worthy of further study and provide some insights into the requirements about the aromatic region to give enhanced activity.

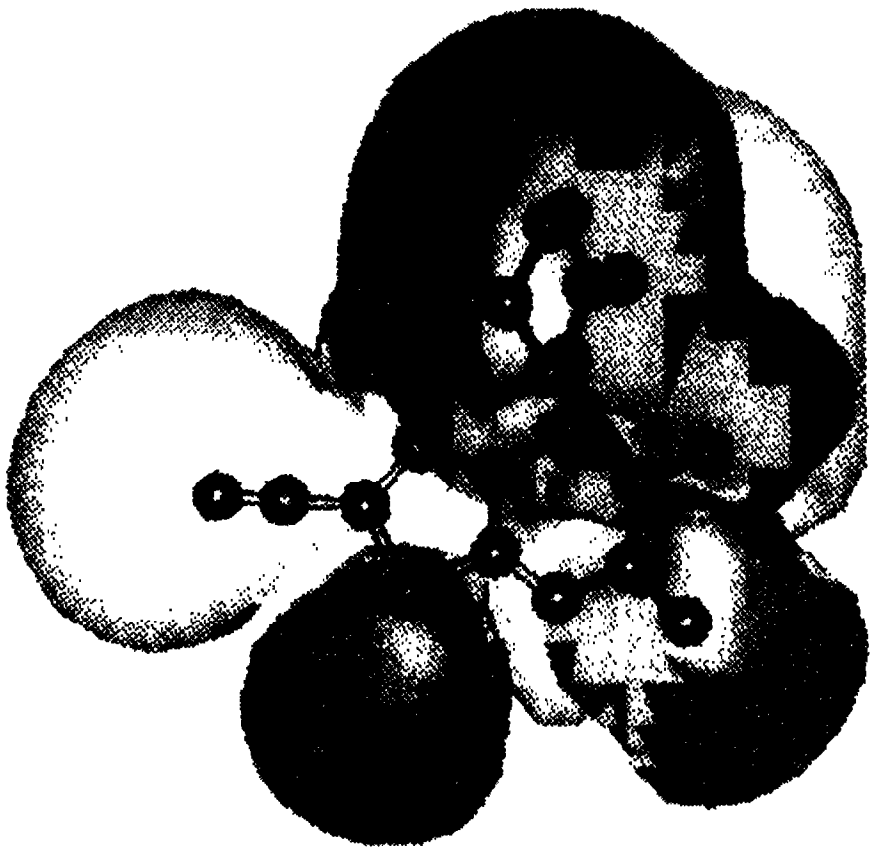


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Figure 2. Electropotential map[17] of *trans*-2-cyano-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H*-thieno[2,3-*b*]pyran (**30**). Negative electropotential areas are depicted in light grey and positive areas are depicted in dark grey. Surfaces represent 2 kcal/mol

Experimental Section

Melting point determinations were done on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infra-red (IR) spectra were obtained on a Perkin-Elmer IR8. Nuclear magnetic resonance (^{1}H 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. 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 1 and 2.

trans-*3,6-Dibromo-5,6-dihydro-7-hydroxy-5,5-dimethyl-7H-thieno[3,4-b]pyran (4)*

NBS (7.65 g, 43.0 mmol) was added to a solution of **3**[1] (10.2 g, 41.7 mmol) in DMSO (110 mL) and H_2O (1.13 mL, 62.6 mmol). After stirring at room temperature for 1 h, the reaction was quenched with H_2O. The product was extracted with Et_2O, washed several times with H_2O, dried and evaporated to give **4** as a brown oil, 12.1 g (85%); IR (neat): 1572, 1457 cm^{-1}; MS: m/z 341 (MH^+); NMR ($CDCl_3$): δ 1.42 (s, 3H), 1.66 (s, 3H), 2.55 (br s, 1H, exchanges with D_2O), 4.02 (d, J = 9.6 Hz, 1H), 4.86 (d, J = 9.6 Hz, 1H), 7.29 (s, 1H).

3-Bromo-5,6-dihydro-6,7-epoxy-5,5-dimethyl-7H-thieno-[3,4-b]pyran (5)

A solution of **4** (3.36 g, 9.81 mmol) in DMF (50 mL) was treated with NaH (60% in oil, 0.43 g, 10.8 mmol). After stirring at room temperature for 2 h, the solution was poured into H_2O (150 mL) and extracted with Et_2O. The organic phase was washed several times with H_2O, dried and evaporated to give **5** as a brown oil, 2.65 g, (94%). The oil was used without further purification. MS: m/z 261 (MH^+); NMR ($CDCl_3$): δ 1.27 (s, 3H), 1.62 (s, 3H), 3.39 (d, J = 7.0 Hz, 1H), 3.98 (d, J = 7.0 Hz, 1H), 7.30 (s, 1H).

trans-*7-Azido-3-bromo-5,6-dihydro-6-hydroxy-5,5-dimethyl-7H-thieno[3,4-b] pyran (6)*

A solution of **5** (2.65 g, 10.1 mmol) in acetone (40 mL) and H_2O (20 mL) was treated with NaN_3 (2.63 g, 40.6 mmol). After stirring at room temperature for 2 h, the solution was poured into H_2O (200 mL) and extracted with Et_2O. The organic phase was washed with H_2O several times, dried and evaporated. Recrystallization from hexanes gave **6** as a colorless solid, 2.0 g (65%), m.p. 80–87 °C; IR (KBr): 2106, 1576, 1465 cm^{-1}; MS: m/z 304 (MH^+); NMR ($CDCl_3$): δ 1.28 (s, 3H), 1.52 (s, 3H), 2.31 (d, J = 4.9 Hz, 1H, exchanges with D_2O), 3.70 (dd, J = 4.9 and 8.7 Hz, 1H, simplifies to d, J = 8.7 Hz, with D_2O exchange), 4.35 (dd, J = 1.4 and 8.7 Hz, 1H), 7.23 (d, J = 1.4 Hz, 1H). Anal. ($C_9H_{10}BrN_3O_2S$) C, H, N.

trans-*7-Amino-5,6-dihydro-6-hydroxy-5,5-dimethyl-7H-thieno[3,4-b]pyran (7a)*

A suspension of LAH (1.99 g, 52.5 mmol) in THF (100 mL) was treated with **6** (5.32 g, 17.5 mmol) then heated to reflux for 2 h. The reaction was carefully quenched by adding sequentially H_2O (2 mL), 15% NaOH (2 mL) and H_2O (6 mL). The inorganics were removed by filtration through a pad of silica gel eluting with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$, and the solvent was evaporated to give **7a**, 3.07 g (88%): m.p. 114–116 °C; MS: m/z 200 (MH^+); NMR ($CDCl_3$): δ 1.22 (s, 3H), 1.47 (s, 3H), 2.34 (br s, 3H, exchanges with D_2O), 3.36 (d, J = 9.8 Hz, 1H), 3.66 (dd, J = 1.4 and 9.8 Hz, 1H), 6.28 (d, J = 3.4 Hz, 1H), 7.10 (dd, J = 1.4 and 3.4 Hz, 1H).

trans-*7-Amino-3-bromo-5,6-dihydro-6-hydroxy-5,5-dimethyl-7H-thieno[3,4-b]pyran (7b)*

A solution of **6** (1.32 g, 4.34 mmol) and triphenylphosphine (1.25 g, 4.77 mmol) in THF (40 mL) was heated to reflux for 2 h. The solution was cooled to room temperature, treated with H_2O (1 mL) and stirred at room temperature for 16 h. NH_4OH (1N, 30 mL) and Et_2O (30 mL) were added. The aqueous layer was separated, and the organic layer was washed in HCl (1N, 30 mL). The combined aqueous layers were neutralized with 50% NaOH. The product was extracted into CH_2Cl_2 and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give **7b** as a colorless solid, 1.07 g (96%), m.p. 170–172 °C; IR (KBr): 3353, 3129, 3086, 2991, 2985, 2977, 1565, 1464 cm^{-1}; MS: m/z 278 (MH^+); NMR (DMSO-d_6): δ 1.10 (s, 3H), 1.37 (s, 3H), 1.95 (br s, 2H, exchanges with D_2O), 3.15 (m, 1H), 3.50 (dd, J = 1.6 and 9.4 Hz, 1H), 5.44 (d, J = 5.1 Hz, 1H, exchanges with D_2O), 7.42 (d, J = 1.6 Hz, 1H).

trans-*7-(5-Chloropentamido)-5,6-dihydro-6-hydroxy-5,5-dimethyl-7H-thieno[3,4-b]pyran (8a)*

5-Chlorovaleryl chloride (2.04 mL, 15.8 mmol) was added to a 0 °C solution of **7a** (3.0 g, 15.1 mmol) and Et_3N (6.3 mL, 45.2 mmol) in CH_2Cl_2 (50 mL). After 1 h, the solution was poured onto a silica gel column and eluted with 3% MeOH/CH_2Cl_2 to give the **8a** as an amber oil, 4.83 g (100%); IR (neat): 3294, 1645, 1561, 1541, 1453 cm^{-1}; NMR ($CDCl_3$): δ 1.27 (s, 3H), 1.46 (s, 3H), 1.68–1.96 (m, 4H), 2.25–2.46 (m, 2H), 3.48–3.70 (m, 3H), 4.60 (br s, 1H), 4.97 (m, 1H), 6.20 (br d, 1H), 6.36 (d, J = 3 Hz, 1H), 7.08 (dd, J = 1.0 and 3.0 Hz, 1H).

trans-*3-Bromo-7-(5-chloropentamido)-5,6-dihydro-6-hydroxy-5,5-dimethyl-7H-thieno[3,4-b]pyran (8b)*

An amber oil; IR (neat): 3293, 1639, 1573, 1535 cm^{-1}; MS: m/z 396 (MH^+); NMR ($CDCl_3$): δ 1.28 (s, 3H), 1.50 (s, 3H), 1.85 (m, 4H), 2.36 (m, 2H), 3.57 (m, 3H), 4.31

(d, J = 2.8 Hz, 1H, exchanges with D_2O), 4.96 (m, 1H), 5.80 (br s, 1H, exchanges with D_2O), 7.06 (d, J = 1.6 Hz, 1H).

trans-*5,6-Dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7H-thieno[3,4-b]pyran (9a)*

A 0 °C solution of **8a** (4.8 g, 15.1 mmol) in DMF (50 mL) was treated with NaH (60% in oil, 0.63 g, 15.8 mmol). After stirring at room temperature for 2 h, the solution was poured into H_2O (250 mL) and extracted with CH_2Cl_2. The organic phase was washed several times with H_2O, then purified by flash chromatography (3% MeOH/CH_2Cl_2) to give a solid. Trituration in Et_2O gave **9a** as a colorless solid, 2.92 g (69%); IR (KBr): 3430, 2973, 1613, 1563, 1488 cm^{-1}; MS: m/z 282 (MH^+); NMR ($CDCl_3$): δ 1.27 (s, 3H), 1.48 (s, 3H), 1.78–1.88 (m, 4H), 2.56 (m, 2H), 3.04 (m, 1H), 3.20 (m, 1H), 3.42 (d, J = 4.9 Hz, 1H, exchanges with D_2O), 3.75 (dd, J = 4.9 Hz, J = 10.1 Hz, 1H), 5.83 (dd, J = 1.4 and 10.1 Hz, 1H), 6.36 (d, J = 3.4 Hz, 1H), 6.86 (dd, J = 1.4 and 3.4 Hz, 1H). Anal. ($C_{14}H_{19}NO_3S$) C, H, N.

trans-*3-Bromo-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7H-thieno[3,4-b]pyran (9b)*

IR (KBr): 3500–3200, 1612, 1575, 1489 cm^{-1}; MS: m/z 360 (MH^+); NMR ($CDCl_3$): δ 1.28 (s, 3H), 1.53 (s, 3H), 1.72–1.88 (m, 4H), 2.55 (m, 2H), 3.05 (m, 1H), 3.27 (m, 1H), 3.34 (d, J = 5.3 Hz, 1H, exchanges with D_2O), 3.75 (dd, J = 5.3 and 10.2 Hz, 1H), 5.82 (d, J = 10.2 Hz, 1H), 6.86 (d, J = 1.6 Hz, 1H). Anal. ($C_{14}H_{18}BrNO_3S$) C, H, N.

trans-*3-Chloro-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7H-thieno[3,4-b]pyran (10)*

A solution of sulfuryl chloride (1.0 M, 1.5 mL, 1.5 mmol) was added to a solution of **9a** (0.40 g, 1.42 mmol) in CH_2Cl_2 (10 mL) at -10 °C and stirred at -10 °C for 1.5 h. The solution was washed with saturated $NaHCO_3$. The product was purified by flash chromatography (3% MeOH in CH_2Cl_2). Trituration in Et_2O gave **10**, 0.34 g (75%), as a colorless solid; IR (KBr): 3500–3200, 1612, 1304, 1092 cm^{-1}; MS: m/z 316 (MH^+); NMR ($CDCl_3$): δ 1.29 (s, 3H), 1.54 (s, 3H), 1.75–1.90 (m, 4H), 2.54 (m, 2H), 3.05–3.22 (m, 2H), 3.53 (br d, J = 5.5 Hz, 1H), 3.75 (dd, J = 5.5 and 10.2 Hz, 1H), 5.80 (d, J = 10.2 Hz, 1H), 6.67 (d, J = 1.5 Hz, 1H). Anal. ($C_{14}H_{18}ClNO_3S$) C, H, N.

trans-*3-Acetyl-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7H-thieno[3,4-b]pyran (11)*

A solution of **31** (0.55 g, 1.5 mmol) in MeOH (10 mL) was treated with K_2CO_3 (0.23 g, 1.65 mmol) and stirred at room temperature for 2 h. The mixture was poured into H_2O (100 mL) and the product was collected by filtration. Trituration in Et_2O gave **11**, 0.42 g (87%), as a colorless solid; IR (KBr): 3500–3300, 1640, 1615, 1426, 1409 cm^{-1}; MS: m/z 324 (MH^+); NMR ($CDCl_3$): δ 1.36 (s, 3H), 1.58 (s, 3H), 1.67–1.90 (m, 4H), 2.52 (s, 3H), 2.56 (m, 2H), 3.09–3.15 (m, 2H), 3.55 (br d, 1H), 3.78 (dd, J = 5.5 and 10.2 Hz, 1H), 5.80 (d, J = 10.2 Hz, 1H), 7.16 (d, J = 1.4 Hz, 1H). Anal. ($C_{16}H_{21}NO_4S$) C, H, N.

trans-*1,3-Dibromo-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7H-thieno[3,4-b]pyran (12)*

A solution of **9b** (0.78, 2.15 mmol) in CH_2Cl_2 (10 mL) was treated with Br_2 (0.12 mL, 2.26 mmol) at 0 °C for 1 h. The product was purified by flash chromatography using 3% MeOH in CH_2Cl_2 as the eluant. Trituration in Et_2O gave **12**, 0.88 g (93%) as a colorless solid; IR (KBr): 3500–3200, 1607, 1572, 1491 cm^{-1}; MS: m/z 438 (MH^+); NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.52 (s, 3H), 1.82–1.89 (m, 4H), 2.54 (m, 2H), 3.05 (m, 1H), 3.27 (m, 1H), 3.71 (d, J = 3.5 Hz, 1H), 3.78 (dd, J = 3.5 and 9.3 Hz, 1H), 5.75 (d, J = 9.3 Hz, 1H). Anal. ($C_{14}H_{17}Br_2NO_3S$) C, H, N.

trans-*1-Acetyl-6-acetoxy-3-bromo-5,6-dihydro-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7H-thieno[3,4-b]pyran*

IR (neat): 1748, 1652, 1438 cm^{-1}; MS: m/z 444 (MH^+); NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.50 (s, 3H), 1.50–1.80 (m, 4H), 2.15 (s, 3H), 2.40 (s, 3H), 2.54 (m, 2H), 3.00–3.20 (m, 2H), 5.20 (m, 1H), 6.10 (m, 1H).

trans-*1-Acetyl-3-bromo-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7H-thieno[3,4-b]pyran (13)*

IR (KBr): 1666, 1610, 1599, 1441 cm^{-1}; MS: m/z 402 (MH^+); NMR ($CDCl_3$): δ 1.22 (s, 3H), 1.53 (s, 3H), 1.62–1.83 (m, 4H), 2.43 (s, 3H), 2.64 (m, 4H), 3.79 (dd, J = 2.0 and 8.9 Hz, 1H), 4.47 (d, J = 3.5 Hz, 1H), 5.96 (d, J = 8.9 Hz, 1H).

trans-*1-Acetyl-5,6-dihydro-6-hydroxy-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7H-thieno[3,4-b]pyran (14)*

Compound **13** (0.27 g, 0.66 mmol) in MeOH (20 mL) was hydrogenated at 40 psi over 10% Pd/C (30 mg) for 20 h. The catalyst was removed by filtration, and the solvent was evaporated. The product was purified by flash chromatography (3% MeOH/CH_2Cl_2) as the eluant and recrystallized from CH_2Cl_2/hexane, to give **14**, 0.16 g (75%) as a colorless solid; IR (KBr): 3500–3300, 1660, 1634, 1489, 1435 cm^{-1}; MS: m/z 324 (MH^+); NMR ($CDCl_3$): δ 1.22 (s, 3H), 1.48 (s, 3H), 1.65–1.81 (m, 4H), 2.48 (s, 3H), 2.40–2.90 (m, 4H), 3.80 (dd, J = 2.1 and 8.9 Hz, 1H), 4.52 (d, J = 2.1 Hz, 1H), 5.94 (d, J = 8.9 Hz, 1H), 6.69 (s, 1H). Anal. ($C_{16}H_{21}NO_4S \cdot 1/4H_2O$) C, H, N.

2,5-Dibromo-5,6-dihydro-6,6-dimethyl-4H-thieno[2,3-b]-pyran-4-one (16)

Bromine (4.2 mL, 82.4 mmol) was added dropwise to a solution of **15**[1] (7.5 g, 41.2 mmol) in HOAc (70 mL) at r.t. After 1 h, the solution was poured into H_2O (300 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was washed with H_2O then saturated aq. $NaHCO_3$, dried

over $MgSO_4$, and the solvent was evaporated. The residue was purified by flash chromatography (5% Et_2O/pentanes) to give 8.1 g (58%) of **16** as an orange solid, m.p. 97–99 °C; IR (KBr): 1687, 1527, 1491 cm^{-1}; MS: m/z 339 (MH^+); NMR ($CDCl_3$): δ 1.61 (s, 3H), 1.69 (s, 3H), 4.20 (s, 1H), 7.10 (s, 1H). Anal. ($C_9H_8Br_2O_2S$) C, H.

cis-*2,5-Dibromo-5,6-dihydro-4-hydroxy-6,6-dimethyl-4H-thieno[2,3-b]pyran (17)*

A solution of **16** (2.5 g, 7.35 mmol) in EtOH (30 mL) was treated with $NaBH_4$ (1.0 g, 26.4 mmol). After stirring at room temperature for 16 h, the solution was poured into H_2O (200 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with H_2O, dried and evaporated to give **17** as an amber oil, 1.69 g (67%), which was used without further purification. IR (neat): 3600–3200, 1566, 1467 cm^{-1}; MS: m/z 342 (MH^+); NMR ($CDCl_3$): δ 1.52 (s, 3H), 1.61 (s, 3H), 2.42 (d, J = 9.5 Hz, 1H), 4.34 (d, J = 4.4 Hz, 1H), 4.70 (dd, J = 9.5 and 4.4 Hz, 1H), 6.81 (s, 1H).

cis-*2,5-Dibromo-4-chloro-5,6-dihydro-6,6-dimethyl-4H-thieno[2,3-b]pyran (18)*

Thionyl chloride (1.8 mL, 24.6 mmol) was added to a solution of **17** (1.7 g, 4.9 mmol) in CH_2Cl_2 (30 mL). After stirring for 1 h, the solution was washed with saturated aq. $NaHCO_3$ (2 x 300 mL), dried and evaporated to give **18**, 1.7 g (96%) as a yellow oil, which was used without further purification. IR (neat): 1566, 1472 cm^{-1}; MS: m/z 356 (MH^+); NMR ($CDCl_3$): δ 1.51 (s, 3H), 1.66 (s, 3H), 4.27 (d, J = 6.7 Hz, 1H), 5.10 (d, J = 6.7 Hz, 1H), 6.78 (s, 1H).

trans-*2,5-Dibromo-5,6-dihydro-4-hydroxy-6,6-dimethyl-4H-thieno[2,3-b]pyran (19)*

Silica gel, 230–400 mesh, (1.0 g) was added to a solution of **18** (1.6 g, 4.6 mmol) in 5% Et_2O in pentanes (30 mL). The resultant mixture was stirred at room temperature for 30 min and filtered through a pad of silica gel eluting with 5 to 20% Et_2O in pentanes until all the product had been eluted. The combined fractions were evaporated to give **19**, 1.1 g (73%) as an amber oil. IR (neat): 3600–3200, 1570, 1469 cm^{-1}; MS: m/z 342 (MH^+); NMR ($CDCl_3$): δ 1.52 (s, 3H), 1.60 (s, 3H), 2.43 (d, J = 5.0 Hz, 1H), 4.06 (d, J = 7.1 Hz, 1H), 4.76 (dd, J = 5.0 and 7.1 Hz, 1H), 6.80 (s, 1H).

trans-*4-Azido-2-bromo-5,6-dihydro-5-hydroxy-6,6-dimethyl-4H-thieno[2,3-b]pyran (20)*

A 0 °C solution of **19** (1.15 g, 3.36 mmol) in DMF (25 mL) was treated with NaH (60% in oil, 134 mg, 3.36 mmol). After stirring at room temperature for 2 h, the reaction was cooled to 0 °C and NaN_3 (635 mg, 10.8 mmol) in H_2O (2 mL) was added. After stirring at room temperature for 1 h, the resultant solution was poured into H_2O (150 mL), extracted with CH_2Cl_2 (50 mL), washed several times with H_2O, dried and evaporated to give **20** as a brown oil, 1.0 g (98%), which was used without further purification. IR (neat) 3600–3200, 2101, 1663, 1568, 1470 cm^{-1}; MS: m/z 303 (MH^+); NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.48 (s, 3H), 2.42 (d, J = 5.3 Hz, 1H), 3.72 (dd, J = 7.5 and 5.3 Hz, 1H), 4.21 (d, J = 7.5 Hz, 1H), 6.76 (s, 1H).

trans-*4-Amino-5,6-dihydro-5-hydroxy-6,6-dimethyl-4H-thieno[2,3-b]pyran (21)*

A solution of **20** (1.0 g, 3.3 mmol) in THF (10 mL) was added to a mixture of LAH (0.37 g, 9.9 mmol) in THF (50 mL). The mixture was heated to reflux for 2 h. The reaction was quenched by sequential addition of H_2O (0.4 mL), 15% aqueous NaOH (0.4 mL) and H_2O (1.2 mL). $MgSO_4$ was added to the mixture and the inorganics were removed by filtration. The inorganics were washed with CH_2Cl_2, dried and evaporated to give **21** as a colorless solid, 0.59 g (90%), m.p. 107–109 °C; IR (neat): 3400–2700, 1567, 1456 cm^{-1}; MS: m/z 200 (MH^+); NMR ($CDCl_3$): δ 1.26 (s, 3H), 1.50 (s, 3H), 2.05 (br s, 3H), 3.36 (d, J = 8.8 Hz, 1H), 3.56 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 5.8 Hz, 1H), 6.71 (d, J = 5.8 Hz, 1H).

trans-*4-(5-Chloropentamido)-5,6-dihydro-5-hydroxy-6,6-dimethyl-4H-thieno[2,3-b]pyran*

5-Chlorovaleryl chloride (0.42 mL, 3.25 mmol) was added to a 0 °C solution of **21** (0.59 g, 2.96 mmol) and Et_3N (1.44 mL, 10.4 mmol) in CH_2Cl_2 (25 mL). After stirring at room temperature for 1 h, the residue was purified by flash chromatography (2.5% MeOH/CH_2Cl_2) to give the product as an amber oil, 0.76 g (81%); MS: m/z 318 (MH^+); NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.48 (s, 3H), 1.83–1.88 (m, 4H), 2.25–2.30 (m, 2H), 3.54–3.60 (m, 2H), 3.65 (d, J = 8.1 Hz, 1H), 4.83 (dd, 1H), 5.84 (br d, 1H, exchanges with D_2O), 6.51 (d, J = 5.8 Hz, 1H), 6.61 (d, J = 5.8 Hz, 1H), 8.45 (br s, 1H, exchanges with D_2O).

trans-*5,6-Dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxo-piperidin-1-yl)-4H-thieno[2,3-b]pyran (22)*

A 0 °C solution of *trans*-4-(5-chloropentamido)-5,6-dihydro-5-hydroxy-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyran (0.75 g, 2.36 mmol) in DMF (25 mL) was treated with NaH (60% in oil, 104 mg, 2.60 mmol). After stirring at room temperature for 1 h, the solution was poured into H_2O (200 mL), extracted with CH_2Cl_2, washed with H_2O, dried and evaporated. The residue was purified by flash chromatography (2.5% MeOH/CH_2Cl_2) to give **22**, 0.47 g (71%), as a colorless solid; IR (KBr): 3328, 1607, 1563, 1490 cm^{-1}; MS: m/z 282 (MH^+); NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.50 (s, 3H), 1.74–1.87 (m, 4H), 2.50–2.56 (m, 2H), 3.03–3.20 (m, 2H), 3.74–3.81 (m, 2H, collapses to a d, J = 9.5 Hz, 1H with D_2O), 5.64 (d, J = 9.5 Hz, 1H), 6.44 (d, J = 5.8 Hz, 1H), 6.48 (d, J = 5.8 Hz, 1H). Anal. ($C_{14}H_{19}NO_3S$) C, H, N.

trans-*4-(5-Chlorobutamido)-5,6-dihydro-5-hydroxy-6,6-dimethyl-4*H-*thieno[2,3-b]pyran*

An amber oil; IR (neat): 3500–3200, 1645, 1541, 1459 cm^{-1}; MS: m/z 304 (MH^+); NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.48 (s, 3H), 2.12–2.20 (m, 2H), 2.46–2.52 (m, 2H), 3.64 (t, J = 6.1 Hz, 2H), 4.65 (br s, 1H, exchanges with D_2O), 4.83 (dd, J = 1.2 and 6.8 Hz, 1H), 5.99 (br d, 1H, exchanges with D_2O), 6.51 (d, J = 5.8 Hz, 1H), 6.62 (d, J = 5.8 Hz, 1H)

trans-*5,6-Dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopyrrolidin-1-yl)-4*H-*thieno[2,3-b]pyran (23)*

IR (KBr): 3500–3200, 1687, 1650, 1568, 1461 cm^{-1}; MS: m/z 268 (MH^+); NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.51 (s, 3H), 2.03–2.56 (m, 2H), 2.54 (m, 2H), 3.13 (d, J = 5.0 Hz, 1H), 3.23–3.29 (m, 2H), 3.77 (dd, J = 5.0 and 9.2 Hz, 1H), 5.12 (d, J = 9.2 Hz, 1H), 6.43 (d, J = 5.8 Hz, 1H), 6.48 (d, J = 5.8 Hz, 1H). Anal. ($C_{13}H_{17}NO_3S$) C, H, N.

trans-*2-Bromo-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-b]pyran (24)*

IR (KBr): 3500–3100, 1613, 1598, 1568, 1466 cm^{-1}; MS: m/z 360 (MH^+); NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.48 (s, 3H), 1.78–1.87 (m, 2H), 2.53 (m, 2H), 3.20 (d, J = 1.4 Hz, 1H), 3.06–3.16 (m, 2H), 3.72 (d, J = 9.2 Hz, 1H), 5.60 (d, J = 9.2 Hz, 1H), 6.46 (s, 1H). Anal. ($C_{14}H_{18}BrNO_3S$) C, H, N.

trans-*2-Chloro-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-b]pyran (25)*

NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.48 (s, 3H), 1.77–1.87 (m, 4H), 2.50–2.56 (m, 2H), 3.03–3.20 (m, 2H), 3.74–3.81 (m, 2H, collapses to a doublet, 1H, with D_2O), 5.58 (d, J = 9.2 Hz, 1H), 6.31 (s, 1H); IR (KBr): 1613, 1599, 1572, 1490 cm^{-1}; MS: m/z 316 (MH^+). Anal. ($C_{14}H_{18}ClNO_3S$) C, H, N.

trans-*2-Acetyl-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-b]pyran (26)*

IR (KBr): 3500–3300, 1641, 1634, 1607, 1487 cm^{-1}; MS: m/z 324 (MH^+); NMR ($CDCl_3$): δ 1.36 (s, 3H), 1.54 (s, 3H), 1.80–1.89 (m, 4H), 2.43 (s, 3H), 2.57 (m, 2H), 3.09 (m, 2H), 3.62 (d, J = 4.7 Hz, 1H), 3.77 (dd, J = 4.7 and 9.4 Hz, 1H), 5.72 (d, J = 9.4 Hz, 1H), 7.13 (s, 1H). Anal. ($C_{16}H_{21}NO_4S$) C, H, N.

trans-*5-Benzyloxy-2-bromo-5,6-dihydro-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-b]pyran (27)*

Sodium hydride (60%, 0.40 g, 10.0 mmol) was added to a solution of **22** (3.43 g, 9.52 mmol) in DMF (50 mL) at 0 °C. After stirring at 0 °C for 1 h, benzyl bromide (1.2 mL, 0.010 mmol) was added to the solution, and the solution was stirred for an additional 1 h. The solution was poured into H_2O (300 mL), and the product was extracted into CH_2Cl_2, washed several times with H_2O and dried over $MgSO_4$, and purified by flash chromatography (1% MeOH/CH_2Cl_2) to give **27**, 3.3 g (77%), as a colorless solid, m.p. 170–171 °C; IR (KBr): 3059, 2943, 1642, 1576, 1483 cm^{-1}; MS: m/z 450 (MH^+); NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.52 (s, 3H), 1.55–1.76 (m, 4H), 2.37–2.47 (m, 2H), 2.88–2.96 (m, 2H), 3.65 (br s, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.71 (d, J = 11.7 Hz, 1H), 5.87 (br s, 1H), 6.40 (s, 1H), 7.27–7.38 (m, 5H). Anal. ($C_{21}H_{24}BrNO_3S$) C, H, N.

trans-*2-Carbomethoxy-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-b]pyran (28)*

In a stainless steel Parr apparatus, a solution of **24** (1.0 g 2.78 mmol), Et_3N (0.66 mL, 4.72 mmol) and bis(triphenylphosphino)-palladium(II) chloride (60 mg) over CO (160 psi) was heated to 100 °C for 2 days. The solvent was evaporated, and the resultant residue was purified by flash chromatography (3% MeOH/CH_2Cl_2) and recrystallized from toluene to give **28**, 0.59 (63%), as a colorless solid; IR (KBr): 3418, 1702, 1607, 1494, 1456 cm^{-1}; MS: m/z 340 (MH^+); NMR ($CDCl_3$): δ 1.34 (s, 3H), 1.53 (s, 3H), 1.79–1.86 (m, 4H), 2.53–2.56 (m, 2H), 3.07 (m, 2H), 3.78 (m, 2H), 3.83 (s, 3H), 5.70 (d, J = 9.2 Hz, 1H), 7.26 (s, 1H). Anal. ($C_{16}H_{21}NO_5S$) C, H, N.

trans-*5-Benzyloxy-2-carbomethoxy-5,6-dihydro-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-b]pyran (29)*

A colorless solid; m.p. 155–156 °C. IR (KBr): 1701, 1647, 1462, 1437 cm^{-1}; MS: m/z 430 (MH^+); NMR ($CDCl_3$): δ 1.37 (s, 3H), 1.56 (s, 3H), 1.61–1.77 (m, 4H), 2.39–2.47 (m, 2H), 2.92–2.96 (m, 2H), 3.70 (br s, 1H), 3.81 (s, 3H), 4.62 (d, J = 11.7 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 5.97 (br s, 1H), 7.21 (s, 1H), 7.27–7.39 (m, 5H). Anal. ($C_{23}H_{27}NO_5S$) C, H, N.

trans-*5-Benzyloxy-2-carboxamido-5,6-dihydro-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-b]pyran*

A solution of **29** (2.67 g, 6.22 mmol) and NH_4OH (30 mL) in MeOH (60 mL) in a stainless steel Parr reactor was heated to 100 °C for 8 h. The solvent was evaporated, and the residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give the product, 1.5 g (58%), as a colorless solid, m.p. 204–207 °C; IR (KBr): 2942, 1648, 1619, 1470, 1463 cm^{-1}; MS: m/z 415 (MH^+); NMR ($CDCl_3$): δ 1.26 (s, 3H), 1.53 (s, 3H), 1.61–1.80 (m, 4H), 2.25–2.35 (m, 2H), 2.85 (m, 1H), 3.17 (m, 1H), 3.90 (m, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.73 (d, J = 11.8 Hz, 1H), 5.70 (br s, 1H), 7.22 (br s, 1H, exchanges with D_2O), 7.25 (s, 1H), 7.28–7.35 (m, 5H), 7.80 (br s, 1H, exchanges with D_2O) Anal. ($C_{22}H_{26}N_2O_4S$) C, H, N.

trans-*5-Benzyloxy-2-cyano-5,6-dihydro-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-b]pyran*

Trifluoroacetic anhydride (1.0 mL, 6.97 mmol) was slowly added to a solution of *trans*-5-benzyloxy-2-carboxamido-

5,6-dihydro-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H*-thieno [2,3-*b*]pyran (1.33 g, 3.32 mmol) and Et_3N (0.51 mL, 3.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, and the product was purified by flash chromatography (1% MeOH/CH_2Cl_2) to give the product, 1.09 g (82%), as a colorless solid, m.p. 119–124 °C; IR (KBr): 2214, 1619, 1563, 1459 cm^{-1}; MS: m/z 397 (MH^+); NMR ($CDCl_3$): δ 1.38 (s, 3H), 1.60 (s, 3H), 1.35–1.74 (m, 4H), 2.45–2.53 (m, 2H), 2.73–3.00 (m, 2H), 3.70 (br s, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 5.90 (br s, 1H), 6.97 (s, 1H), 7.28–7.40 (m, 5H).

trans-*2-Cyano-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-*b*]pyran (30)*

A 1 M solution of BBr_3 (12.7 mL, 12.7 mmol) in CH_2Cl_2 was slowly added to a solution of *trans*-5-benzyloxy-2-cyano-5,6-dihydro-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H*-thieno[2,3-*b*]pyran (0.97 g, 2.54 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After stirring for 1 h at 0 °C, the solution was shaken in a separatory funnel with H_2O. The organic layer was separated and dried over $MgSO_4$. The product was purified by flash chromatography (2% MeOH/CH_2Cl_2) and recrystallized from CH_2Cl_2/hexanes to give **30**, 0.57 g (76%), as a colorless solid; IR (KBr): 3500–3200, 2945, 2208, 1614, 1560, 1489 cm^{-1}; MS: m/z 307 (MH^+); NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.54 (s, 3H), 1.78–1.89 (m, 4H), 2.54 (m, 2H), 3.02–3.10 (m, 2H), 3.77 (d, *J* = 9.4 Hz, 1H), 3.85 (br s, 1H, exchanges with D_2O), 5.69 (d, *J* = 9.4 Hz, 1H), 7.04 (s, 1H). Anal. ($C_{15}H_{18}N_2O_3S$) C, H, N.

trans-*6-Acetoxy-3-acetyl-5,6-dihydro-5,5-dimethyl-7-(2-oxopiperidin-1-yl)-7*H-*thieno[3,4-*b*]pyran (31)*

A suspension of **9a** (0.90 g, 3.19 mmol) in Ac_2O (10 mL) was treated with perchloric acid (70%, 8 drops) at 0 °C. The resultant orange solution was stirred for 4 h at 0 °C, then poured into H_2O (80 mL) and stirred for 1 h. The product was extracted into CH_2Cl_2 and washed twice with H_2O and with saturated aqueous Na_2CO_3. The product was purified by flash chromatography (3% MeOH/CH_2Cl_2) and recrystallized from CH_2Cl_2/hexanes to give **31**, 0.71 g (60%), as a colorless solid; IR (KBr): 1744, 1647, 1557, 1451, 1419 cm^{-1}; MS: m/z 366 (MH^+); NMR ($CDCl_3$): δ 1.44 (s, 3H), 1.48 (s, 3H), 1.69–1.83 (m, 4H), 2.11 (s, 3H), 2.48 (m, 2H), 2.52 (s, 3H), 3.00 (m, 1H), 3.23 (m, 1H), 5.20 (d, *J* = 10.0 Hz, 1H), 6.11 (d, *J* = 10.0 Hz, 1H), 7.18 (d, *J* = 1.5 Hz, 1H). Anal. ($C_{18}H_{23}NO_5S$) C, H, N.

trans-*2-Acetyl-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopiperidin-1-yl)-4*H-*thieno[2,3-*b*]pyran (32)*

IR (KBr): 1746, 1643, 1483, 1455 cm^{-1}; MS: m/z 366 (MH^+); NMR ($CDCl_3$): δ 1.43 (s, 3H), 1.44 (s, 3H), 1.66–1.85 (m, 4H), 2.10 (s, 3H), 2.43 (s, 3H), 2.48 (m, 2H), 2.96 (m, 1H), 3.24 (m, 1H), 5.20 (d, *J* = 9.5 Hz, 1H), 6.00 (d, *J* = 9.5 Hz, 1H), 7.11 (d, *J* = 0.3 Hz, 1H). Anal. ($C_{18}H_{23}NO_5S$) C, H, N.

trans-*2-Bromo-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopyrrolidin-1-yl)-4*H-*thieno[2,3-*b*]pyran (33)*

IR (KBr): 1662, 1571, 1464 cm^{-1}; MS: m/z 346 (MH^+); NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.50 (s, 3H), 2.04–2.11 (m, 2H), 2.51 (m, 2H), 3.22–3.35 (m, 2H), 3.53 (d, *J* = 5.6 Hz, 1H, exchanges with D_2O), 3.74 (m, 1H), 3.83 (s, 3H), 5.04 (d, *J* = 9.2 Hz, 1H), 6.43 (s, 1H). Anal. ($C_{13}H_{16}BrNO_3S$) C, H, N.

trans-*2-Chloro-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopyrrolidin-1-yl)-4*H-*thieno[2,3-*b*]pyran (34)*

IR (KBr): 1663, 1644, 1575, 1479 cm^{-1}; MS: m/z 302 (MH^+); NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.50 (s, 3H), 2.04–2.13 (m, 2H), 2.48 (m, 2H), 3.20–3.36 (m, 2H), 3.42 (d, *J* = 5.5 Hz, 1H, exchanges with D_2O), 3.72–3.77 (m, 1H), 3.83 (s, 3H), 5.02 (d, *J* = 9.2 Hz, 1H), 6.28 (s, 1H). Anal. ($C_{13}H_{16}ClNO_3S$) C, H, N.

trans-*2-Acetyl-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopyrrolidin-1-yl)-4*H-*thieno[2,3-*b*]pyran (35)*

IR (KBr): 3415, 1659, 1643, 1635, 1443, 1420 cm^{-1}; MS: m/z 310 (MH^+); NMR (DMSO-d_6): δ 1.26 (s, 3H), 1.46 (s, 3H), 1.95–2.00 (m, 2H), 2.32–2.42 (m, 5H), 3.02 (m, 1H), 3.30 (m, 1H), 3.72 (m, 1H), 3.74 (m, 1H), 4.85 (d, *J* = 9.6 Hz, 1H), 5.73 (d, *J* = 5.9 Hz, 1H, exchanges with D_2O), 7.38 (s, 1H). Anal. ($C_{15}H_{19}NO_4S$) C, H, N.

trans-*2-Carbomethoxy-5,6-dihydro-5-hydroxy-6,6-dimethyl-4-(2-oxopyrrolidin-1-yl)-4*H-*thieno[2,3-*b*]pyran (36)*

IR (KBr): 1713, 1685, 1655, 1485, 1463 cm^{-1}; MS: m/z 326 (MH^+); NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.54 (s, 3H), 2.06–2.14 (m, 2H), 2.50–2.56 (m, 2H), 3.18–3.30 (m, 2H), 3.62 (d, *J* = 5.8 Hz, 1H, exchanges with D_2O), 3.74 (m, 1H), 3.83 (s, 3H), 5.12 (d, *J* = 9.4 Hz, 1H), 7.23 (s, 1H). Anal. ($C_{15}H_{19}NO_5S$) C, H, N.

Antihypertensive activity

Antihypertensive activity was assessed using a direct measurement of systolic and diastolic arterial blood pressure in spontaneously hypertensive rats (SHR).[14] 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 the 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 and after a 60 min postsurgical recovery period, rats with mean arterial pressures >150mm Hg 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 4–6 SHR received a single oral dose of drug or vehicle, administered by gavage at doses of 0.003 to 20 mg/kg and were monitored continuously for 4 h post-dosing. Compounds were solubilized in distilled H_2O. Data were expressed as the percentage change from mean pre-drug values for each rat. Differences from pre-drug values were analyzed using

regression analysis over the linear portion of the dose–response curves. The oral ED_{30} (dose that produces a 30% reduction in mean arterial pressure) was calculated for each drug.

Potassium channel activation

The activity and mechanism of action of test compounds was further investigated in isolated rings of rat thoracic aorta using a modification of a previously published procedure.[19] Rings of vascular smooth muscle (3–4 mm) were suspended in 10 mL tissue baths of Krebs bicarbonate buffer at 37 °C, oxygenated with 95% O_2/5% CO_2 under 2 g of passive tension and contracted with a submaximal concentration of phenylephrine (0.1 μM) throughout the study. Tissues were pretreated with either glybenclamide (10 μM, Sigma Chemical, St Louis, MO) or the equivalent volume of vehicle (10% DMSO). A cumulative concentration response to test compound was generated. At the end of the experiment, all tissues received 10 μg/mL of nitroglycerine (Eli Lilly, Indianapolis, IN) to induce maximal relaxation. Data are reported in Table 3 as percent of maximal relaxation of phenylephrine-induced tension and depicted in Figure 1.

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