Bicyclic Acylguanidine Na^+/H^+ Antiporter Inhibitors

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Received May 5, 1998

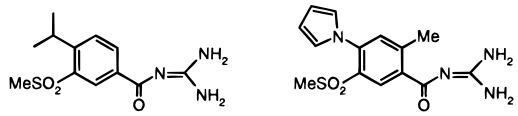
Blockade of the Na^+/H^+ exchange has been shown to diminish the serious consequences of myocardial ischemia. The aim of this investigation was to alter the structure of the common benzoylguanidine NHE inhibitors in such a way that the 3-methylsulfonyl and 4-alkyl group form a ring. The new benz-fused five-, six-, and seven-membered ring sulfones were prepared by internal Heck reaction. Benz-fused five-membered ring sulfones could also be prepared by internal aldol-type condensation using ketones or nitriles as acceptor groups. In the final step, the carboxyl groups were converted to acylguanidines preferentially by guanidine treatment of the esters or acid chlorides. The compounds were tested as their methanesulfonate salts. The inhibition of the Na^+/H^+ antiport activity was determined by observing the uptake of $^{22}Na^+$ into acidified rabbit erythrocytes. Additionally, the inhibition of the antiport activity was assessed also by the platelet swelling assay (PSA), in which the swelling of human platelets was induced by the incubation in the presence of a weak organic acid. On average, the IC_{50} values in the PSA turned out to be about 10-fold higher than in the erythrocyte assay primarily due to a higher Na^+ concentration in the PSA; however, the order of the compounds' potency was not substantially altered. The new compounds were found to be highly active with peak values ranging within the cariporide and EMD 96785 standards.

Introduction

Changes in intracellular pH (pH_i) have been implicated in the pathophysiology of essential hypertension, myocardial ischemia, postischemic dysfunction, and cellular death. However, the cells possess a means by which pH_i can be controlled and regulated. These mechanisms become vital, e.g., for the correction of intracellular acidosis during and following a period of myocardial ischemia. One of the major alkalizing exchangers (antiporters) that exists in the myocardial cell is the Na^+/H^+ exchanger (NHE), which extrudes protons by countertransport of Na^+ ions.[1] At least five distinct isoforms of the exchanger have been identified, which differ in terms of structure and sensitivity to inhibition by pharmacological agents. It appears that subtype 1 is the predominant isoform in mammalian myocardium. There is a growing body of evidence that the Na^+/H^+ antiporter plays a key role in the pathophysiology of cardiac ischemia and reperfusion.

Although activation of the Na^+/H^+ antiporter is essential for the restoration of normal pH_i, it results in a deleterious Na^+ overload after a prolonged period of ischemia. Due to coupling via the Na^+/Ca^{2+} exchanger, this causes—in the face of a complete lack of ATP resynthesis—cellular Ca^{2+} overload and finally serious contractile dysfunction, arrhythmias, and cellular death. Blockade of the Na^+/H^+ exchange has recently been shown experimentally to be a useful approach to limiting Ca^{2+} influx and its serious consequences during ischemia and reperfusion.[2] The first subtype 1 specific NHE inhibitor cariporide[3] (Hoechst Marion Roussel, Chart 1) is currently undergoing clinical evaluation in high-risk cardiac patients. Merck KGaA has started clinical trials with the structurally similar benzoylguanidine compound EMD 96785[4] in the treatment of acute myocardial infarction using an intravenous form of administration. Structure−activity relationships for the [2-methyl-5-(methylsulfonyl)benzoyl]guanidines have shown that the 4-position could be broadly varied. Substitution with alkyl groups led to highly active compounds, resulting in the idea of including both functions the 4-alkyl and the 5-methylsulfonyl groups in a fused ring.

Chart 1. Na^+/H^+ Antiporter Inhibitors under Clinical Development



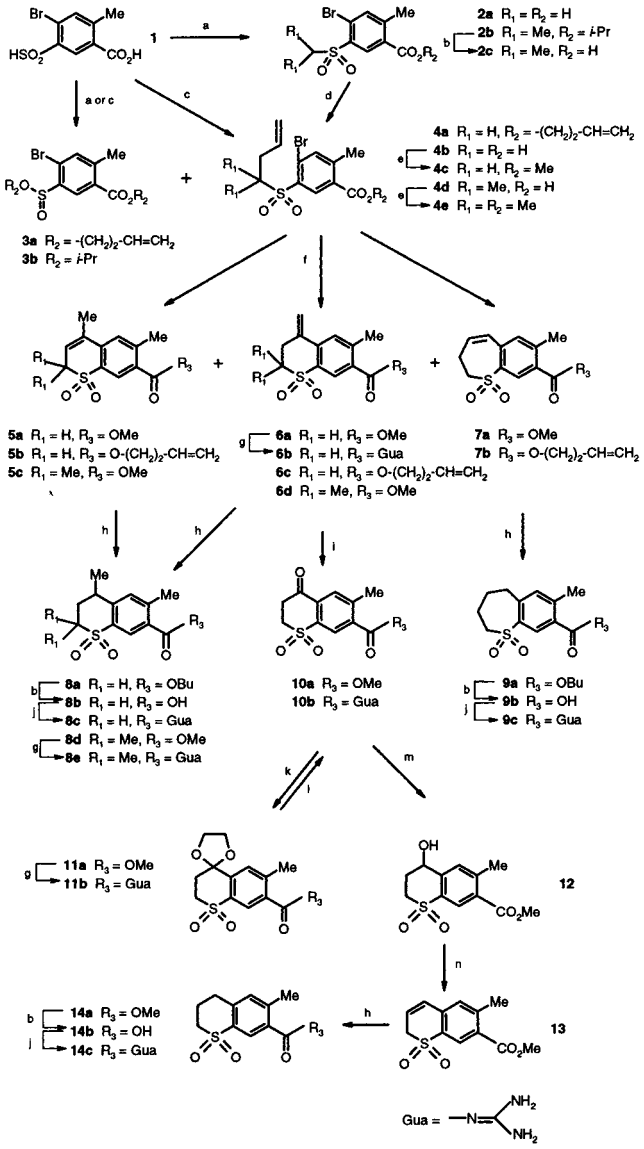
Chemistry

Benz-fused five-, six-, and seven-membered ring sulfones are known in great numbers.[5] As a rule, the sulfonyl group is produced by oxidation after ring closure. In exceptional cases, the cyclic sulfones can be prepared more directly by radical cyclization of 1-bromo-2-(but-3-enyl-1-sulfonyl)benzene compounds,[6] by electrophilic ring closure of *trans*-2-arylsulfonyl-1,2-diphenylvinyl *p*-bromobenzenesulfonates,[7] or by Friedel−Crafts cycliacylation of arylsulfonylacyl chlorides.[8] None of these methods was suitable for the synthesis of the desired higher substituted species. For our purposes, we have successfully used the internal aldol condensation[9] or Heck reaction.[10]

While alkylation of 2-bromo-4-methyl-5-carboxybenzenesulfinic acid (**1**) with MeI afforded only sulfone **2a**,[4] considerable proportions of the corresponding sulfinate esters **3a** and **3b** resulted with harder alkylating agents such as 4-bromo-1-butene and isopropyl iodide in DMF besides **2b** and **4a** (Scheme 1).[5] Alkylation of the

S0022-2623(98)01031-0 CCC: $15.00
Published on Web 08/21/1998

Scheme 1[a]

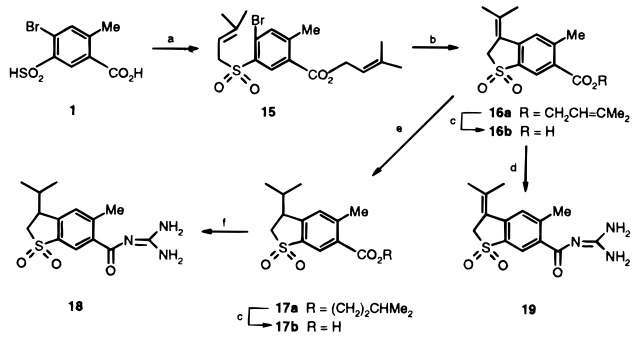


[a] (a) *i*-PrI, K_2CO_3, DMF, 90 °C; (b) NaOH, MeOH; (c) $CH_2{=}CH(CH_2)_2$-Br, K_2CO_3, DMF, 90 °C; (d) $(i\text{-Pr})_2NH$, BuLi, $CH_2{=}CHCH_2Br$, THF, −70 °C; (e) MeI, K_2CO_3, DMF; (f) Pd(II) catalyst,[20] NEt_3, DMF, 80 °C; (g) guanidine, MeOH, 50 °C; (h) H_2, Pd/C, MeOH; (i) O_3, CH_2Cl_2; (j) $SOCl_2$, guanidine, glyme; (k) $HOCH_2CH_2OH$, TsOH, PhMe, reflux; (l) HCl, dioxane; (m) $NaBH_4$, MeOH; (n) TsOH, PhMe, reflux.

sulfones **2a** and **2c** with allyl bromide followed by esterification gave the (but-3-enyl-1-sulfonyl)benzoic acid methyl esters **4c** and **4e**.

Compounds **4a**, **4c**, and **4e** were cyclized using standard Heck conditions. This led to isomeric mixtures due to double bond migration which typically takes place with this reaction.[11] Benz-fused six-membered ring sulfones with an exocyclic double bond were mainly formed, and in the case of **4c**, the ratio of isomers **5a**, **6a**, and **7a** was 31:62:7 (HPLC and NMR analysis). Compounds **5** and **6** were further reacted as a mixture, because the separation of the pure isomers proved to be nearly impossible. The saturated sulfones **8** and **9** were prepared by catalytic hydrogenation from **5**, **6**, or **7**, respectively. Ozonolysis of **6a** gave ketone **10a**, which was protected as its ethylene ketal **11a**, converted to the acylguanidine **11b** (see below), and ketone **10b** was

Scheme 2[a]



[a] (a) 3-Chloro-3-methyl-1-butene, K_2CO_3, DMF, 90 °C; (b) Pd(II) catalyst,[20] NEt_3, DMF, 110 °C; (c) NaOH, MeOH; (d) 2-chloro-1-methylpyridinium iodide, guanidine-HCl, $(i\text{-Pr})_2NEt$, NMP; (e) H_2, Pd/C; (f) $SOCl_2$, guanidine, glyme.

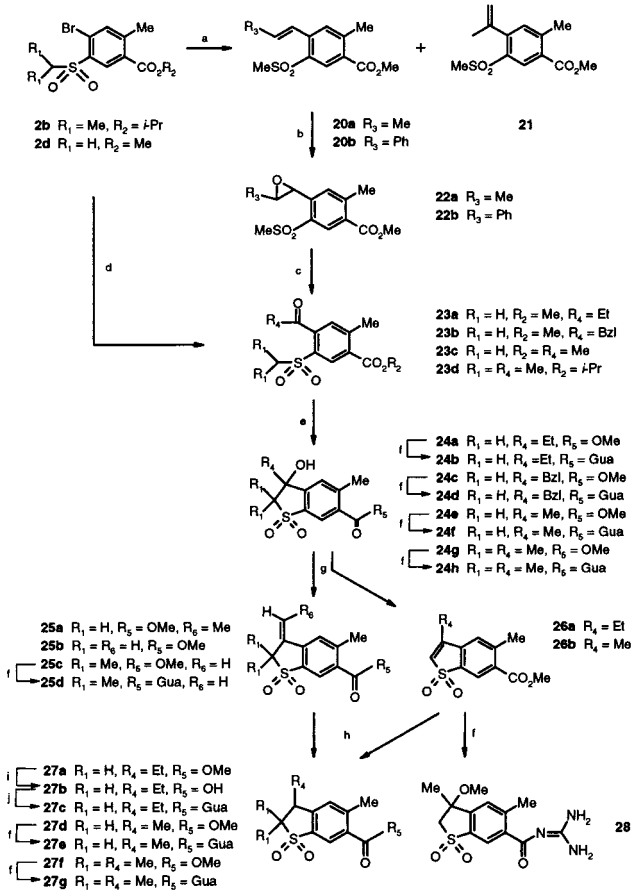
recovered on deprotection. **10a** was also reduced (→ **12**) and transferred via olefin **13** to the saturated structure **14a**.

Alkylation of **1** with 3-chloro-3-methyl-1-butene yielded the (3-methyl-but-2-enyl-1-sulfonyl)benzoic acid ester **15** under allyl inversion[12] as the only isolable product (Scheme 2). Subsequent Heck reaction formed the five-membered ring sulfone **16a** with an exocyclic double bond, which was further transformed to the saturated benzoic acid **17b** by hydrogenation and saponification.

In Scheme 3, the preparation of benz-fused five-membered ring sulfones is demonstrated by internal aldol condensation (**23** → **24**) with sodium methoxide.[9] The required 4-acetyl groups were introduced in corresponding 4-bromobenzoates **2** using (1-ethoxyvinyl)-tributylstannane in Pd-catalyzed Stille coupling followed by acidic hydrolysis of the intermediate enol ethers.[13] Alternatively, the ketones **23** were prepared by a sequence of standard reactions starting with a Heck olefination. After removal of the byproduct **21**, the olefins **20** were oxidized with 3-chloroperoxybenzoic acid (CPBA) and the epoxides **22** were rearranged using BF_3 etherate. The trans configuration of the olefins **20** (coupling constants of the olefinic protons of ≥15 Hz) should be preserved on epoxidation. Water elimination of **24** resulted in mixtures of exo- and endocyclic olefins **25** and **26**, which could not be entirely separated. In **24g**, 2-substitution produces the exocyclic olefin **25c**. A surprising product of the acylguanidine formation in methanol under basic conditions was adduct **28**. Obviously, Michael addition in **26b**, which is in equilibrium with the exocyclic form, had taken place. Hydrogenation of **25** and **26** gave the saturated benzothiophen dioxide system **27**.

Similarly as was shown with ketones in Scheme 3, the 4-cyano-5-(methylsulfonyl)benzoic acid esters **30** were cyclized using sodium methoxide in methanol (Scheme 4).[14] The enamines **31** thus formed in reasonable yield gave cyclic ketones **32** upon acidic hydrolysis. The nitriles **30** were obtained in two steps from appropriate 2-halobenzenesulfinic acids **1a** as reported recently.[4] The keto group in **32** was removed via borohydride reduction (→ **38**), H_2O elimination (→ **39**), and hydrogenation to give the saturated heterocycle **40**. Further simple transformations shown in Scheme 4 are hydrogenation of the enamine (**31c** → **33a**) and formation of ketal **34a**, oxime **35a**, and oxime ether **35c**, as

Scheme 3[a]

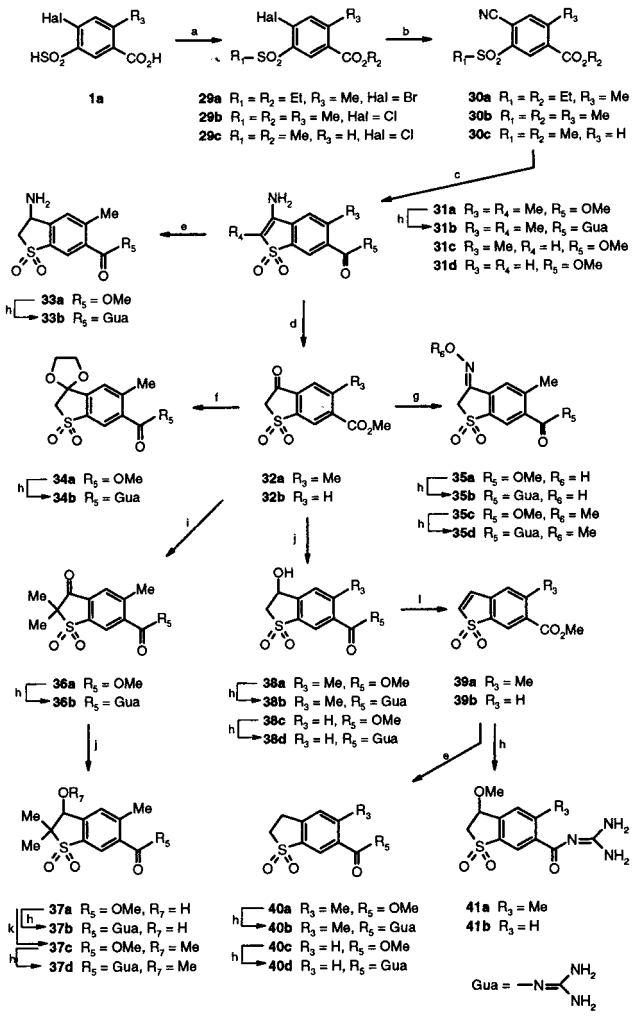


[a] (a) $MeCH{=}CH_2$ or $PhCH{=}CH_2$, Pd(II) catalyst,[20] NEt_3, DMF, 118 °C; (b) CPBA, CH_2Cl_2; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, reflux; (d) (1-ethoxyvinyl)tributylstannane, LiCl, $Pd(PPh_3)_4$, THF, reflux, HCl; (e) Na, MeOH, 40 °C; (f) guanidine, MeOH, 50 °C; (g) TsOH, PhMe, reflux; (h) H_2, Pd/C, MeOH; (i) NaOH, MeOH; (j) $SOCl_2$, guanidine, glyme.

well as a 2-fold alkylation in 2-position (→ **36a**), the latter all starting from ketone **32a**. In addition to that, 2,2-dimethyl compound **36a** was reduced (→ **37a**) and etherified (→ **37c**). NOE experiments revealed *Z*-configuration of the oxime derivatives **35a** and **35c**.

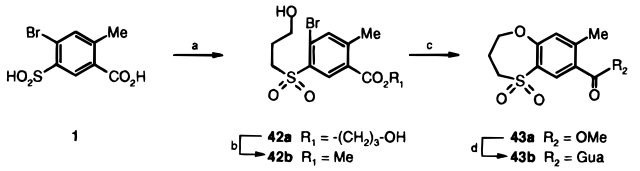
The preparation of O-containing ring sulfones **43** and **48** (Schemes 5 and 6) was achieved by intramolecular nucleophilic substitution reaction. A suitable precursor for the seven-membered ring compound **43a** was alcohol **42b**, which could be obtained as before via alkylation of the sulfinic acid **1** with 3-iodopropanol. Its six-ring equivalent **48b**, however, suffered retro-Michael ring opening to the 2-vinylsulfonyl phenol. To prevent this, the structure was stabilized by two additional methyl groups (→ **48a**), the precursor of which (→ **46)** was synthesized by formaldehyde treatment of isopropyl sulfone **45b** using LDA for deprotonation. This reaction also took place at a methyl adjacent to the carboxy group forming a considerable amount of lactone **47** besides. The 4,4-dimethyl-1,1-dioxothiochroman system **55** was prepared more conventionally (Scheme 7).[15] Michael addition of *m*-thiocresol (**50**) to methyl vinyl ketone and mesityl oxide, respectively, gave ketones **51**, which were converted to the tertiary alcohols **52** by Grignard addition of MeMgI. These were cyclized using Friedel–Crafts conditions (→ **53**) followed by perborate (→ **54**)

Scheme 4[a]



[a] (a) EtI, K_2CO_3, NMP, 60 °C; (b) CuCN, NMP, 160 °C; (c) Na/MeOH, 50 °C; (d) HCl, dioxane, reflux; (e) H_2, Pd/C, DMF or MeOH; (f) $HOCH_2CH_2OH$, TsOH, PhMe, reflux; (g) $HONH_2{\cdot}HCl$ or $MeONH_2{\cdot}HCl$, MeOH, H_2O, reflux; (h) guanidine, MeOH, 50 °C; (i) NaH, MeI, DMF; (j) $NaBH_4$, CH_2Cl_2/MeOH; (k) MeI, DMF, 40 °C; (l) TsCl, pyridine, reflux.

Scheme 5[a]



[a] (a) $I(CH_2)_3OH$, K_2CO_3, DMF, 65 °C; (b) NaOH, CH_2N_2, MeOH; (c) NaH, NMP, 60 °C; (d) guanidine, MeOH, 50 °C.

and permanganate oxidation to give sulfonylbenzoic acids **55a** and **55c**.

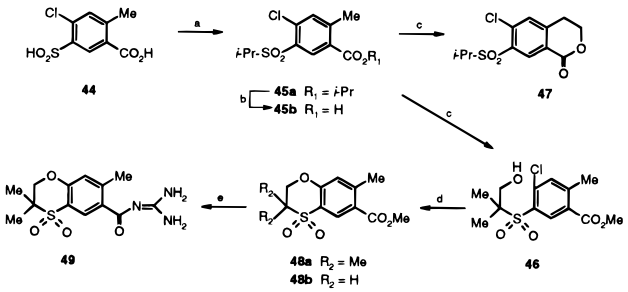
In the final step of each synthesis, the carboxylic acids prepared were reacted with guanidine to give acylguanidines (Schemes 1–7). Esters (method P) and acid chlorides (method Q) are suitable derivatives for this acylation reaction. Further methods can be used, such as Mukaiyama's procedure[16] (method S), which enables conversion of free acids. Physicochemical data of the prepared acylguanidines are summarized in Table 1. The compounds were characterized either as free bases or as their methanesulfonic and hydrochloric salts. The

Table 1. Acylguanidines of Schemes 1-7

compd	method	yield (%)	mp (°C)	recrystn solvent	formula	anal[a]	$^{22}Na^+$ UIA[b] IC_{50}[c] (nM)	PSA[d] IC_{50}[e] (nM)
6b	P	27	214−215	MeCN	$C_{13}H_{15}N_3O_3S\cdot CH_4O_3S\cdot 0.75H_2O$	C, H, N, S	29	1366
8c	Q	38	204−205	H_2O	$C_{13}H_{17}N_3O_3S$	C, H, N, S	45	655
8e	P	25	256	Me_2CO/MeOH	$C_{15}H_{21}N_3O_3S\cdot CH_4O_3S\cdot 0.25H_2O$	C, H, N, S	38	1099
9c	Q	48	168−170 dec	Me_2CO	$C_{13}H_{17}N_3O_3S\cdot CH_4O_3S$	C, H, N, S	19	274
10b	R	82	314	dioxane/H_2O	$C_{12}H_{13}N_3O_4S\cdot HCl$	C, H, Cl, N, S	96	3666
11b	P	49	237−238	Et_2O	$C_{14}H_{17}N_3O_5S\cdot 0.5H_2O$	C, H, N, S	130	1181
14c	Q	40	305	Me_2CO	$C_{12}H_{15}N_3O_3S\cdot CH_4O_3S$	C, H, N, S	95	14292
18	Q	65	194−196	H_2O	$C_{14}H_{19}N_3O_3S\cdot 0.25H_2O$	C, H, N, S	21	77
19	S	22	299	Me_2CO	$C_{14}H_{17}N_3O_3S\cdot CH_4O_3S\cdot 0.25H_2O$	C, H, N, S	54	5034
24b	P	35	218−220	Me_2CO	$C_{13}H_{17}N_3O_4S\cdot CH_4O_3S\cdot 0.5H_2O$	C, H, N, S	34	77
24d	P	16	225	Me_2CO	$C_{18}H_{19}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	43	157
24f	P	60	214−216	Me_2CO/MeOH	$C_{12}H_{15}N_3O_4S\cdot CH_4O_3S\cdot 0.25H_2O$	C, H, N, S	30	115
24h	P	28	195−196	Me_2CO	$C_{14}H_{19}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	17	102
25d	P	8	245−246	MeOH	$C_{14}H_{17}N_3O_3S\cdot CH_4O_3S$	C, H, N, S	13	114
27c	Q	23	178	Et_2O	$C_{13}H_{17}N_3O_3S$	C, H, N, S	24	78
27e	P	36	245−248	Me_2CO/MeOH	$C_{12}H_{15}N_3O_3S\cdot CH_4O_3S$	C, H, N, S	44	182
27g	P	56	212−213	Me_2CO/MeOH	$C_{14}H_{19}N_3O_3S\cdot CH_4O_3S$	C, H, N	14	306
28	P	21	214−215	MeOH	$C_{13}H_{17}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	40	321
31b	P	39	269−270	MeOH/CH_2Cl_2	$C_{12}H_{14}N_4O_3S\cdot CH_4O_3S$	C, H, N, S	56	2322
33b	P	27	242−243	EtOAc	$C_{11}H_{14}N_4O_3S$	C, H, N, S	116	692
34b	P	9	285−287	MeOH	$C_{13}H_{15}N_3O_5S\cdot CH_4O_3S$	C, H, N, S	60	485
35b	P	14	250	MeOH	$C_{11}H_{12}N_4O_4S\cdot CH_4O_3S$	C, H, N, S	16	197
35d	P	33	284	EtOAc	$C_{12}H_{14}N_4O_4S\cdot CH_4O_3S$	C, H, N, S	45	521
36b	P	19	250−251	MeOH	$C_{13}H_{15}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	93	354
37b	P	23	262−263	MeOH	$C_{13}H_{17}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	28	258
37d	P	57	284−285	MeOH	$C_{14}H_{19}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	27	138
38b	P	13	258−260	MeOH	$C_{11}H_{13}N_3O_4S\cdot CH_4O_3S$	C, H, N	70	1054
38d	P	50	204−206	MeOH	$C_{10}H_{11}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	1500	NE[f]
40b	P	36	299−301	MeOH	$C_{11}H_{13}N_3O_3S\cdot CH_4O_3S$	C, H, N, S	60	587
40d	P	76	264−265	MeOH	$C_{10}H_{11}N_3O_3S\cdot CH_4O_3S$	C, H, N, S	790	NE
41a	P	72	249−251	MeOH	$C_{12}H_{15}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	96	208
41b	P	40	233−234	MeOH	$C_{11}H_{13}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	700	NE
43b	P	35	224−226	Me_2CO/MeOH	$C_{12}H_{15}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	28	537
49	P	28	243−244	MeOH	$C_{13}H_{17}N_3O_4S\cdot CH_4O_3S$	C, H, N, S	36	843
55b	Q	43	270−271	MeOH	$C_{13}H_{17}N_3O_3S\cdot CH_4O_3S$	C, H, N, S	2200	NT[g]
55d	Q	27	267−268	MeOH/CH_2Cl_2	$C_{15}H_{21}N_3O_3S\cdot CH_4O_3S$	C, H, N, S	360	2076
cariporide							26	117
EMD 96785							8	32

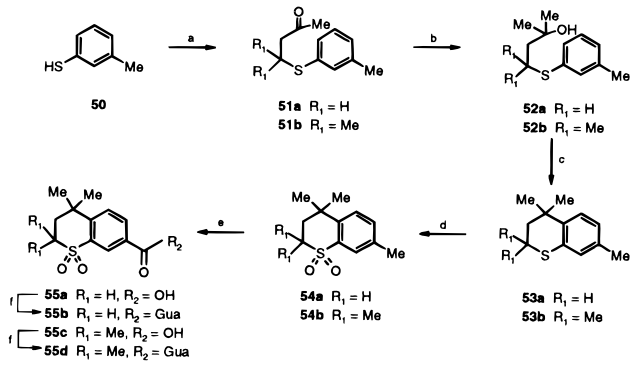
[a] Analyses for the elements indicated were within ±0.4% of the theoretical values. [b] $^{22}Na^+$ uptake inhibition assay. [c] Drug concentration to achieve half-maximal inhibition of the EIPA-sensitive $^{22}Na^+$ uptake into rabbit erythrocytes. [d] Platelet swelling assay. [e] Drug concentration to achieve half-maximal inhibition of acid-induced swelling in human platelets. [f] Compounds with IC_{50} values of >100 μM. [g] Not tested.

Scheme 6[a]



[a] (a) *i*-PrI, DMF; (b) NaOH; (c) LDA, CH_2O, THF, −35 °C, MeI, K_2CO_3, MeCOEt; (d) NaH, NMP, 60 °C; (e) guanidine, MeOH, 60 °C.

Scheme 7[a]



[a] (a) Methyl vinyl ketone or mesityl oxide, NEt_3, $CHCl_3$, reflux; (b) MeMgI, Et_2O; (c) $AlCl_3$, CS_2, reflux; (d) $NaBO_3$, AcOH, 55 °C; (e) $KMnO_4$, Aliquat, pyridine, H_2O, reflux; (f) $SOCl_2$, guanidine, glyme.

different preparation methods (P−S) are described at the end of the Experimental Section.

Results and Discussion

The Na^+/H^+ antiport activity was assessed by observing the uptake of $^{22}Na^+$ into acidified rabbit erythrocytes.[4,17] The EIPA-sensitive portion of the $^{22}Na^+$ uptake into acidified erythrocytes was taken as the Na^+/H^+-dependent $^{22}Na^+$ uptake. With the exception of the hydrochloride **10b**, all compounds were tested as their methanesulfonate salts. IC_{50} values of the new acylguanidines are given in Table 1 and are compared with the leads cariporide and EMD 96785. As a fundamental result of investigating the structure−activity relationship of a large number of benzoylguanidines, we recently demonstrated the superiority of the 2-methyl species over their respective demethyl counterparts.[4] The same

holds true for the bicyclic acylguanidines described here. In those cases where both forms could be compared (**38b** and **38d**, **40b** and **40d**, and **41a** and **41b**), the methyl analogues were found to be more potent by a factor of at least 6. Low in vitro activity was also found for two compounds of the six-membered ring series (**55b** and **55d**) in which the methyl analogues are missing.

The remaining compounds of Table 1 all have a methyl group adjacent to the acylguanidine, which obviously favors the spatial orientation for receptor docking. The ring size seems not to have a particular influence on the biological activity of the new Na^+/H^+ antiporter inhibitors. An opinion about the seven-membered ring cannot be formulated because the number is too small (**9c** and **43b**), though, only **9c** is superior to its unsubstituted six- and five-ring analogues (**14c** and **40b**). The most active compounds (**24h**, **25d**, **27g**, and **35b**) can be found among the five-ring compounds, but a weak candidate (**33b**) is also found within this class. Dimethyl substitution adjacent to the sulfonyl group seems to be advantageous. This can particularly be stated in direct comparison with the unsubstituted species (**8e** vs **8c**, **24h** vs **24f**, and **27g** vs **27e**). Substitution at the α-position of the aromatic ring as well as the insertion of oxygen into the carbon chain in that position gave varying results.

In summary, it was thus established that the new bicyclic acylguanidines belong to a group of potent Na^+/H^+ antiporter inhibitors, some exceeding the in vitro activity of cariporide and measuring up to the standard of Merck's EMD 96785. In our previous paper on [2-methyl-5-(methylsulfonyl)benzoyl]guanidines,[4] we have presented, among others, highly potent compounds bearing alkyl groups in the 4-position. The object of this study was to fit together the 4-alkyl and the 5-methylsulfonyl groups in a fused ring. This concept was only partly realized as some peak values of the ring-open compounds could not be fully reached.

For the measurement of NHE activity and its inhibition by appropriate compounds, the so-called platelet swelling assay was introduced by Livne et al.,[18] which was further developed into a simple optical test by Rosskopf.[19] After addition of platelet-rich plasma to an acidic buffer containing sodium propionate, the undissociated acid will diffuse into the platelets, causing an intracellular acidification. This in turn will lead to an activation of the NHE, which results in the accumulation of Na^+ ions and obligate H_2O molecules. The increase in platelet cell volume can be followed photometrically by a decrease in the optical density (OD) of the platelet containing incubation buffer. In the presence of an NHE inhibitor, this decrease in OD can be suppressed. The platelet swelling assay appears to be useful in characterizing newly derived NHE inhibitors with regard to their effect on human NHE since human blood and platelet-rich plasma can be obtained easily. Therefore, the compounds described in this paper have also been investigated with regard to their inhibitory activity in the platelet swelling test.

In Table 1, the results of this investigation are summarized. It is obvious from comparison with the results of the $^{22}Na^+$ uptake inhibition assay that the IC_{50} values in the platelet swelling test are higher. On average, the IC_{50} values in the platelet swelling test turned out to be about 10-fold higher than in the erythrocyte assay. However, this increase in the apparent IC_{50} values can be attributed to an essential difference in the assay conditions. While in the erythrocyte-based assay the Na^+ concentration in the incubation buffer was 10 mM, the Na^+ concentration in the platelet swelling test was 12-fold higher (120 mM). In pilot experiments, we had been able to show that the apparent IC_{50} values in both assays are dependent on the extracellular Na^+ concentration. The order of potency of the compounds was not affected substantially by the different sensitivity of the assays (Spearman's rank correlation coefficient $\rho = 0.65$).

Conclusion

The in vitro NHE activity of the bicyclic acylguanidines prepared was assessed with two independent methods: (a) the $^{22}Na^+$ uptake inhibition assay with rabbit erythrocytes and (b) the platelet swelling assay with human platelet-rich plasma. This is the first study comparing both methods with a considerable number of compounds. Obviously due to different Na^+ concentrations in the two assays, the IC_{50} values in the platelet swelling assay are about 1 order of magnitude higher than those in the erythrocyte assay. The potency order in both biological tests was largely retained, and in structure−activity relationship studies, high activities were found with the new compounds. Those compounds bearing a 2-methyl group were considerably more active than the respective demethyl analogues. The activity of cariporide but not that of EMD 96785 could be exceeded with some of the new compounds; in general, the superiority of the monocyclic over the bicyclic acylguanidines could be established. Inhibition of Na^+/H^+ antiport represents a novel principle in the therapy of myocardial ischemia and its deleterious consequences. The effectiveness of NHE inhibitors has already been impressively confirmed in animal experiments. Clinical studies are under way with the two benzoylguanidines cariporide and EMD 96785 in the prevention and treatment of myocardial infarction, respectively. The platelet swelling assay using human platelet-rich plasma appears to be useful in the context of clinical studies with EMD 96785, in volunteers as well as in patients, to determine ex vivo the degree of NHE inhibition after intravenous administration.

Experimental Section

Melting points were determined with a Büchi 535 melting point apparatus and are uncorrected. IR and NMR spectra are consistent with the structures cited and were recorded on a Bruker IFS 48 IR spectrophotometer and a Bruker AM 250 or DRX 500 NMR spectrometer, respectively. All NMR spectra were recorded in DMSO-d_6, and chemical shifts are given in parts per million (δ) downfield from tetramethylsilane. J values are in hertz. Microanalyses were obtained with an elementar vario EL analyzer. Silica gel 60 (particle size of 0.063−0.200 mm, from Merck KGaA, Darmstadt, Germany) was used for column chromatography.

Method A. 4-Bromo-5-(but-3-enyl-1-sulfonyl)-2-methylbenzoic Acid But-3-enyl Ester (4a). A mixture of 2-bromo-4-methyl-5-carboxybenzenesulfinic acid[4] (**1**, 10 g, 35.8 mmol), 4-bromo-1-butene (10 mL, 98.5 mmol), and K_2CO_3 (20 g, 145 mmol) was heated in DMF (50 mL) at 90 °C for 1 h. H_2O (500 mL) was added; the reaction mixture was extracted with EtOAc (3 × 150 mL), and the combined organic layers were dried, filtered, and concentrated. The residue was chromato-

graphed on a silica gel column (petroleum ether → Et_2O as a gradient elution). The chromatographically homogeneous nonpolar fractions were combined to give a colorless oil of 4-bromo-5-(but-3-enyloxysulfinyl)-2-methylbenzoic acid but-3-enyl ester (**3a**, 2.93 g, 21%): NMR δ 2.33 (q, J = 6.4, 2H), 2.50 (m, 2H), 2.58 (s, 3H), 3.75 (m, 1H), 4.08 (m, 1H), 4.36 (t, J = 6.5, 2H), 5.02−5.22 (m, 4H), 5.65−5.95 (m, 2H), 7.82 (s, 1H), 8.19 (s, 1H); IR (capillary film) 1725, 1251, 1149, 1093 cm^{-1}. Anal. ($C_{16}H_{19}BrO_4S$) C, H, Br, S.

4a was obtained from the polar fractions as a colorless oil (5.21 g, 38%): NMR δ 2.35 (q, J = 7.7, 2H), 2.50 (m, 2H), 2.60 (s, 3H), 3.60 (t, J = 7.6, 2H), 4.37 (t, J = 6.5, 2H), 4.97−5.22 (m, 4H), 5.66−5.99 (m, 2H), 7.96 (s, 1H), 8.41 (s, 1H); IR (capillary film) 1725, 1258, 1242, 1139, 1090 cm^{-1}. Anal. ($C_{16}H_{19}BrO_4S$) C, H, Br, S.

Similarly prepared were the following compounds.

4-Bromo-2-methyl-5-(propanyl-2-sulfonyl)benzoic acid isopropyl ester (2b): 25% yield; mp 64−65 °C (petroleum ether); NMR δ 1.22 (d, J = 6.9, 6H), 1.35 (d, J = 6.2, 6H), 2.61 (s, 3H), 3.83 (sept, J = 6.8, 1H), 5.17 (sept, J = 6.2, 1H), 7.97 (s, 1H), 8.36 (s, 1H); IR (KBr) 1717, 1315, 1288, 1251, 1086 cm^{-1}. Anal. ($C_{14}H_{19}BrO_4S$) C, H, Br, S.

4-Bromo-5-(isopropoxysulfinyl)-2-methylbenzoic acid isopropyl ester (3b): 14% yield; mp 55−56 °C [petroleum ether/(i-Pr)$_2$O]; NMR δ 1.21 (d, J = 6.2, 3H), 1.34 (m, 9H), 2.58 (s, 3H), 4.61 (sept, J = 6.2, 1H), 5.17 (sept, J = 6.3, 1H), 7.80 (s, 1H), 8.17 (s, 1H); IR (KBr) 1712, 1241, 1103, 1086 cm^{-1}. Anal. ($C_{14}H_{19}BrO_4S$) C, H, Br, S.

4-Bromo-2-methyl-5-(propanyl-2-sulfonyl)benzoic Acid (2c). 2c was prepared by ester hydrolysis of **2b** according to method E in 84% yield as white crystals: mp 210−211 °C (Me_2-CO/EtOAc); NMR δ 1.20 (d, J = 6.7, 6H), 2.62 (s, 3H), 3.80 (sept, J = 6.8, 1H), 7.94 (s, 1H), 8.40 (s, 1H); IR (KBr) 1694, 1314, 1302, 1255 cm^{-1}. Anal. ($C_{11}H_{13}BrO_4S$) C, H, S.

Method B. 4-Bromo-5-(but-3-enyl-1-sulfonyl)-2-methylbenzoic Acid Methyl Ester (4c). A 1 L, three-necked flask equipped with a mechanical stirrer, dropping funnel, drying tube, N_2 inlet, and a thermometer was charged with dry THF (400 mL). After the THF solution was cooled to −70 °C, diisopropylamine (21 mL, 149 mmol), butyllithium (92 mL, 1.6 M hexane solution, 147 mmol), and 4-bromo-2-methyl-5-(methylsulfonyl)benzoic acid[4] (**2a**, 16.5 g, 56.3 mmol) dissolved in THF (200 mL) were slowly added, and the mixture was stirred for an additional 1 h at this temperature. Allyl bromide (15 mL, 177 mmol) was dropped in at −70 °C, and the cold bath was removed. After a 30 min period of stirring, H_2O (300 mL) was added with care, and the mixture was washed with EtOAc (250 mL), acidified, and extracted with EtOAc (2 × 200 mL). The combined organic phases were dried and evaporated, leaving an oily mixture of acids (20 g). This was esterified with MeI (20 mL, 320 mmol) and K_2CO_3 (50 g, 362 mmol) in DMF (200 mL) at room temperature overnight. H_2O (800 mL) was added; the reaction mixture was extracted with EtOAc (3 × 200 mL), and the combined organic layers were dried, filtered, and concentrated. After separation of a nonpolar byproduct by silica gel chromatography (petroleum ether → Et_2O), the title compound **4c** (5.56 g) was isolated in a 28% overall yield: mp 88−89 °C; NMR δ 2.36 (q, J = 5.1, 2H), 2.61 (s, 3H), 3.61 (t, J = 7.6, 2H), 3.88 (s, 3H), 4.98−5.10 (m, 2H), 5.68−5.84 (m, 1H), 7.97 (s, 1H), 8.41 (s, 1H); IR (KBr) 1707, 1310, 1296, 1259, 1149 cm^{-1}. Anal. ($C_{13}H_{15}BrO_4S$) C, H, Br, S.

An analytical sample of the 4-bromo-5-(but-3-enyl-1-sulfonyl)-2-methylbenzoic acid (**4b**) was prepared by alkaline resaponification from **4c**: mp 149−150 °C (Et_2O/EtOAc); NMR δ 2.35 (q, J = 7.3, 2H), 2.61 (s, 3H), 3.60 (t, J = 7.7, 2H), 4.97−5.10 (m, 2H), 5.68−5.84 (m, 1H), 7.93 (s, 1H), 8.41 (s, 1H), 13.50 (s br, 1H). Anal. ($C_{12}H_{13}BrO_4S$) C, H, S.

4-Bromo-2-methyl-5-(2-methylpent-4-enyl-2-sulfonyl)-benzoic Acid Methyl Ester (4e). 4e was similarly prepared from **2c** as white crystals in a 24% overall yield: mp 91−92 °C [(i-Pr)$_2$O/petroleum ether]; NMR δ 1.26 (s, 6H), 2.42 (d, J = 7.4, 2H), 2.61 (s, 3H), 3.88 (s, 3H), 5.16 (m, 2H), 5.72−5.88 (m, 1H), 7.96 (s, 1H), 8.36 (s, 1H); IR (KBr) 1707, 1308, 1256, 1161, 1097 cm^{-1}. Anal. ($C_{15}H_{19}BrO_4S$) C, H, Br, S.

Method C. 7-Methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiepine-8-carboxylic Acid Methyl Ester (7a). A mixture of the ester **4c** (3.8 g, 11 mmol) and *trans*-di(μ-acetato)-bis[(*o*-di-*o*-tolylphosphino)benzyl]dipalladium(II)[20] (300 mg, 0.32 mmol) in NEt_3 (8 mL) and DMF (4 mL) was stirred under an N_2 atmosphere at 80 °C for 3 h. A second portion of the Pd catalyst (200 mg, 0.21 mmol) was added, and the solution was heated for an additional 1 h. The Et_3N portion of the mixture was stripped, and the remaining dark oil was chromatographed on silica gel (petroleum ether → Et_2O) and triturated with (i-Pr)$_2$O to give a mixture of isomers **5a**, **6a**, and **7a** (1.35 g, 46%) as a white solid. HPLC analysis showed a 7:93 ratio of compound **7a**:**5a** and **6a**, which were not split [t_R = 10.69 and 11.37, 0.1 M NaH_2PO_4/MeCN (3:2), flow rate of 1 mL/min, LiChrosorb RP-18 (5 μm), 250-4; Merck KGaA, catalog no. 1.50333]. A 610 mg portion of the mixture was chromatographed again on a Merck Prebar 250-50 steel cartridge (LiChrospher Si 60, 10 μm), with gradient elution (petroleum ether → Et_2O). The combined nonpolar fractions were triturated with (i-Pr)$_2$O to give a 1:3 mixture of isomers **5a** and **6a** (450 mg, 34%); NMR data of **5a** δ 2.21 (q, J = 1.6, 3H), 2.65 (s, 3H), 3.88 (s, 3H), 4.21 (d br, J = 5.2, 2H), 6.24 (t br, 1H), 7.59 (s, 1H), 8.24 (s, 1H); NMR data of **6a** δ 2.61 (s, 3H), 3.13 (t, J = 6.4, 2H), 3.58 (t, J = 6.4, 2H), 3.87 (s, 3H), 5.52 (t, J = 1.4, 1H), 6.07 (s, 1H), 7.90 (s, 1H), 8.20 (s, 1H).

The homogeneous polar fractions were combined, triturated with (i-Pr)$_2$O, and dried to obtain the title compound **7a** (34 mg, 2.6%): mp 147 °C; NMR δ 2.59 (s, 3H), 2.83 (m, 2H), 3.61 (t, J = 6.5, 2H), 3.88 (s, 3H), 6.14−6.23 (m, 1H), 6.59 (d br, J = 13.1, 1H), 7.53 (s, 1H), 8.39 (s, 1H). Anal. ($C_{13}H_{14}O_4S$) C, H, S. Analogous treatment of **4a** and **4e** gave isomeric mixtures of **5b**, **6c**, **7b** or **5c** and **6d**, respectively, which were further reacted without separation.

Method D. 4,6-Dimethyl-1,1-dioxo-1λ^6-thiochroman-7-carboxylic Acid Butyl Ester (8a) and 7-Methyl-1,1-dioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo[*b*]thiepine-8-carboxylic Acid Butyl Ester (9a). A mixture of isomeric esters **5b**, **6c**, and **7b** (5 g, 16.3 mmol) was hydrogenated with a Pd/C catalyst (5%, 1 g) in MeOH (50 mL) at atmospheric pressure for 1 h. The solvent was removed, and the residue was chromatographed on silica gel (petroleum ether → Et_2O). The homogeneous nonpolar fractions were combined to yield compound **9a** (385 mg, 8%) as a white solid on trituration with (i-Pr)$_2$O: mp 81−82 °C; NMR δ 0.94 (t, J = 8.9, 3H), 1.42 (m, 2H), 1.70 (m, 4H), 2.09 (m, 2H), 2.58 (s, 3H), 3.10 (m, 2H), 3.37 (t br, J = 5.9, 2H), 4.29 (t, J = 6.5, 2H), 7.43 (s, 1H), 8.31 (s, 1H); IR (KBr) 1720, 1287, 1248, 1092 cm^{-1}. Anal. ($C_{16}H_{22}O_4S$) C, H, S.

The homogeneous polar fractions of the main component (2.65 g) were combined and further purified by Kugelrohr distillation (0.2 Torr, 200 °C bath temperature) to give **8a** (1.85 g, 37%) as a syrup; NMR δ 0.94 (t, J = 7.3, 3H), 1.36 (d, J = 7.0, 3H), 1.43 (m, 2H), 1.71 (qi, J = 7.0, 2H), 2.06−2.22 (m, 1H), 2.42−2.52 (m, 1H), 2.57 (s, 3H), 3.17 (m, 1H), 3.43−3.63 (m, 2H), 4.29 (t, J = 6.5, 2H), 7.47 (s, 1H), 8.15 (s, 1H); IR (capillary film) 1728, 1308, 1254, 1102 cm^{-1}. Anal. ($C_{16}H_{22}O_4S$) C, H, S.

2,2,4,6-Tetramethyl-1,1-dioxo-1λ^6-thiochroman-7-carboxylic Acid Methyl Ester (8d). Analogous hydrogenation of a **5c**/**6d** mixture furnished compound **8d** as white crystals in 88% yield: mp 128−129 °C (THF); NMR δ 1.32 (s, 3H), 1.39 (s, 3H), 1.40 (d, J = 6.9, 3H), 2.11−2.31 (m, 2H), 2.62 (s, 3H), 3.15−3.25 (m, 1H), 3.90 (s, 3H), 7.57 (s, 1H), 8.24 (s, 1H); IR (KBr) 1727, 1282, 1249, 1094 cm^{-1}. Anal. ($C_{15}H_{20}O_4S\cdot 0.25H_2O$) C, H; S: calcd, 10.66; found, 11.31.

Method E. 4,6-Dimethyl-1,1-dioxo-1λ^6-thiochroman-7-carboxylic Acid (8b). A mixture of ester **8a** (600 mg, 1.94 mmol), 1 N NaOH (10 mL), and MeOH (15 mL) was stirred at room temperature for 2 h. The MeOH portion was evaporated, and the resulting aqueous phase was diluted with ice/water (20 mL) and acidified with 1 N HCl to give **8b** (460 mg, 93%): mp 158−160 °C; NMR δ 1.36 (d, J = 7.2, 3H), 2.06−2.21 (m,

1H), 2.41−2.54 (m, 1H), 2.58 (s, 3H), 3.11−3.24 (m, 1H), 3.41−3.61 (m, 2H), 7.43 (s, 1H), 8.17 (s, 1H), 13.19 (s br, 1H); IR (KBr) 1701, 1300, 1282, 1261, 1106 cm^{-1}. Anal. ($C_{12}H_{14}O_4S$) C, H, S.

7-Methyl-1,1-dioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo[*b*]-thiepine-8-carboxylic Acid (9b). Alkaline hydrolysis of **9a** gave **9b** in 56% yield: mp 236−238 °C (H_2O); NMR δ 1.74 (m br, 2H), 2.09 (m br, 2H), 2.59 (s, 3H), 3.09 (m, 2H), 3.36 (t, J = 5.9, 2H), 7.39 (s, 1H), 8.33 (s, 1H), 13.20 (s br, 1H). Anal. ($C_{12}H_{14}O_4S\cdot0.5H_2O$) C, H, S.

Method F. 6-Methyl-1,1,4-trioxo-1λ^6-thiochroman-7-carboxylic Acid Methyl Ester (10a). An isomeric mixture of **5a** and **6a** (1:3, 3.05 g, 11.5 mmol) in CH_2Cl_2 (100 mL) was ozonized (model 503 Fischer ozone generator, flow rate of 50 mL/min) at −70 °C for 45 min until the solution turned blue. Me_2S (1 mL, 13.7 mmol) was added, and the mixture was allowed to stand overnight at room temperature. The solvent was removed, and the residue was triturated with Et_2O to obtain a white solid of the title compound (2.10 g, 89% referring to the **6a** proportion): mp 108−110 °C dec; NMR δ 2.64 (s, 3H), 3.29 (t, J = 6.3, 2H), 3.91 (s, 3H), 4.04 (t, J = 6.3, 2H), 7.95 (s, 1H), 8.23 (s, 1H); IR (KBr) 1730, 1692, 1310, 1290, 1266, 1251, 1109, 868 cm^{-1}. Anal. ($C_{12}H_{12}O_5S\cdot0.25H_2O$) C, H, S.

Method G. 6′-Methyl-1′,1′-dioxo[1,3-dioxolan-2,4′-1λ^6-thiochroman]-7′-carboxylic Acid Methyl Ester (11a). Ketone **10a** (2.7 g, 10.1 mmol), *p*-toluenesulfonic acid (150 mg, 0.87 mmol), and ethylene glycol (3 mL, 53.6 mmol) were refluxed in absolute PhMe (90 mL) for 2 h with a Dean-Stark apparatus. The solvent was evaporated and the residue purified by chromatography (silica gel, petroleum ether → Et_2O → EtOAc). The homogeneous fractions were combined, evaporated, and triturated with Et_2O to give **11a** (1.35 g, 43%): mp 176−177 °C; NMR δ 2.48−2.58 (m, 2H), 2.61 (s, 3H), 3.69 (m, 2H), 3.88 (s, 3H), 4.13 (m, 2H), 4.25 (m, 2H), 7.60 (s, 1H), 8.14 (s, 1H); IR (KBr) 1731, 1292, 1251, 1105, 1086 cm^{-1}. Anal. ($C_{14}H_{16}O_6S$) C, H, S.

Method H. 4-Hydroxy-6-methyl-1,1-dioxo-1λ^6-thiochroman-7-carboxylic Acid Methyl Ester (12). Ketone **10a** (2.1 g, 7.83 mmol) in MeOH (100 mL) was reduced with $NaBH_4$ (500 mg, 13.2 mmol). The solvent was evaporated, and the residue was taken up in H_2O (200 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were dried and evaporated, and the residue was triturated with Et_2O (1.55 g, 72%): mp 125−126 °C; NMR δ 2.25−2.39 (m, 1H), 2.44−2.58 (m, 1H), 2.59 (s, 3H), 3.52−3.69 (m, 2H), 3.87 (s, 3H), 4.80 (q, J = 6.1, 1H), 5.94 (d, J = 6.2, 1H), 7.59 (s, 1H), 8.13 (s, 1H); IR (KBr) 3483, 1722, 1303, 1264, 1122, 1104, 1045 cm^{-1}. Anal. ($C_{12}H_{14}O_5S\cdot0.5H_2O$) C, H, S.

Method I. 6-Methyl-1,1-dioxo-1,2-dihydro-1λ^6-thiochromene-7-carboxylic Acid Methyl Ester (13). A mixture of the foregoing compound **12** (1.5 g, 9.30 mmol) and *p*-toluenesulfonic acid (100 mg, 0.58 mmol) was refluxed in absolute PhMe (100 mL) for 100 h with a Dean-Stark apparatus. The solvent was evaporated and the residue purified by chromatography (silica gel, EtOAc → MeOH). The homogeneous fractions were combined, evaporated, and triturated with Et_2O (740 mg, 53%). An analytical sample was prepared by recrystallization from *i*-PrOH: mp 185−186 °C; NMR δ 2.61 (s, 3H), 3.88 (s, 3H), 4.28 (m, 2H), 6.41 (m, 1H), 6.87 (d br, J = 10.2, 1H), 7.51 (s, 1H), 8.22 (s, 1H); IR (KBr) 1715, 1301, 1276, 1253, 1135, 1104 cm^{-1}. Anal. ($C_{12}H_{12}O_4S$) C, H, S.

6-Methyl-1,1-dioxo-1λ^6-thiochroman-7-carboxylic acid methyl ester (14a) was prepared by hydrogenation of the foregoing compound **13** according to method D in a 78% yield: mp 109 °C; NMR δ 2.33 (m, 2H), 2.55 (s, 3H), 3.01 (t, J = 6.2, 2H), 3.51 (m, 2H), 3.86 (s, 3H), 7.35 (s, 1H), 8.17 (s, 1H). Anal. ($C_{12}H_{14}O_4S\cdot0.25H_2O$) C, H, S.

6-Methyl-1,1-dioxo-1λ^6-thiochroman-7-carboxylic acid (14b) was prepared by alkaline hydrolysis of the foregoing ester **14a** according to method E in a 73% yield: mp 174 °C; NMR δ 2.31−2.41 (m, 2H), 2.59 (s, 3H), 3.04 (t, J = 6.3, 2H), 3.54 (m, 2H), 7.35 (s, 1H), 8.21 (s, 1H), 13.20 (s br, 1H); IR (KBr) 1702, 1308, 1291, 1261, 1111 cm^{-1}. Anal. ($C_{11}H_{12}O_4S$) C, H, S.

4-Bromo-2-methyl-5-(3-methylbut-2-enyl-1-sulfonyl)-benzoic Acid 3-Methylbut-2-enyl Ester (15). The title compound was prepared with 3-chloro-3-methyl-1-butene in a manner similar to that described in method A in 45% yield: oil; NMR δ 1.49 (s, 3H), 1.67 (s, 3H), 1.75 (d, J = 4.0, 6H), 4.22 (d, J = 7.7, 2H), 4.81 (d, J = 7.0, 2H), 5.09 (t, J = 7.9, 1H), 5.44 (t, J = 7.2, 1H), 7.95 (s, 1H), 8.30 (s, 1H); IR (capillary film) 1722, 1320, 1248, 1152, 1085 cm^{-1}. Anal. ($C_{18}H_{23}BrO_4S$) C, H, Br, S.

3-Isopropylidene-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid 3-methylbut-2-enyl ester (16a) was prepared in a similar manner from the foregoing compound **15** as described by method C: 16% yield; mp 165−166 °C (Et_2O); NMR δ 1.75 (d, J = 4.4, 6H), 1.98 (s, 3H), 2.21 (s, 3H), 2.63 (s, 3H), 4.33 (s, 2H), 4.80 (d, J = 7.4, 2H), 5.47 (t, J = 7.2, 1H), 7.77 (s, 1H), 8.06 (s, 1H). Anal. ($C_{18}H_{22}O_4S\cdot0.25H_2O$) C, H, S.

3-Isopropylidene-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid (16b) was prepared from the foregoing compound using method E: 79% yield; mp 150 °C (H_2O); NMR δ 1.98 (s, 3H), 2.21 (s, 3H), 2.65 (s, 3H), 4.33 (s, 2H), 7.75 (s, 1H), 8.08 (s, 1H), 13.30 (s br, 1H); IR 1699, 1592, 1295, 1262 cm^{-1}. Anal. ($C_{13}H_{14}O_4S$) H, S; C: calcd, 58.62; found, 56.47.

3-Isopropyl-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic Acid (17b). Hydrogenation of **16a** followed by alkaline hydrolysis (methods D and E) furnished the title compound in a 29% overall yield: mp 160−162 °C (Et_2O); NMR δ 0.71 (d, J = 6.8, 3H), 1.01 (d, J = 6.8, 3H), 2.36−2.47 (m, 1H), 2.62 (s, 3H), 3.40 (q, J = 8.7, 1H), 3.58−3.72 (m, 2H), 7.55 (s, 1H), 8.01 (s, 1H), 13.30 (s br, 1H); IR 1704, 1299, 1256, 1109 cm^{-1}. Anal. ($C_{13}H_{16}O_4S$) C, H, S.

5-(Methylsulfonyl)-2-methyl-4-propen-1-ylbenzoic Acid Methyl Ester (20a). This compound was obtained by Heck reaction performed as described in method C by treatment of **2d**[4] with condensed propene in a glass bomb at 118 °C for 24 h: 52% yield; mp 112−114 °C (Et_2O); NMR δ 1.96 (dd, J = 6.8, J = 1.7, 3H), 2.61 (s, 3H), 3.18 (s, 3H), 3.86 (s, 3H), 5.58 (dq, J = 15.6, J = 5.1, 1H), 7.16 (dd, J = 15.7, J = 1.7, 1H), 7.75 (s, 1H), 8.35 (s, 1H). Anal. ($C_{13}H_{16}O_4S$) C, H, S.

The byproduct 5-(methylsulfonyl)-2-methyl-4-propen-2-ylbenzoic acid methyl ester (**21**) was isolated from the nonpolar fractions in a manner analogous to method C: 5% yield; mp 72−74 °C [(i-Pr)$_2$O]; NMR δ 2.11 (s, 3H), 2.60 (s, 3H), 3.22 (s, 3H), 3.88 (s, 3H), 5.00 (s, 1H), 5.34 (t, J = 1.6, 1H), 7.36 (s, 1H), 8.38 (s, 1H); IR (KBr) 1734, 1308, 1299, 1251, 525 cm^{-1}. Anal. ($C_{13}H_{16}O_4S$) C, H, S.

5-(Methylsulfonyl)-2-methyl-4-styrylbenzoic acid methyl ester (20b) was prepared by treatment of **2d**[4] with styrene under Heck conditions (method C) in 81% yield; mp 146−148 °C (i-PrOH); NMR δ 2.67 (s, 3H), 3.25 (s, 3H), 3.88 (s, 3H), 7.34−7.46 (m, 3H), 7.51 (d, J = 16.1, 1H), 7.64 (m, 2H), 7.89 (d, J = 16.4, 1H), 8.01 (s, 1H), 8.41 (s, 1H); IR (KBr) 1718, 1298, 1247, 1140, 1096, 523 cm^{-1}. Anal. ($C_{18}H_{18}O_4S$) C, H, S.

Method J. 5-(Methylsulfonyl)-2-methyl-4-(3-methyl-2-oxiranyl)benzoic Acid Methyl Ester (22a). Compound **20a** (600 mg, 2.24 mmol) was treated with 3-chloroperbenzoic acid (70%, 1 g, 4.06 mmol) in CH_2Cl_2 (20 mL) for 24 h at room temperature. The mixture was concentrated to a small volume and chromatographed on silica gel (petroleum ether → Et_2O). The chromatographically homogeneous fractions were combined, evaporated, and triturated with petroleum ether to give **22a** (480 mg, 76%) as a white solid: mp 98−99 °C; NMR δ 1.42 (d, J = 4.9, 3H), 3.02 (qd, J = 5.1, J = 2.1, 1H), 3.29 (s, 3H), 3.88 (s, 3H), 4.31 (d, J = 1.8, 1H), 7.38 (s, 1H), 8.33 (s, 1H). Anal. ($C_{13}H_{16}O_5S$) C, H, S.

5-(Methylsulfonyl)-2-methyl-4-(3-phenyl-2-oxiranyl)-benzoic acid methyl ester (22b) was prepared from **20b** by method J: 84% yield; mp 112 °C; NMR δ 2.65 (s, 3H), 3.22 (s, 3H), 3.89 (s, 3H), 4.04 (d, J = 2.0, 1H), 4.73 (d, J = 1.7, 1H),

7.42 (m, 5H), 7.56 (s, 1H), 8.36 (s, 1H); IR (KBr) 1719, 1315, 1136, 1105 cm^{-1}. Anal. ($C_{18}H_{18}O_5S \cdot 0.25H_2O$) C, H, S.

Method K. 5-(Methylsulfonyl)-2-methyl-4-propionylbenzoic Acid Methyl Ester (23a). Epoxide **22a** (19.5 g, 68.6 mmol) and $BF_3 \cdot Et_2O$ (50 mL, 398 mmol) were heated under reflux in CH_2Cl_2 (300 mL) for 5 h. The solvent was evaporated, and the residue was purified by silica gel chromatography (petroleum ether → Et_2O) to give **23a** (11.6 g, 59%) as white crystals on trituration with $(i\text{-Pr})_2O$: mp 141−142 °C; NMR δ 1.09 (t, J = 7.2, 3H), 2.64 (s, 3H), 2.93 (q, J = 7.1, 2H), 3.27 (s, 3H), 3.90 (s, 3H), 7.71 (s, 1H), 8.33 (s, 1H); IR (KBr) 1729, 1710, 1304, 1256, 1143 cm^{-1}. Anal. ($C_{13}H_{16}O_5S$) C, H, S.

5-(Methylsulfonyl)-2-methyl-4-(phenylacetyl)benzoic acid methyl ester (23b) was prepared as above from epoxide **22b** in 54% yield: mp 133−134 °C (Et_2O); NMR δ 2.66 (s, 3H), 3.27 (s, 3H), 3.91 (s, 3H), 4.32 (s, 2H), 7.26−7.38 (m, 5H), 7.84 (s, 1H), 8.36 (s, 1H); IR (KBr) 1729, 1718, 1299, 1254, 1137 cm^{-1}. Anal. ($C_{18}H_{18}O_5S$) C, H, S.

Method L. 4-Acetyl-2-methyl-5-(methylsulfonyl)benzoic Acid Methyl Ester (23c). To a solution of 4-bromo-2-methyl-5-(methylsulfonyl)benzoic acid methyl ester[4] (**2d**, 12.9 g, 41.7 mmol) in THF (324 mL) were added (1-ethoxyvinyl)-tributylstannane (15 mL, 44.4 mmol), dried LiCl (5.52 g, 130 mmol), and $Pd(PPh_3)_4$ (1.01 g, 0.874 mmol). Under an argon atmosphere, the suspension was heated at reflux for 48 h while two additional portions of (1-ethoxyvinyl)tributylstannane (2 × 15 mL, 88.8 mmol) were added. The reaction mixture was diluted with Et_2O (750 mL) and consecutively washed with H_2O, NH_4OH (5%), and brine. The organic layer was dried and concentrated, yielding 4-(1-ethoxyvinyl)-2-methyl-5-(methylsulfonyl)benzoic acid methyl ester as a semisolid residue.

The crude enol ether thus obtained (12.5 g) was stirred in THF (100 mL) and HCl (2 N, 30 mL) at room temperature for 48 h. After dilution with Et_2O (150 mL), the mixture was washed with a saturated $NaHCO_3$ solution and H_2O, and the organic phase was dried and evaporated to produce the title compound **23c** (10.5 g, 93% overall yield) upon crystallization from MeOH: mp 114−115 °C; NMR δ 2.59 (s, 3H), 2.64 (s, 3H), 3.29 (s, 3H), 3.90 (s, 3H), 7.78 (s, 1H), 8.34 (s, 1H); IR (KBr) 1722, 1705, 1437, 1304, 1251 cm^{-1}. Anal. ($C_{12}H_{14}O_5S$) C, H, S.

4-Acetyl-2-methyl-5-(propyl-2-sulfonyl)benzoic acid isopropyl ester (23d) was prepared as above from **2b** in 81% overall yield: mp 97 °C (petroleum ether); NMR δ 1.19 (d, J = 6.7, 6H), 1.35 (d, J = 6.0, 6H), 2.57 (s, 3H), 2.63 (s, 3H), 3.52 (sept, J = 6.8, 1H), 5.18 (sept, J = 6.3, 1H), 7.74 (s, 1H), 8.18 (s, 1H); IR (KBr) 1717, 1705, 1358, 1303, 1245, 1138, 1098 cm^{-1}. Anal. ($C_{16}H_{22}O_5S$) C, H, S.

Method M. 3-Hydroxy-3,5-dimethyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester (24e). To a freshly prepared solution of Na (2.4 g, 104 mmol) in dry MeOH (120 mL) was added 4-acetyl-2-methyl-5-(methylsulfonyl)benzoic acid methyl ester (**23c**, 12 g, 44.4 mmol), and the mixture was stirred under a N_2 atmosphere at 40 °C for 45 min. After dilution with ice/water (350 mL), the mixture was immediately acidified with HCl and extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with H_2O, dried, and evaporated, and the residue was recrystallized from Et_2O to give **24e** (10.8 g, 90%): mp 116−118 °C; NMR δ 1.61 (s, 3H), 2.63 (s, 3H), 3.57 (d, J = 13.4, 1H), 3.84 (d, J = 13.2, 1H), 3.87 (s, 3H), 6.24 (s, 1H), 7.69 (s, 1H), 8.04 (s, 1H); IR (KBr) 1721, 1605, 1565, 1433, 1303, 1273, 1178, 1095 cm^{-1}. Anal. ($C_{12}H_{14}O_5S$) C, H, S.

Analogously prepared were the following compounds.

3-Ethyl-3-hydroxy-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (24a): 80% yield; mp 105−107 °C [$(i\text{-Pr})_2O$]; NMR δ 0.90 (t, J = 7.5, 3H), 1.77−2.01 (m, 2H), 2.62 (s, 3H), 3.49 (d, J = 13.7, 1H), 3.86 (d, 13.7, 1H), 3.87 (s, 3H), 6.12 (s, 1H), 7.63 (s, 1H), 8.04 (s, 1H); IR (KBr) 3473, 1726, 1289, 1257, 1100 cm^{-1}. Anal. ($C_{13}H_{16}O_5S$) C, H, S.

3-Benzyl-3-hydroxy-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (24c): 85% yield; mp 140−142 °C (Et_2O); NMR δ 2.54 (s, 3H), 3.10 (d, J = 13.8, 1H), 3.17 (d, J = 13.8, 1H), 3.42 (d, J = 13.4, 1H), 3.78 (d, J = 13.4, 1H), 3.87 (s, 3H), 6.34 (s, 1H), 7.15 (m, 2H), 7.27 (m, 3H), 7.36 (s, 1H), 8.06 (s, 1H); IR (KBr) 3466, 1729, 1289, 1259 cm^{-1}. Anal. ($C_{18}H_{18}O_5S$) C, H, S.

3-Hydroxy-2,2,3,5-tetramethyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (24 g): 18% yield; mp 151−152 °C (CH_2Cl_2/MeOH); NMR δ 1.19 (s, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 2.63 (s, 3H), 3.87 (s, 3H), 6.11 (s, 1H), 7.66 (s, 1H), 8.07 (s, 1H); IR (KBr) 3460, 1710, 1279, 1162, 1089 cm^{-1}. Anal. ($C_{14}H_{18}O_5S$) C, H, S.

2,2,5-Trimethyl-3-methylene-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (25c) was prepared from **24g** according to method I in 98% yield: mp 141−142 °C (EtOAc); NMR δ 1.49 (s, 6H), 2.63 (s, 3H), 3.87 (s, 3H), 5.66 (s, 1H), 6.22 (s, 1H), 7.98 (s, 1H), 8.15 (s, 1H); IR (KBr) 1735, 1292, 1249, 1095 cm^{-1}. Anal. ($C_{14}H_{16}O_4S$) C, H, S.

3-Ethyl-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester (27a). Dehydratation of hydroxy compound **24a** according to method I gave a mixture of olefins **25a** and **26a**, which was hydrogenated using method D to yield 37% **27a** in all: mp 88 °C [$(i\text{-Pr})_2O$]; NMR δ 0.96 (t, J = 7.4, 3H), 1.58−1.76 (m, 1H), 1.93−2.09 (m, 1H), 2.61 (s, 3H), 3.37 (dd, J = 13.2, J = 7.9, 1H), 3.57 (m, 1H), 3.77 (dd, J = 13.2, J = 5.2, 1H), 3.86 (s, 3H), 7.59 (s, 1H), 8.03 (s, 1H). Anal. ($C_{13}H_{16}O_4S$) C, H, S.

3,5-Dimethyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]-thiophene-6-carboxylic acid methyl ester (27d) was prepared as above from **24e** via the mixture of **25b** and **26b** in 70% overall yield: mp 134−135 °C; NMR δ 1.43 (d, J = 6.9, 3H), 2.61 (s, 3H), 3.30 (dd, J = 13.3, J = 5.8, 1H), 3.69 (m, 1H), 3.82 (dd, J = 13.3, J = 7.6, 1H), 3.86 (s, 3H), 7.62 (s, 1H), 8.04 (s, 1H); IR (KBr) 1700, 1296, 1260, 1132, 1102 cm^{-1}. Anal. ($C_{12}H_{14}O_4S$) C, H, S.

3-Ethyl-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid (27b) was prepared from **27a** by alkaline hydrolysis (method E): 75% yield; mp 172−174 °C; NMR δ 0.96 (t, J = 7.4, 3H), 1.58−1.75 (m, 1H), 1.92−2.09 (m, 1H), 2.62 (s, 3H), 3.36 (dd, J = 13.4, J = 5.4, 1H), 3.56 (sept, J = 4.4, 1H), 3.76 (dd, J = 13.3, J = 7.9, 1H), 7.56 (s, 1H), 8.01 (s, 1H), 13.25 (s br, 1H); IR (KBr) 1703, 1308, 1107 cm^{-1}. Anal. ($C_{12}H_{14}O_4S$) C, H, S.

2,2,3,5-Tetramethyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (27f) was prepared from olefin **25c** by catalytic hydrogenation (method D): 48% yield; white crystals; mp 104 °C [$(i\text{-Pr})_2O$]; NMR δ 1.15 (s, 3H), 1.32 (d, J = 7.0, 3H), 1.37 (s, 3H), 2.61 (s, 3H), 3.30 (q, J = 7.2, 1H), 3.86 (s, 3H), 7.55 (s, 1H), 8.07 (s, 1H); IR (KBr) 1705, 1286, 1248, 1163 cm^{-1}. Anal. ($C_{14}H_{18}O_4S$) C, H, S.

4-Bromo-5-(ethylsulfonyl)-2-methylbenzoic acid ethyl ester (29a) was prepared according to method A from 2-bromo-4-methyl-5-carboxybenzenesulfinic acid[4] and EtI in 1-methyl-2-pyrrolidinone (NMP) at 60 °C: 63% yield; white crystals; mp 78−79 °C [CH_2Cl_2/$(i\text{-Pr})_2O$]; NMR δ 1.14 (t, J = 7.4, 3H), 1.34 (t, J = 7.0, 3H), 2.61 (s, 3H), 3.51 (q, J = 7.4, 2H), 4.35 (q, J = 7.2, 2H), 7.94 (s, 1H), 8.39 (s, 1H); IR (KBr) 1724, 1315, 1253, 1150, 1092 cm^{-1}. Anal. ($C_{12}H_{15}BrO_4S$) C, H, Br, S.

4-Cyano-5-(ethylsulfonyl)-2-methylbenzoic Acid Ethyl Ester (30a). A mixture of the foregoing compound **29a** (15 g, 44.7 mmol), CuCN (6.01 g, 67.1 mmol), and NMP (120 mL) was stirred under a N_2 atmosphere at 160 °C for 16 h. This was poured into H_2O (500 mL); EtOAc (400 mL) was added, and the mixture was stirred for an additional 30 min. After filtration through Celite, the aqueous layer was separated and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with H_2O (4 × 300 mL), dried, and evaporated to give compound **30a** (11.2 g, 89%) as beige crystals on recrystallization from CH_2Cl_2/$(i\text{-Pr})_2O$: mp 105−106 °C; NMR δ 1.18 (t, J = 7.4, 3H), 1.35 (t, J = 7.2, 3H), 2.65 (s, 3H), 3.48 (q, J = 7.4, 2H), 4.38 (q, J = 7.0, 2H), 8.24 (s, 1H), 8.35 (s, 1H); IR (KBr) 2225, 1721, 1460, 1328, 1305, 1257, 1139, 1106 cm^{-1}. Anal. ($C_{13}H_{15}NO_4S$) C, H, N, S.

Similarly prepared were the following compounds.

4-Cyano-2-methyl-5-(methylsulfonyl)benzoic acid methyl ester (30b): 67% yield; yellowish crystals; mp 154−156 °C (EtOAc/MeOH); NMR δ 2.64 (s, 3H), 3.39 (s, 3H), 3.92 (s, 3H), 8.23 (s, 1H), 8.40 (s, 1H); IR (KBr) 2238, 1729, 1315, 1252, 1141, 1102, 524 cm^{-1}. Anal. ($C_{11}H_{11}NO_4S$) C, H, N, S.

4-Cyano-5-(methylsulfonyl)benzoic acid methyl ester (30c): 29% yield; white crystals; mp 159 °C (EtOAc); NMR δ 3.44 (s, 3H), 3.95 (s, 3H), 8.32−8.44 (m, 2H), 8.53 (m, 1H); IR (KBr) 2231, 1738, 1309, 1288, 1163, 761, 528 cm^{-1}. Anal. ($C_{10}H_9NO_4S$) C, H, N, S.

3-Amino-5-methyl-1,1-dioxo-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester (31c). In analogy to method M, nitrile **30b** was cyclized in NaOMe/MeOH at 50 °C for 3 h in 69% yield: mp 238−240 °C dec (CH_2Cl_2/MeOH); NMR δ 2.61 (s, 3H), 3.87 (s, 3H), 5.61 (s, 1H), 7.17 (s, 2H), 7.89 (s, 1H), 7.99 (s, 1H); IR (KBr) 3432, 1712, 1667, 1253, 1102 cm^{-1}. Anal. ($C_{11}H_{11}NO_4S\cdot 0.25H_2O$) C, H, N, S.

3-Amino-2,5-dimethyl-1,1-dioxo-1*H*-1λ^6-benzo[*b*]-thiophene-6-carboxylic acid methyl ester (31a) was prepared as above from **30a** as pale greenish crystals in 48% yield: mp 284−286 °C (CH_2Cl_2/MeOH); NMR δ 1.89 (s, 3H), 2.61 (s, 3H), 3.86 (s, 3H), 6.71 (s, 2H), 7.83 (s, 1H), 8.01 (s, 1H); IR (KBr) 3422, 3351, 1728, 1657, 1251, 1090 cm^{-1}. Anal. ($C_{12}H_{13}NO_4S$) C, H, N, S.

Method N. 5-Methyl-1,1,3-trioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester (32a). Enamine **31c** (29.7 g, 115 mmol) in aqueous HCl (2 N, 300 mL) and dioxane (600 mL) was heated under reflux for 1 h. The solution was concentrated under reduced pressure to approximately $^1/_3$ of its volume and then left to stand in an ice bath to produce the title compound (29.2 g, 92%) as yellow crystals: mp 194−195 °C; NMR δ 2.65 (s, 3H), 3.92 (s, 3H), 4.63 (s, 2H), 7.98 (s, 1H), 8.37 (s, 1H); IR (KBr) 1730, 1706, 1300, 1205, 1132 cm^{-1}. Anal. ($C_{11}H_{10}O_5S\cdot 0.25H_2O$) C, H, S.

1,1,3-Trioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester (32b). This compound was prepared as above from **30c** using method M followed by acidic hydrolysis without purification of the intermediate enamine **31d**: 45% overall yield; yellow crystals; mp 194−195 °C (Me_2-CO/MeOH); NMR δ 3.95 (s, 3H), 4.67 (s, 2H), 8.13 (d, J = 8.1, 1H), 8.41 (dd, J = 8.1, J = 1.2, 1H), 8.48 (s, 1H); IR (KBr) 1721, 1305, 1287, 1232, 1206 cm^{-1}. Anal. ($C_{10}H_8O_5S$) C, H, S.

3-Amino-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo-[*b*]thiophene-6-carboxylic acid methyl ester (33a) was prepared by hydrogenation of **31c** in DMF using method D: 55% yield; mp 158−159 °C (MeOH); NMR δ 2.42 (s, 2H), 2.62 (s, 3H), 3.31 (dd, J = 13.4, J = 7.4, 1H), 3.87 (s, 3H), 3.89 (dd, J = 13.1, J = 7.0, 1H), 4.61 (t, J = 7.0, 1H), 7.73 (s, 1H), 8.03 (s, 1H); IR (KBr) 1705, 1266, 1128, 1103 cm^{-1}. Anal. ($C_{11}H_{13}$-NO_4S) C, H, N, S.

1,1-Dioxo-5-methylspiro[2,3-dihydro-1*H*-1λ^6-benzo[*b*]-thiophene-3,2′-dioxolane]-6-carboxylic acid methyl ester (34a) was prepared from **32a** using method G: 68% yield; white crystals; mp 149−151 °C (petroleum ether/EtOAc); NMR δ 2.62 (s, 3H), 3.88 (s, 3H), 3.92 (s, 2H), 4.21 (AA′BB′, 4H), 7.73 (s, 1H), 8.14 (s, 1H); IR (KBr) 1732, 1304, 1269, 1092 cm^{-1}. Anal. ($C_{13}H_{14}O_6S$) C, H, S.

3-(Hydroxyimino)-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester (35a). A suspension of ketone **32a** (1.5 g, 3.80 mmol) and hydroxylamine·HCl (500 mg, 7.20 mmol) in H_2O (10 mL) and MeOH (200 mL) was heated under reflux for 5 h; meanwhile, the solution became clear. The solution was concentrated to some extent, and white crystals of **35a** (1.2 g, 77%) were separated on cooling: mp 260−262 °C; NMR δ 2.63 (s, 3H), 3.88 (s, 3H), 4.52 (s, 2H), 7.88 (s, 1H), 8.19 (s, 1H), 12.52 (s, 1H); IR (KBr) 1731, 1695, 1598, 1442, 1404, 1386, 1374, 1328, 1257 cm^{-1}. Anal. ($C_{11}H_{11}NO_5S$) C, H, N, S.

3-(Methoxyimino)-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (35c) was prepared analogously from **32a** and methoxylamine·HCl: 64% yield; white crystals; mp 210 °C (MeOH); NMR δ 2.63 (s, 3H), 3.88 (s, 3H), 4.06 (s, 3H), 4.57 (s, 2H), 7.88 (s, 1H), 8.20 (s, 1H); IR (KBr) 1737, 1708, 1596, 1441, 1319, 1301, 1270, 1248 cm^{-1}. Anal. ($C_{12}H_{13}NO_5S$) C, H, N, S.

2,2,5-Trimethyl-1,1,3-trioxo-2,3-dihydro-1*H*-1λ^6-benzo-[*b*]thiophene-6-carboxylic Acid Methyl Ester (36a). To a slightly cooled solution of NaH (60% in mineral oil, 7.87 g, 197 mmol) in DMF (400 mL) was added compound **32a** (25 g, 96.6 mmol) in portions under a N_2 atmosphere. Then MeI (18.4 mL, 295 mmol) was dropped in, and the mixture was stirred overnight at room temperature. H_2O was cautiously added, and the mixture was extracted with EtOAc (2 × 400 mL). The combined organic phases were washed with H_2O (5 × 200 mL), dried, and evaporated to give a reddish-brown residue (∼28 g). This was recrystallized from MeOH, and the crystalline crop (∼18 g) thus obtained was further purified by column chromatography on silica gel with (i-Pr)$_2$O as the solvent, yielding **36a** (14.0 g, 51%): mp 154−156 °C; NMR δ 1.52 (s, 6H), 2.65 (s, 3H), 3.92 (s, 3H), 8.04 (s, 1H), 8.43 (s, 1H). Anal. ($C_{13}H_{14}O_5S$) C, H, S.

3-Hydroxy-2,2,5-trimethyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (37a) was prepared from the foregoing compound by $NaBH_4$ reduction in CH_2Cl_2/MeOH (method H): 75% yield; mp 115−116 °C [(i-Pr)$_2$O]; NMR δ 1.12 (s, 3H), 1.43 (s, 3H), 2.62 (s, 3H), 3.87 (s, 3H), 4.94 (d, J = 5.8, 1H), 6.52 (d, J = 6.1, 1H), 7.59 (s, 1H), 8.09 (s, 1H); IR (KBr) 3500, 1725, 1292, 1250, 1080 cm^{-1}. Anal. ($C_{13}H_{16}O_5S$) C, H, S.

3-Methoxy-2,2,5-trimethyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (37c) was prepared by similar MeI treatment of **37a** at 40 °C as described in method B: 48% yield; mp 129 °C (MeOH); NMR δ 1.25 (s, 3H), 1.44 (s, 3H), 2.63 (s, 3H), 3.59 (s, 3H), 3.87 (s, 3H), 4.74 (s, 1H), 7.66 (s, 1H), 8.11 (s, 1H); IR (KBr) 1726, 1294, 1099 cm^{-1}. Anal. ($C_{14}H_{18}O_5S$) C, H, S.

3-Hydroxy-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (38a) was prepared from **32a** by $NaBH_4$ reduction (method H): 82% yield; white crystals; mp 164−166 °C (Me_2CO/petroleum ether); NMR δ 2.62 (s, 3H), 3.37 (dd, J = 13.8, J = 5.5, 1H), 3.88 (s, 3H), 4.03 (dd, J = 13.7, J = 7.1, 1H), 5.43 (q br, 1H), 6.41 (d, J = 6.3, 1OH), 7.64 (s, 1H), 8.08 (s, 1H); IR (KBr) 3431, 1703, 1326, 1310, 1273, 1113 cm^{-1}. Anal. ($C_{11}H_{12}O_5S$) C, H, S.

3-Hydroxy-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]-thiophene-6-carboxylic acid methyl ester (38c) was prepared from **32b** by $NaBH_4$ reduction (method H): 48% yield; mp 129−130 °C (CH_2Cl_2/MeOH); NMR δ 3.41 (dd, J = 13.7, J = 5.4, 1H), 3.91 (s, 3H), 4.08 (dd, J = 13.7, J = 7.1, 1H), 5.48 (d br, J = 3.9, 1H), 6.48 (d, J = 4.2, 1H), 7.84 (d, J = 8.1, 1H), 8.17 (d, J = 1.5, 1H), 8.29 (dd, J = 8.1, J = 1.5, 1H); IR (KBr) 3429, 1723, 1322, 1288, 1149, 1119 cm^{-1}. Anal. ($C_{10}H_{10}O_5S$) C, H, S.

5-Methyl-1,1-dioxo-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester (39a). A mixture of alcohol **38a** (15.9 g, 62.0 mmol) and *p*-toluenesulfonyl chloride (12.5 g, 65.6 mmol) in pyridine (75 mL) was heated under reflux for 3 h. This was poured into HCl (2 N, 250 mL) while the mixture was being cooled, and the separated precipitate was recrystallized from EtOAc, yielding beige crystals of **39a** (7.0 g, 47%): mp 178 °C; NMR δ 2.60 (s, 3H), 3.87 (s, 3H), 7.50 (d, J = 7.0, 1H), 7.57 (s, 1H), 7.63 (d, J = 7.0, 1H), 8.11 (s, 1H); IR (KBr) 1723, 1299, 1255, 1166, 1101 cm^{-1}. Anal. ($C_{11}H_{10}O_4S$) C, H, S.

1,1-Dioxo-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (39b) was prepared as above from **38c** in 48% yield as beige crystals: mp 164 °C (EtOAc); NMR δ 3.91 (s, 3H), 7.57 (d, J = 6.7, 1H), 7.73 (dd, J = 7.0, J = 0.9, 1H), 7.76 (d, J = 7.3, 1H), 8.22 (d, J = 0.6, 1H), 8.25 (dd, J = 7.9, J = 1.5, 1H); IR (KBr) 1724, 1301, 1279, 1255, 1155, 1136, 1109 cm^{-1}. Anal. ($C_{10}H_8O_4S$) C, H, S.

5-Methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]-thiophene-6-carboxylic acid methyl ester (40a) was prepared by hydrogenation of **39a** (method D): 76% yield; white crystals; mp 178 °C (MeOH); NMR δ 2.59 (s, 3H), 3.37 (t, J = 6.9, 2H), 3.62 (t, J = 6.8, 2H), 3.86 (s, 3H), 7.52 (s, 1H), 8.05

(s, 1H); IR (KBr) 1718, 1290, 1259, 1108 cm^{-1}. Anal. ($C_{11}H_{12}O_4S$) C, H, S.

1,1-Dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carboxylic acid methyl ester (40c) was prepared by hydrogenation of **39b** (method D): 83% yield; white crystals; mp 143 °C (EtOAc); NMR δ 3.45 (t, $J = 6.7$, 2H), 3.66 (t, $J = 6.7$, 2H), 3.90 (s, 3H), 7.71 (d, $J = 8.1$, 1H), 8.16 (d, $J = 1.5$, 1H), 8.20 (dd, $J = 8.1$, $J = 1.5$, 1H); IR (KBr) 1717, 1299, 1260, 1120 cm^{-1}. Anal. ($C_{10}H_{10}O_4S$) C, H, S.

4-Bromo-5-(3-hydroxypropyl-1-sulfonyl)-2-methylbenzoic acid methyl ester (42b) was prepared from sulfinic acid **1** and 3-iodo-1-propanol using method A. Silica gel chromatography (petroleum ether → EtOAc) achieved insufficient enrichment of the 3-hydroxypropyl ester **42a**. For that reason, this was further transesterified to the methyl ester **42b** by alkaline hydrolysis (method E) followed by CH_2N_2 treatment in MeOH/CH_2Cl_2. Silica gel chromatography with petroleum ether/EtOAc (3:1) gave crystalline **42b** in 58% overall yield: mp 108−109 °C (MeOH); NMR δ 1.62−1.73 (m, 2H), 2.61 (s, 3H), 3.43 (q, $J = 5.8$, 2H), 3.55 (m, 2H), 3.88 (s, 3H), 4.67 (t, $J = 5.3$, 1H), 7.98 (s, 1H), 8.41 (s, 1H); IR (KBr) 3551, 1728, 1251, 1147, 1093 cm^{-1}. Anal. ($C_{12}H_{15}BrO_5S$) C, H, Br, S.

Method O. 8-Methyl-5,5-dioxo-3,4-dihydro-2*H*-5λ^6-benzo[1,5]oxathiepine-7-carboxylic Acid Methyl Ester (43a). To a suspension of NaH (60% in mineral oil, 40 mg, 1.0 mmol) in NMP (2 mL) under N_2 was added the foregoing **42b** (351 mg, 0.999 mmol) in portions. After the mixture was stirred for 24 h at 60 °C, the cold solution was poured into HCl (10%, 10 mL) while the solution was cooled. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with H_2O (4 × 30 mL), dried, filtered, and evaporated. The resinous residue was purified by silica gel chromatography with heptane/EtOAc (1:1) to give white crystals of the title compound (67.8 mg, 24%): mp 149−151 °C; NMR δ 2.26 (m, 2H), 2.58 (s, 3H), 3.56 (t, $J = 5.9$, 2H), 3.86 (s, 3H), 4.25 (t, $J = 5.0$, 2H), 7.23 (s, 1H), 8.28 (s, 1H); IR (KBr) 1716, 1295, 1287, 1265, 1246 cm^{-1}. Anal. ($C_{12}H_{14}O_5S \cdot 0.5H_2O$) C, H, S.

4-Chloro-2-methyl-5-(propyl-2-sulfonyl)benzoic acid isopropyl ester (45a) was prepared from 2-chloro-4-methyl-5-carboxybezenesulfinic acid[4] (**44**) and *i*-PrI at room temperature according to method A: white crystals; 26% yield; mp 71−72 °C (petroleum ether); NMR δ 1.21 (d, $J = 6.8$, 6H), 1.35 (d, $J = 6.2$, 6H), 2.62 (s, 3H), 3.74 (sept, $J = 6.8$, 1H), 5.17 (sept, $J = 6.2$, 1H), 7.78 (s, 1H), 8.33 (s, 1H); IR (KBr) 1726, 1316, 1248, 1084 cm^{-1}. Anal. ($C_{14}H_{19}ClO_4S$) C, H, Cl, S.

4-Chloro-2-methyl-5-(propyl-2-sulfonyl)benzoic acid (45b) was prepared by ester hydrolysis of **45a** according to method E in 99% yield as white crystals: mp 206−207 °C (H_2O); NMR δ 1.27 (d, $J = 6.8$, 6H), 2.69 (s, 3H), 3.60 (sept, $J = 6.8$, 1H), 7.83 (s, 1H), 8.46 (s, 1H), 13.50 (s br, 1H); IR (KBr) 1692, 1314, 1254, 1147, 938 cm^{-1}. Anal. ($C_{11}H_{13}ClO_4S$) C, H, Cl, S.

4-Chloro-5-(1-hydroxy-2-methylpropyl-2-sulfonyl)-2-methylbenzoic Acid Methyl Ester (46) and 6-Chloro-7-(propane-2-sulfonyl)isochroman-1-one (47). A 1 L, three-necked flask equipped with a mechanical stirrer, dropping funnel, drying tube, N_2 inlet, and thermometer was charged with dry THF (250 mL) and $(i\text{-Pr})_2NH$ (22.4 mL, 160 mmol). After the mixture was cooled to −70 °C, BuLi (97.4 mL, 1.6 M hexane solution, 160 mmol) was slowly added followed by compound **45b** (19.6 g, 70.8 mmol) and the color indicator 2,2′-dipyridyl (5 mg, 0.032 mmol) dissolved in THF (280 mL). The mixture was stirred for an additional 1 h at this temperature. The solution was allowed to warm to −35 °C, and monomeric formaldehyde, which was separately generated from paraformaldehyde[21] (10.6 g), was introduced until the red color of the indicator disappeared. The reaction was quenched by the addition of a saturated NH_4Cl solution (20 mL), and the resultant mixture was poured into H_2O (2.5 L), which was cooled and acidified with HCl. After separation of phases, the aqueous layer was extracted with EtOAc (3 × 500 mL). All organic layers were combined, dried, filtered, and evaporated, leaving a resinous residue (∼21 g). This was esterified by stirring the material with MeI (13.3 mL, 213 mmol) and K_2CO_3 (17.7 g, 106 mmol) in MeCOEt (200 mL) for 3 h at room temperature. After filtration and evaporation of the solvent, a gum resulted (∼24 g), which was chromatographed on silica gel with petroleum ether/EtOAc (4:1). After removal of some starting material, the chromatographically homogeneous nonpolar fractions of compound **46** (4.1 g, 18%) were combined and recrystallized from CH_2Cl_2/Et_2O: mp 135−136 °C; NMR δ 1.27 (s, 6H), 2.60 (s, 3H), 3.58 (d, $J = 5.6$, 2H), 3.88 (s, 3H), 5.01 (t, $J = 5.6$, 1H), 7.72 (s, 1H), 8.36 (s, 1H); IR (KBr) 3479, 1709, 1306, 1102 cm^{-1}. Anal. ($C_{13}H_{17}ClO_5S$) C, H, Cl, S. The polar component, compound **47** (6.3 g, 31%), was recrystallized from CH_2Cl_2/Et_2O: mp 128−130 °C; NMR δ 1.22 (d, $J = 6.8$, 6H), 3.18 (t, $J = 6.0$, 2H), 3.77 (sept, $J = 6.8$, 1H), 4.58 (t, $J = 6.0$, 2H), 7.88 (s, 1H), 8.42 (s, 1H); IR (KBr) 1735, 1311, 1228, 1139, 1100, 1038 cm^{-1}. Anal. ($C_{12}H_{13}ClO_4S$) C, H, Cl, S.

3,3,7-Trimethyl-4,4-dioxo-3,4-dihydro-2*H*-4λ^6-benzo[1,4]-oxathiine-6-carboxylic acid methyl ester (48a) was prepared by cyclization of **46** using method O: 76% yield; mp 143 °C (MeOH/CH_2Cl_2); NMR δ 1.32 (s, 6H), 2.50 (s, 3H), 3.79 (s, 3H), 4.53 (s, 2H), 7.03 (s, 1H), 8.15 (s, 1H); IR (KBr) 1722, 1291, 1254, 1101, 1070 cm^{-1}. Anal. ($C_{13}H_{16}O_5S$) C, H, S.

4-Methyl-4-(3-methylphenylthio)pentan-2-one (51b). To an ice-cold solution of *m*-thiocresol (**50**, 50 g, 386 mmol) and mesityl oxide (44.6 mL, 386 mmol) in $CHCl_3$ (200 mL) was added NEt_3 (2.23 mL, 16.1 mmol). The mixture was heated at reflux for 24 h, allowed to cool to room temperature, and washed with NaOH (10%, 2 × 75 mL). The combined aqueous layers were extracted with Et_2O (3 × 75 mL). The organics were then combined, washed with H_2O and brine, dried, filtered, and concentrated. Following vacuum distillation, the title compound **51b** (80.4 g, 94%) was obtained as a clear yellowish liquid: bp 99−104 °C (0.3 mbar); NMR δ 1.30 (s, 6H), 2.09 (s, 3H), 2.33 (s, 3H), 2.67 (s, 2H), 7.22−7.32 (m, 4H); IR (capillary film) 1717, 1358, 1118, 783, 697 cm^{-1}. Anal. ($C_{13}H_{18}OS$) C, H, S.

4-(3-Methylphenylthio)butan-2-one (51a) was analogously prepared: 85% yield; pale yellowish oil; bp 92 °C (0.3 mbar); NMR δ 2.09 (s, 3H), 2.28 (s, 3H), 2.75 (t, $J = 7.1$, 2H), 3.08 (t, $J = 7.1$, 2H), 6.98−7.23 (m, 4H); IR (capillary film) 1717, 1592, 1476, 1361, 775 cm^{-1}. Anal. ($C_{11}H_{14}OS$) C, H, S.

2,4-Dimethyl-4-(3-methylphenylthio)pentan-2-ol (52b). To a solution of methylmagnesium iodide in dry Et_2O (500 mL), freshly prepared from Mg (17.5 g, 0.72 mol) and MeI (45 mL, 720 mmol), was added dropwise compound **51b** (80 g, 360 mmol) in Et_2O (150 mL). The solution was stirred at room temperature for 3 h and poured slowly onto ice. The resulting mixture was neutralized with diluted H_2SO_4 (pH ∼6.5); the Et_2O layer was separated, and the aqueous layer was extracted with Et_2O (3 × 150 mL). The organic layers were combined and dried. Evaporation of the solvent gave an oil which was vacuum distilled to give **52b** (77.2 g, 90%) as a yellow liquid: bp 97−104 °C (0.3 mbar); NMR δ 1.19 (s, 6H), 1.33 (s, 6H), 1.76 (s, 2H), 2.32 (s, 3H), 7.20−7.30 (m, 4H); IR (capillary film) 3447, 2970, 2924, 1366, 1182, 782, 697 cm^{-1}. Anal. ($C_{14}H_{22}OS$) C, H, S.

2-Methyl-4-(3-methylphenylthio)butan-2-ol (52a) was analogously prepared: 86% yield; colorless liquid; bp 115 °C (0.4 mbar); NMR δ 1.12 (s, 6H), 1.64 and 2.95 (m, AA′BB′, 4H), 2.28 (s, 3H), 4.30 (s, 1H), 6.95−7.22 (m, 4H); IR (capillary film) 3408, 2970, 2929, 1593, 1475, 773, 689 cm^{-1}. Anal. ($C_{12}H_{18}OS$) C, H, S.

2,2,4,4,7-Pentamethylthiochroman (53b). To standard equipment was added $AlCl_3$ (172 g, 1.29 mol) in dry CS_2 (600 mL). To the stirred suspension was added dropwise a solution of alcohol **52b** (77 g, 323 mmol) in CS_2 (200 mL) at room temperature over the course of 1 h. The resulting suspension was heated at reflux while it was stirred overnight. After cooling to room temperature, the suspension was poured onto ice, and the aqueous layer, which separated, was extracted with Et_2O (3 × 200 mL). The organic extracts were combined, extracted with H_2O and brine, and then dried. Evaporation of the solvent gave **53b** (70 g, 98%) as a reddish-brown oil, which was suitable for direct use: NMR δ 1.32 (s, 6H), 1.35

(s, 6H), 1.90 (s, 2H), 2.19 (s, 3H), 6.85 (s br, 1H), 6.90 (d br, J = 8.0, 1H), 7.33 (d, J = 8.0, 1H); IR (capillary film) 2961, 2919, 1489, 1365, 812 cm^{-1}. Anal. ($C_{14}H_{20}S$) C, H, S.

4,4,7-Trimethylthiochroman (53a) was analogously prepared: 89% yield; yellowish liquid; bp 65−70 °C (0.1 mbar); NMR δ 1.24 (s, 6H), 1.86 and 2.98 (m, AA′BB′, 4H), 2.17 (s, 3H), 6.78−7.28 (m, ABX, 3H); IR (capillary film) 2959, 2936, 1489, 1450, 810 cm^{-1}. Anal. ($C_{12}H_{16}S$) C, H, S.

2,2,4,4,7-Pentamethyl-1,1-dioxo-1λ^6-thiochroman (54b). To a suspension of thiochroman **53b** (1 g, 4.54 mmol) in glacial acetic acid (10 mL) was added sodium perborate·$3H_2O$ (2.09 g, 13.6 mmol) in portions. After the mixture was stirred at 55 °C for 4 h, this was poured into ice/water (100 mL). The precipitate was isolated and recrystallized from (i-Pr)$_2$O/CH_2Cl_2 to obtain **54b** (490 mg, 42%) as white crystals: mp 175−176 °C; NMR δ 1.33 (s, 6H), 1.36 (s, 6H), 2.24 (s, 2H), 2.36 (s, 3H), 7.40−7.62 (m, 3H); IR (KBr) 1278, 1128, 827, 714 cm^{-1}. Anal. ($C_{14}H_{20}O_2S$·$0.2H_2O$) C, H, S.

2,2,4,4-Tetramethyl-1,1-dioxo-1λ^6-thiochroman-7-carboxylic Acid (55c). $KMnO_4$ (31.3 g, 198 mmol) was added portionwise to a boiling solution of compound **54b** (10 g, 39.1 mmol) and methyltrioctylammonium chloride (2 mL, 4.03 mmol) in pyridine (75 mL) and H_2O (150 mL). After the mixture was refluxed for an additional 1 h, MnO_2 was filtered off from the hot suspension using a further quantum of hot H_2O. The solution was washed with EtOAc (2 × 100 mL) and acidified. The precipitate was collected and recrystallized from EtOAc/MeOH, yielding **55c** as white crystals (5.8 g, 53%): mp 224−225 °C; NMR δ 1.36 (s, 6H), 1.42 (s, 6H), 2.29 (s, 2H), 7.82 (d, J = 8.4, 1H), 8.13 (dd, J = 8.4, J = 1.9, 1H), 8.33 (d, J = 1.9, 1H), 13.35 (s br, 1H); IR (KBr) 1695, 1294, 1128, 710 cm^{-1}. Anal. ($C_{14}H_{18}O_4S$) C, H, S.

4,4-Dimethyl-1,1-dioxo-1λ^6-thiochroman-7-carboxylic acid (55a) was analogously prepared from **53a** via **54a**, which was not characterized: white crystals; 37% overall yield; mp 236−238 °C; NMR δ 1.39 (s, 6H), 2.31 and 3.59 (AA′BB′, 4H), 7.78 (d, J = 8.4, 1H), 8.09 (dd, J = 8.4, J = 1.9, 1H), 8.25 (d, J = 1.9, 1H), 13.40 (s br, 1H); IR (KBr) 1690, 1297, 1146, 1132 cm^{-1}. Anal. ($C_{12}H_{14}O_4S$) C, H, S.

Method P. *N*-(6′-Methyl-1′,1′-dioxo[1,3-dioxolan-2,4′-1λ^6-thiochroman]-7′-carbonyl)guanidine (11b). Free guanidine base was prepared by consecutive addition of Na (180 mg, 7.83 mmol) and guanidine·HCl (700 mg, 7.33 mmol) to dry MeOH (20 mL). After being stirred for 30 min at room temperature under N_2 protection, the suspension was filtered. Methyl carboxylate **11a** (350 mg, 1.12 mmol) was added, to the filtrate, and the mixture was stirred for 3 h at 50 °C. H_2O (100 mL) was added, and the solution was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried and evaporated, and the residue was triturated with Et_2O, yielding **11b** (190 mg, 49%): mp 237−238 °C; NMR δ 2.54 (AA′BB′, 2H), 2.56 (s, 3H), 3.61 (AA′BB′, 2H), 4.11 (AA′BB′, 2H), 4.21 (AA′BB′, 2H), 7.40 (s, 1H), 8.13 (s, 1H); IR (KBr) 3449, 1662, 1612, 1600, 1529, 1352, 1291, 1113 cm^{-1}. Anal. ($C_{14}H_{17}N_3O_5S$·$0.5H_2O$) C, H, N, S.

Method Q. *N*-(7-Methyl-1,1-dioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo[*b*]thiepine-8-carbonyl)guanidine Methanesulfonate (9c). Acid **9b** (160 mg, 0.608 mmol) was chlorinated with $SOCl_2$ (7 mL, 96.5 mmol) at 120 °C for 2 h. Excessive $SOCl_2$ was removed by the aid of a water-jet pump, and the remaining acid chloride was used without further purification. The preparation of guanidine base (3 mmol) in MeOH was carried out as described in the preceding instructions. The MeOH was removed in vacuo and the residue taken up in 1,2-dimethoxyethane (10 mL). The acid chloride was also taken up in 1,2-dimethoxyethane (10 mL) and then the mixture added to the guanidine solution. The mixture was stirred for 2 h at room temperature and evaporated. On trituration with ice/water (10 mL), the acylguanidine (125 mg) deposited. A part of the dried base (60 mg) was converted in the methanesulfonate **9c** (55 mg, 48% overall yield) by addition of $MeSO_3H$ (0.02 mL, 0.308 mmol) to the cooled Me_2CO solution (10 mL): mp 168−170 °C dec; NMR (DMSO-d_6 and TFA) δ 1.70−1.85 (m, 2H), 2.06−2.20 (m, 2H), 2.50 (s, 3H), 3.10−3.20 (m, 2H), 3.34−3.42 (m, 2H), 7.48 (s, 1H), 8.13 (s, 1H); IR (KBr) 3434, 1608, 1527, 1358, 1287, 1116 cm^{-1}. Anal. ($C_{13}H_{17}N_3O_3S$·CH_4O_3S) C, H, N, S.

Method R. *N*-(6-Methyl-1,1,4-trioxo-1λ^6-thiochroman-7-carbonyl)guanidine Hydrochloride (10b). Ketal **11b** (410 g, 1.18 mmol) was stirred in HCl/dioxane (3 N, 100 mL) and H_2O (5 mL) at 70 °C for 5 h. The solution was concentrated (∼20 mL), and the crystals of **10b** (320 mg, 82%) that separated were sucked off and washed with Me_2CO (7 mL): mp 314 °C; NMR δ 2.57 (s, 3H), 3.29 (t, J = 6.3, 2H), 4.04 (t, J = 6.2, 2H), 7.97 (s, 1H), 8.12 (s, 1H), 8.45 (s br, 2H), 8.65 (s br, 2H), 12.25 (s br, 1H); IR (KBr) 1721, 1699, 1327, 1290, 1254 cm^{-1}. Anal. ($C_{12}H_{13}N_3O_4S$·HCl) C, H, Cl, N, S.

Method S. *N*-(3-Isopropylidene-5-methyl-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-benzo[*b*]thiophene-6-carbonyl)guanidine Methanesulfonate (19). Acid **16b** (420 mg, 1.58 mmol) and 2-chloro-1-methylpyridinium iodide (450 mg, 1.76 mmol) in NMP (9 mL) were stirred for 20 min. After addition of guanidine·HCl (620 mg, 6.49 mmol), *N*-ethyldiisopropylamine (2.2 mL, 12.9 mmol) was dropped in while the mixture was slightly cooled, and stirring was continued for an additional 1 h. The mixture was poured into ice/water (100 mL) and the resulting mixture acidified, washed with EtOAc (2 × 50 mL), alkalified, and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried, evaporated, and triturated with Et_2O to give **19** (240 mg) as the free base: mp 195−197 °C; NMR (DMSO-d_6 and TFA) δ 1.97 (s, 3H), 2.20 (s, 3H), 2.54 (s, 3H), 4.29 (s, 2H), 7.77 (s, 1H), 8.06 (s, 1H); IR (KBr) 1681, 1600, 1525, 1342, 1301 cm^{-1}. To the solution of the base (200 mg, 0.651 mmol) in Me_2CO (20 mL) was added $MeSO_3H$ (0.042 mL, 0.647 mmol) with a suitable pipet. Then Et_2O was added until the solution became cloudy and crystals of the methanesulfonate **19** (120 mg, 22% overall yield), which separated on cooling, were collected: mp 299 °C. Anal. ($C_{14}H_{17}N_3O_3S$·CH_4O_3S·$0.25H_2O$) C, H, N, S.

$^{22}Na^+$ Uptake Inhibition Assay. The $^{22}Na^+$ uptake inhibition assay into acidified rabbit erythrocytes was carried out as described previously.[4]

Human Platelet-Rich Plasma. The platelet swelling assay was performed according to the methodologies described by Rosskopf[19] and Scholz.[22] Blood was obtained from volunteers by venipuncture after informed consent. The blood was anticoagulated by mixing the blood (9 mL) with a sodium citrate solution (0.106 M, 1 mL). Platelet-rich plasma was obtained by centrifugation of the whole blood at 1000 rpm for 20 min at room temperature. The upper two-thirds of the supernatant was removed, and the pH was adjusted to pH 7.4. The platelet-rich plasma was stored at room temperature until it was used. All measurements were carried out within 4−5 h after obtaining the platelet-rich plasma. The platelet number was determined using the AD-260 autodilutor and the F-800 microcellcounter, both from Sysmex.

Platelet Swelling Assay. Platelet-rich plasma (140 μL) containing 2×10^8 cells (or after an appropriate dilution using a physiological salt solution) was placed in a plastic cuvette (1 cm path length), which was placed in a Perkin-Elmer double-beam 124 D spectrophotometer. Thereafter, the incubation buffer (860 μL with or without the appropriately diluted compound) was added. The final buffer component concentrations were as follows: 120 mM Na propionate, 20 mM K propionate, 20 mM 4-(hydroxyethyl)-1-piperazineethanesulfonic acid, 10 mM glucose, 5 mM KCl, 1 mM $MgCl_2$, 1 mM $CaCl_2$, and 0.86% DMSO (pH 6.6); the thrombocyte concentration was 2×10^8 cells/mL. After the addition of the buffer, the solution in the cuvette was mixed by moving a plastic cuvette mixer slowly once up and down. The change in absorbance at 680 nm was followed for 4 min; for the first 2 min, the absorption values were collected every 10 s, and thereafter, only the 4 min value was registered.

Evaluation of the Results. It has been shown[19] that the decrease in OD follows a monoexponential curve: $OD(t) = OD_{t=0'} \times e^{-bt}$. For the determination of the rate constant b, the logarithm of the normalized $OD(t)/OD_{t=0'}$ values was plotted against time. A straight line was fitted to the data by

linear regression analysis. The steepness of the line corresponds to the rate constant of the OD change. The rate constants b_i obtained in the presence of the various concentrations of the compounds to be investigated were plotted against their respective concentration. A sigmoid curve according to the equation $b(x) = (b_{max} - b_{min})/(1 + IC_{50}/x) + b_{min}$ was fitted to the data by nonlinear least squares regression analysis. As a result of the regression analysis, the IC_{50} values were obtained. The correlation among the potency values of the two assays was assessed by determining Spearman's rank correlation coefficient ρ.[23]

Acknowledgment. We extend our thanks to Heike Ebert, Günther Kritzinger, Horst May, Irina Onofrei, Thomas Weitzel, and Reinhold Zissel for their skillful experimental work and Sylvia Heiss for her assistance with the preparation of the tables and schemes included in this paper.

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JM981031W