Synthesis and Activity of Novel and Selective I_{Ks}-Channel Blockers

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Since the discovery of the I_{Ks}-potassium channel as the slowly activating component of the delayed rectifier current (I_k) in cardiac tissue, the search for blockers of this current has been intense. During the screening of K_{ATP}-channel openers of the chromanol type we found that chromanol 293B was able to block I_{Ks}. Chromanol 293B is a sulfonamide analogue of the K_{ATP}-channel openers but had no activity on this target. Experiments were initiated to improve the activity and properties based on this lead compound. As a screening model we used *Xenopus* oocytes injected with human minK (KCNE1). Variations of the aromatic substituent and the sulfonamide group were prepared, and their activity was evaluated. We found that the greatest influence on activity was found in the aromatic substituents. The most active compounds were alkoxy substituted. We chose HMR1556 ((3R, 4S)-(+)-*N*-[-3-hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-*N*-methyl-ethanesulfonamide) **10a** for development as an antiarrhythmic drug. The absolute configuration, resulting from an X-ray single-crystal structure analysis, was determined.

Introduction

Cardiac arrhythmias are still a major cause of death in the western world, especially in patients with ischemic heart disease. These irregularities are caused by abnormalities in the electrical activity of the heart which may result from excessive sympathetic stimulation and/or changes in the ionic mechanism responsible for the generation and propagation of the normal action potential.

The shape of the action potential of heart cells is strongly controlled by the correct interplay of ion channels.[1] The main ion channels contributing to the action potential are sodium, calcium, and potassium channels. The potassium channels form the most diverse family, and they are responsible for the inward rectification (I_{K1}, I_{KACh}, I_{KATP}), sustained outward (I_{Kur}, I_{Kr}, I_{Ks}) and transient outward (I_{to}) rectification.

The depolarization (upstroke) of the membrane potential—caused by inward sodium current—is followed by a partial early repolarization caused by outward potassium current through rapidly activating and inactivating K^+ channels. The plateau phase depends on a balance of inward (depolarizing) and outward (repolarizing) currents. The depolarizing force not only is mainly a Ca^{2+} influx that slowly declines as L-type Ca^{2+} channels inactivate but also a noninactivating Na^+ current can support the plateau phase. The repolarizing action depends on K^+ efflux due to activation of several voltage-gated potassium channels, mainly the rapidly activating delayed rectifier (I_{Kr}) and the slowly activating delayed rectifier (I_{Ks}) potassium currents.[1]

Most of these ion currents and their ion channels have been the target of antiarrhythmic therapy and have been classified mechanistically into four main classes: class I (sodium channel blockade), class II (β-adrenergic blockade), class III (potassium channel blockade), and class IV (calcium channel blockade).[2]

Some of the antiarrhythmic drugs however are not specific to one mechanism or ion channel but act on several modes; a prominent example is the most used antiarrhythmic drug Amiodarone. It exerts a multiplicity of pharmacological effects, which could be associated with, in part, each of the class I−IV antiarrhythmic agents and is an effective agent in the control of ventricular tachyarrhythmias and fibrillation (VT/VF).[3,4]

In the 1980s CAST (Cardiac Arrhythmia Suppression Trial), with the drugs encainide and flecainide, uncovered the inefficacy and even proarrhythmic risk of sodium channel blockers (class I antiarrhythmics) in patients at relatively low long-term risk for cardiac death.[5−7] The elevated mortality in the treated group was rationalized on the sodium channel blockade activity of these compounds, and the study was terminated.

To circumvent the problems with class I antiarrhythmics, pharmacological and clinical research shifted toward the class III agents, which act on the delayed rectifier potassium current and therefore prolonging the AP. Dofetilide, d-sotalol, E-4031, and MK-499 are examples of so-called pure class III compounds.[8] All of these compounds act selectively on the rapid form of the delayed rectifier potassium channel (I_{Kr}). The antiarrhythmic benefit afforded by class III agents is proposed to result from a sufficient prolongation of myocardial refractoriness such that the wavelength of activation exceeds the path length of the reentrant circuit, thereby preventing the initiation or maintenance of reentrant excitation.[9]

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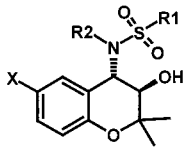
Table 1: Inhibitory Activity of Chromanols on the Human I_{Ks}-Channel Expressed in Xenopus Oocytes



compd	X	R1	R2	IC50 (μM)	chirality
1	CN	Et	Me	6.9	rac
1a	CN	Et	Me	5,0	3R,4S
1b	CN	Et	Me	44,5	3S, 4R
2	CN	Bu	Me	58	rac
3	H	Et	Me	3.1	rac
4	F	Et	Me	1.2	rac
4a	F	Et	Me	0.7	3R,4S
4b	F	Et	Me	2.2	3S,4R
5	Cl	Me	Me	1.1	rac
6	OPr	Me	Me	0.9	rac
7	OBn	Me	Me	0.2	rac
8a	OBn	Et	Me	0.05	3R,4S
8b	OBn	Et	Me	0.4	3S,4R
9	OBu	Me	Me	0.25	rac
10	$O(CH2)_{3CF3}$	Me	Me	0.24	rac
10a	$O(CH2)_{3CF3}$	Me	Me	0.12	3R,4S
10b	$O(CH2)_{3CF3}$	Me	Me	0.44	3S,4R

This class of agents also underwent a series of clinical trials. The SWORD-trial (Survival With Oral D-sotalol) was terminated because of an increase in mortality in the treated patients using the pure I_{Kr}-channel blocker d-sotalol.[10] Also in the recent study, DIAMOND[11] (Danish Investigation of Mortality on Dofetilide) with patients, which were at higher risk of mortality than the SWORD population, the outcome was neutral at the best.

These disappointing results have been attributed to the so-called "negative use-dependence", which was already demonstrated preclinically with various I_{Kr}-channel blockers.[12] This property has two effects:

1. An extended prolongation of the action potential (AP) of heart cells at low heart frequency and at low β-adrenergic status: This prolongation of the AP may lead to early after depolarization (EAD) and under certain circumstances to fatal Torsades de Pointes (TdP).[13,14]

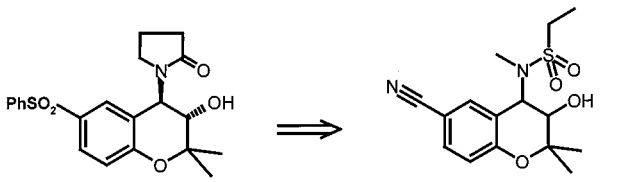
2. A weak prolongation of the AP at high heart rate[15] and high β-adrenergic stimulation:[16,17] This unsatisfactory activity reduces the antiarrhythmic effect of these drugs and the positive effect of the AP prolongation expected from the activity on the AP at normal heart frequency.

It has been shown that I_K consists of two components[18] (I_{Kr} and I_{Ks}). Negative use dependency has been attributed to an increased contribution of the I_{Ks}-channel on the repolarization under elevated heart rate[15] and β-adrenergic activation.[16]

Furthermore, there is evidence that β-adrenergic sympathetic activity is an important factor in the genesis of malignant ventricular tachyarrhythmias.[19] It has been demonstrated that β-adrenergic stimulation attenuates or even reverses the electrophysiological and antiarrhythmic effects of various class I antiarrhythmic agents[20] and class III antiarrhythmics such as D-Sotalol,[21] E-4031,[16] and sematilide.[22] This may be due to an increase of I_{Ks} under these conditions. Therefore I_{Ks}-channel blockers seem to offer a more desirable class III antiarrhythmic profile than the I_{Kr}-channel blockers.

Since the discovery that I_K consists of two kinetically distinct and identifiable currents,[18] the search for selective I_{Ks}-channel blockers has begun. In 1996[23−25] the potent and selective I_{Ks}-channel blocker Chromanol 293B **1** was described. Subsequently this compound was tested in several models. In these studies 293B **1** showed selectivity for the I_{Ks}-channel[26] and confirmed the proposed consequences of I_{Ks}-channel blockade. Examples of the latter include the higher activity under β-adrenergic stimulation[17,27] and the positive usedependence in human cells[26] and the canine heart.[28] Since then I_{Ks}-channel blockers with different structures have been published.[29,30]

However, chromanol 293B **1** did not meet the profile of a development drug. In this article we will describe the variations made in the series of the chromanol structure. Other variations have been described earlier.[31]



HOE 234 (K_{ATP}-channel opener) **Chromanol 293B 1** (I_{Ks}-channel blocker)

Results

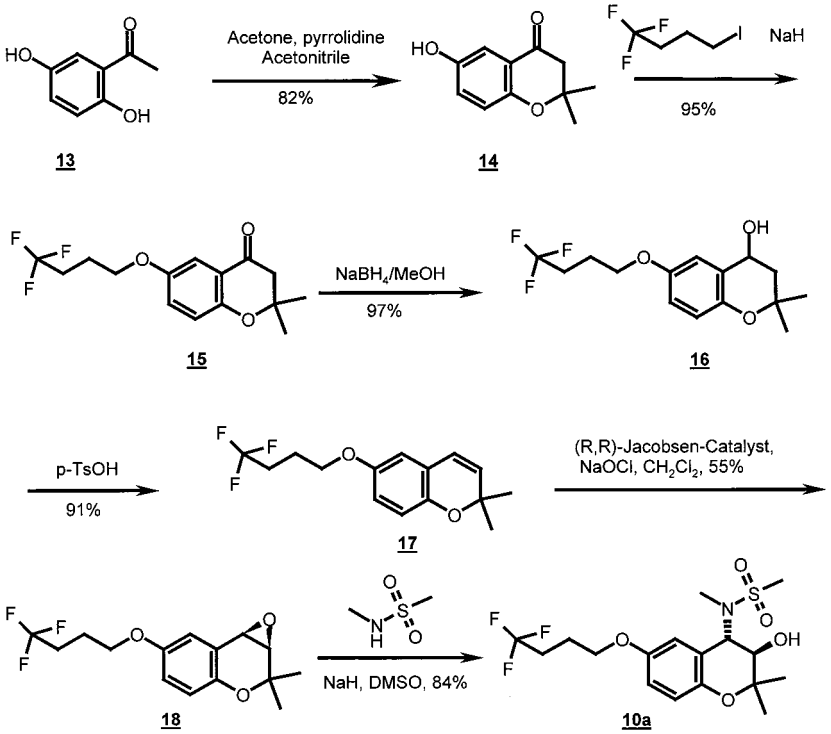
Starting from the pharmacophore of the K_{ATP}-channel openers[32] the first selective I_{Ks}-channel blocker chromanol 293B **1** was found. Besides its described selectivity toward other ion channels **1** was not active on the original target the K_{ATP}-channel.[24,25] We searched for molecules with improved I_{Ks}-channel blocking activity and discovered that variation at the 6-position on the aromatic ring can greatly increase activity. The most potent compounds were 6-ether-substituted compounds **8a** and **10a**. Table 1 shows the IC_{50} values for the selected compounds.

As a screening model for the compounds we used *Xenopus* oocytes injected with c-RNA of human minK (KCNE1), the β-subunit of KvLQT1.[33] Together with the endogenous XKvLQT1, minK forms the functional I_{Ks}-channel.

The lead compound **1** has an IC_{50} value on the I_{Ks}-channel of 6.9 μM as a racemate and 5.0 and 44.5 μM for the two separated enantiomers, respectively. The absolute stereochemistry was determined by X-ray crystallography[34] and is in agreement with the expected outcome of the chiral epoxidation.[35] Increasing the size of the sulfonyl residue from ethyl to butyl (compound **2**) lowered the activity to 58 μM.

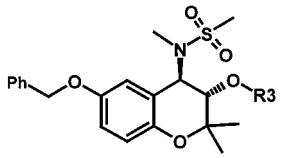
While the unsubstituted chromanol **3** had only a slightly improved activity, the 6-fluoro **4** and 6-chloro **5** derivatives showed half-maximal inhibition of the I_{Ks}-channel at around 1 μM. In the case of the fluoro compound the enantiomers **4a** and **4b** were prepared separately and showed different inhibitory activities with 0.7 and 2.3 μM, respectively.

Scheme 1: Synthesis of (3R, 4S)-(+)-*N*-[-3-Hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-*N*-methylethanesulfonamide **10a**



Surprisingly, a major improvement in the activity was found with the 6-alkoxy derivatives especially with more lipophilic side chains. The 6-propoxy substituted chromanol **6** produced an IC_{50} of 0.9 μM and the slightly bigger butoxy- and trifluorobutoxyether derivatives (entries **9** and **10**) showed inhibitory activities of 0.25 and 0.24 μM, respectively. The enantiomers of the trifluorobutoxy compound were synthesized separately and showed activities of 0.12 μM (**10a**) and 0.24 μM (**10b**), respectively. The benzyl ether **8a** was the most potent compound, which showed an I_{Ks}-blocking activity of 50 nM.

In all cases examined we found the enantiomer with the 3R,4S-configuration to have the higher activity.



R3= Ac (11), R3= Me (12)

The influence of the 3-hydroxy-group was checked by acetylation (**11**) and methylation (**12**) of the 6-benzylether **7** (IC_{50} = 200 nM). In both cases the activity decreased to 13 μM (**11**) and 6.5 μM (**12**), respectively.

(3R,4S)-(+)-*N*-[-3-Hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-*N*-methylethanesulfonamide **10a** was chosen as development compound with the company code HMR1556 and the selectivity toward several other ion channels was evaluated thoroughly.[36] HMR1556 **10a** inhibits the potassium current of I_{Ks}-channels expressed in *Xenopus laevis* oocytes half-maximally at a concentration of 120 nM (IC_{50}).[36] In contrast the currents of the expressed K^+ channels h*erg*, Kv1.5, Kv1.3, and Kir2.1, and also the cationic current HCN2 were blocked little or not at all by 10 μmol/L HMR 1556, showing the selectivity of the compound.[36]

In isolated ventricular myocytes from the guinea pig the whole cell patch clamp method revealed inhibition of the I_{Ks} current with an IC_{50} of 34 nM. Other current components, like I_{Kr} and I_{K1}, were only slightly blocked by **10a** with a concentration of 10 μmol/L, whereas 10 μmol/L **10a** inhibited the transient outward current I_{to} and the sustained outward current I_{sus} in rat ventricular myocytes by 25% and 36%, respectively. The L-type Ca^{2+} channel in guinea pig cardiomyocytes was blocked by 10 μmol/l **10a** by 31%,[36] showing a selectivity of approximately 300-fold to the other ion channels. Further in vitro and in vivo studies have been performed and confirm the proposed activity on cardiac repolarization.[36]

Chemistry

The synthesis of **10a** is shown in Scheme 1 and exemplifies the general synthesis strategy for this class of compounds. We started from the commercially available 2,5-dihydroxyacetophenone **13**, which was cyclized with acetone and pyrrolidine by a variation of a literature procedure.[37] 6-Hydroxy-2,2-dimethylchromanone **14** was obtained in 82% yield. The phenol **14** was alkylated with 4-trifluorobutyl iodid under standard conditions in 95% yield. The chromanone **15** was reduced to the 4-chromanol **16** with $NaBH_4$ (97% yield). Elimination of water under acid catalysis gave rise to 6-trifluorobutyl-2,2-dimethylchromene **17** in 91% yield. For the synthesis of the chiral epoxide we used (R,R)-(−)-*N*,*N*′-bis(3,5-di-tert-butylsalicyliden)-1,2-diaminocyclohexanmanganese(III) chloride (Jacobsen catalyst).[38] We obtained the 3R,4R-epoxide **18** in high optical yield. The epoxide **18** was then opened regio- and stereoselectively by *N*-methylmethanesulfonamide/NaH. The

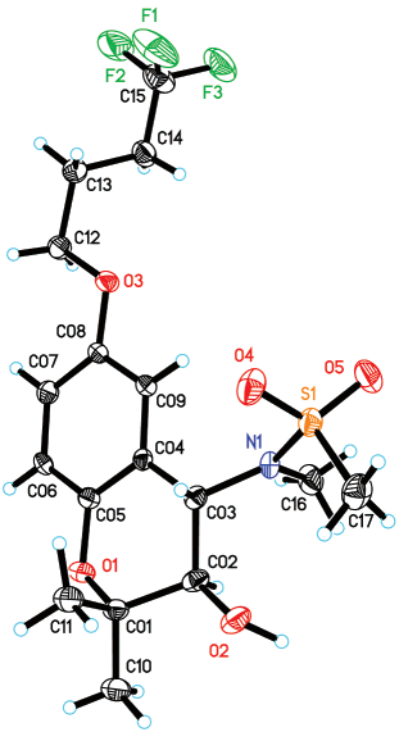


Figure 1. X-ray analysis of **10a**.

other possible regio-isomer was not found at all. The absolute stereochemistry of the chromanol **10a** was proven by X-ray analysis (see Figure 1), and the stereochemical purity was checked by chiral HPLC.

The racemic compounds were synthesized by the same sequence with exception of the epoxidation, which was done in two steps with the bromo hydrin as racemic intermediate as described for similar compounds in the literature.[32]

Summary

There is high medical need for safe and efficient antiarrhythmic drugs. I_{Ks}-channel blockers may provide this kind of drug. Investigation of chromanol structures of the K_{ATP}-channel openers revealed the lead structure chromanol 293B **1**. We succeeded in greatly improving the activity of this class of compounds in blocking the I_{Ks}-channel. We prepared several molecules with various substituents at the 6-position of the aromatic ring and the sulfonamide functionality. Even with only one example shown, a decrease of activity with bulkier substituents on the sulfonyl residue was seen. The major improvements were made by changes in the aromatic substituents. Higher alkoxy substituents such as butoxy exhibited the highest potency. We found compounds with an IC_{50} of as low as 50 nM (**8a**). Enantioselective synthesis was achieved by Jacobson epoxidation of the chromene intermediates and opening of the epoxide without loss of stereochemical information. The two enantiomers had different activities, and the absolute configuration of the more potent compound was determined by X-ray structure analysis and is shown in Figure 1. Surprisingly, the absolute configuration is opposite to that of the more potent K_{ATP}-channel opener compounds, which were the starting point for our investigation. The compounds described are currently under in vivo investigation as antiarrhythmic drugs in several animal models. This gives us the opportunity to evaluate a highly active and selective I_{Ks}-channel blocker in various models of arrhythmia and to prove this new concept for antiarrhythmic drugs. The first more detailed in vitro and in vivo data on HMR1556 **10a** were published recently.[36]

Experimental Section

I. Chemistry. Physical Methods. Solvents and other reagents were used without further purification unless otherwise stated. Column chromatography was carried out on E. Merck silica gel 60 (35−70 and 70−230 mesh). Thin-layer chromatography carried out on TLC glass sheets with silica gel 60F254, layer thickness 0.2 mm, from Merck. The NMR spectra were recorded either on a Varian Gemini 200, a Varian Unity 300, or a Bruker DRX 400. Chemical shifts are reported as δ values from an internal tetramethylsilane standard. DCI mass spectra were measured on a TRIO 2000 using isobutane as reagent gas and ESI mass spectra on a VG BIO-Q. Positive FAB mass spectra were obtained on a VG ZAB2 SEQ in a 3-nitrobenzylic-alcohol matrix using cesium as the target gas. Melting points were obtained with a Büchi melting point B-540 and are not corrected. Enantiomeric purity was determined by a ThermoQuest-HPLC device, using chiral DNBPG- or using a CSP S Whelk-01 column from Daicel.

A crystal of 0.2 × 0.12 × 0.03 mm^3 (crystallized from methanol) was used for the single-crystal structure analysis of **10a**: Bruker AXS four circle diffractometer equipped with a CCD area-detector, Mo−Kα radiation (rotating anode: 0.5 × 5 mm^2 focus), direct methods for solving the phase problem,[39] determination of the absolute configuration with a very high significance [Flack parameter: 0.03(9)], R_1 (all 2091 unique data) = 0.0359. Supporting material for the X-ray structure analysis is available: crystal data and structure refinement, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, torsion angles, hydrogen bonds (2.864 Å) in the crystal cell.

(3R,4S)-(+)-*N*-[3-Hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-*N*-methylethanesulfonamide 10a. 2,2-Dimethyl-6-hydroxychroman-4-one 14. A reaction mixture of 100 g (0.65 mol) of commercially available 2,5-dihydroxyacetophenone **13** in 1 L of acetonitrile, 130 mL (1.55 mol) of pyrrolidine, and 290 mL (3.95 mol) of acetone was heated at 45 °C for 8 h. The solvents were then removed in a vacuum, and the residue was dissolved in 1 L of ethyl acetate. The organic phase was washed twice with dilute hydrochloric acid, stirred with charcoal, and dried over magnesium sulfate and substantially concentrated. The residue was stirred with petroleum ether, and the precipitate was filtered off with suction giving 102 g (82%) of 2,2-dimethyl-6-hydroxychroman-4-one: mp 161 °C; ^{1}H NMR (DMSO-d_6) δ [ppm] 2.44 (s, 6H); 2.82−3.05 (m, 2H); 7,15−7,25 (m, 4H); MS (DCI) *m/e* 204 ($M+H^+$).

2,2-Dimethyl 6-(4,4,4-Trifluorobutoxy)chroman-4-one 15. A solution of 13.4 g (70 mmol) of 2,2-dimethyl-6-hydroxychroman-4-one **14** in 250 mL of DMF was added dropwise to a solution of 2.65 g (88 mmol) of 80% sodium hydride in 170 mL of DMF. The mixture was stirred at room temperature for 1 h, 14.6 g (76 mmol) of 4,4,4-trifluorobutyl iodide was added, and the mixture was left to stand at room temperature overnight. The reaction mixture was poured into 3 L of water. The precipitated product was filtered off with suction, washed with water, and dried under reduced pressure. This gave 20.0 g (95%) of 6-(4,4,4-trifluorobutoxy)-2,2-dimethylchroman-4-one as colorless solid: mp 62 °C; ^{1}H NMR ($CDCl_3$) δ [ppm] = 1.43 (s, 6H), 1,9−2,4 (m, 4H), 2.7 (s; 2H), 4.0 (t; 2H), 6.85 (d; 1H), 7.1 (dd; 1H), 7.25 (d; 1H).

2,2-Dimethyl 6-(4,4,4-Trifluorobutoxy)chroman-4-ol 16. A solution of 20 g (66 mmol) of 2,2-dimethyl 6-(4,4,4-trifluorobutoxy)chroman-4-one **15** and 2.5 g (66 mmol) of sodium borohydride in 100 mL of methanol was stirred at room temperature overnight. The reaction mixture was poured into

ice water, mixed with common salt, and extracted 4 times with ethyl acetate. Drying and concentration of the organic phase gave 19.5 g (97%) of 6-(4,4,4-trifluorobutoxy)-2,2-dimethylchroman-4-ol that was directly converted in the following step.

2,2-Dimethyl 6-(4,4,4-Trifluorobutoxy)chromene 17. A solution of 19.5 g (64 mmol) of 2,2-dimethyl 6-(4,4,4-trifluorobutoxy)chroman-4-ol **16** in 200 mL of toluene was mixed with 0.2 g of *p*-toluenesulfonic acid monohydrate and heated at 100 °C for 22 h. After cooling, the batch was extracted twice with 120 mL of sodium bicarbonate solution each time and stirred with activated carbon. Filtration and concentration under reduced pressure gave 16.7 g (91%) of 6-(4,4,4-trifluorobutoxy)-2,2-dimethyl-2H-chromene **17** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ [ppm] = 1.4 (s, 6H), 1,9−2,4 (m, 4H), 3.95 (t; 2H), 5.65 (d; 1H), 6.25 (d; 1H), 6.5 (d; 1H), 6.6−6.7 (m; 2H).

(3R,4R)-(+)-2,2-Dimethyl-6-(4,4,4-trifluorobutoxy)-3,4-epoxychroman 18. At 0 °C, 38.5 mL (22 mmol) of a 0.55 M sodium hypochlorite solution which had been adjusted to pH 11.3 using disodium hydrogen phosphate were added dropwise to a solution of 2.86 g (10 mmol) of 2,2-dimethyl 6-(4,4,4-trifluorobutoxy)chromene **17** and 0.26 g (0.4 mmol) of (R,R)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-diaminocyclohexanemanganese(III) chloride[38] in 11 mL of methylene chloride. The reaction mixture was stirred vigorously for 1 h, the organic phase was then separated off, and the aqueous phase was extracted once more with a little methylene chloride. The organic phase was filtered through a short silica gel column, and the fractions were concentrated under reduced pressure. This gave 1.65 g (55%) of (3R,4R)-(+)-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)-3,4-epoxychroman **18a** as a solid (mp 90 °C): optical rotation +40,7° (*c* = 1, toluene), +40,5° (*c* = 2, toluene).

(3R,4S)-(+)-*N*-[3-Hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-*N*-methylmethanesulfonamide 10a. *N*-Methylmethanesulfonamide (0.77 g, 7.1 mmol) was added to a suspension of 65 mg (2.7 mmol) of 80% sodium hydride in 3 mL of DMSO under argon, and the mixture was stirred at room temperature for 20 min. (3R,4R)-(+)-2,2-Dimethyl-6-(4,4,4-trifluorobutoxy)-3,4-epoxychroman (1.65 g, 5.5 mmol) **18**, dissolved in 5 mL of DMSO, was added dropwise, and the batch was left to stand at room temperature for 4 days and then heated at 45 °C for a further 9 h. The mixture was subsequently poured into water, and the precipitate was filtered off with suction and dried thoroughly under reduced pressure, giving 1.9 g (84%) of (3R,4S)-(+)-[3-hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-*N*-methylmethanesulfonamide, which was recrystallized from a little 2-propanol (1.4 g; mp 178−179 °C): ^{1}H NMR ($CDCl_3$) δ [ppm] 1.21 (s, 3H); 1.50 (s, 3H); 1.92 −2.10 (m, 2H); 2.25−2.41 (m, 3H); 2.69 (s, 3H); 3.13 (s, 3H); 3.80 (dd, *J* = 10.0 Hz, *J* = 5.1 Hz, 1H); 3.95 (t, *J* = 5.8 Hz, 2H); 4.91 (d, *J* = 10.0 Hz, 1H); 6.73−6.83 (m, 3H); optical purity (HPLC) 100%, [α] = +2.8° (*c* = 1; MeOH), +2.9° (*c* = 2; MeOH).

Anal. Calcd for $C_{17}H_{24}F_3NO_5S$: C, 49.63; H, 5.88; N, 3.40. Found: C, 49.74; H, 5.75; N 3.46%.

Spectral and Analytical Data. *N*-[6-Cyano -3-hydroxy-2,2-dimethyl-chroman-4-yl]-*N*-methylethanesulfonamide 1. ^{1}H NMR ($CDCl_3$) δ [ppm] 1.26 (s, 3H); 1.44−1.61 (m, 6H); 2.69 (s, 3H); 2.70−2.72 (m, 1H); 3.24−3.35 (m, 2H); 3.77−3.85 (m, 1H); 4.87−4.93 (m, 1H); 6.87−6.91 (m, 1H); 7.45−7.50 (m, 1H); 7.62−7.64 (m, 1H); mp 139 °C.

Anal. Calcd for $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64. Found: C, 55.44; H, 6.12; N 8.46%.

(3R,4S)-*N*-[6-Cyano-3-hydroxy-2,2-dimethylchroman-4-yl]-*N*-methylethanesulfonamide 1a. Mp 192 °C; [α] = +3.2° (*c* = 2; MeOH). NMR as **1**.

Anal. Calcd for $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64. Found: C, 55.65; H, 6.22; N 8.77%.

(3S,4R)-*N*-[6-Cyano -3-hydroxy-2,2-dimethylchroman-4-yl]-*N*-methylethanesulfonamide 1b. Mp 192 °C; [α] = −4.2° (*c* = 2; MeOH). NMR as **1**.

Anal. Calcd for $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64. Found: C, 55.39; H, 6.15; N 8.57%.

6-[Cyano-3-hydroxy-2,2-dimethylchroman-4-yl)-*N*-methyl butanesulfonamide 2. ^{1}H NMR ($CDCl_3$) δ [ppm] 1.00 (t, *J* = 8.0 Hz, 3H); 1.45−1.63 (m, 5H); 1.82−1.98 (m, 2H); 2.68−2.74 (m, 4H); 3.22−3.37 (m, 2H); 3.73−3.84 (m, 1H); 4.90 (d, *J* = 10 Hz, 1H); 6.88−6.95 (m, 1H); 7.45−7.49 (m, 1H); 7.63−7.67 (m, 1H); mp 171 °C.

Anal. Calcd for $C_{17}H_{24}N_2O_4S$: C, 57.93; H, 6.86; N, 7.95. Found: C, 58.08; H, 6.95; N 8.07%.

***N*-[3-Hydroxy-2,2-dimethylchroman-4-yl]-*N*-methylethanesulfonamide 3.** ^{1}H NMR ($CDCl_3$) δ [ppm] 1.24 (s, 3H); 1.45−1.56 (m, 6H); 2.64−2.71 (m, 4H); 3.30 (q, *J* = 7.5 Hz, 2H); 3.80 (dd, *J* = 10 Hz, *J* = 4.0 Hz, 1H); 4.88 (d, *J* = 10 Hz, 1H); 6.81−6.86 (m, 1H); 6.91−6.99 (m, 1H); 7.16−7.28 (m, 2H); mp 150 °C.

Anal. Calcd for $C_{14}H_{21}NO_4S$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.01; H, 7.25; N 4.88%.

***N*-[3-Hydroxy-2,2-dimethyl-6-fluorochroman-4-yl]-*N*-methylethanesulfonamide 4.** ^{1}H NMR ($CDCl_3$) δ [ppm] 1.22 (s, 3H); 1.44−1.51 (m, 6H); 2.55−2.57 (d, *J* = 4.6 Hz, 1H); 2.70 (s, 3H); 3.28 (q, *J* = 7.6 Hz, 1H); 3.76−3.84 (m, 1H); 4.85 (d, *J* = 10.0 Hz, 1H); 6.73−7.02 (m, 3H); mp 142 °C.

Anal. Calcd for $C_{14}H_{20}FNO_4S$: C, 52.98; H, 6.35; N, 4.41. Found: C, 53.07; H, 6.49; N 4.55%.

(3R,4S)-*N*-[3-Hydroxy-2,2-dimethyl-6-fluorochroman-4-yl]-*N*-methylethanesulfonamide 4a. Mp 147 °C; [α] = +38.5° (*c* = 2, MeOH), NMR analogue **4**.

Anal. Calcd for $C_{14}H_{20}FNO_4S$: C, 52.98; H, 6.35; N, 4.41. Found: C, 52.87; H, 6.39; N 4.56%.

(3S,4R)-*N*-[3-Hydroxy-2,2-dimethyl-6-fluorochroman-4-yl]-*N*-methylethanesulfonamide 4b. Mp 143 °C; [α] = −42.1° (*c* = 2, MeOH), NMR analogue **4**.

Anal. Calcd for $C_{14}H_{20}FNO_4S$: C, 52.98; H, 6.35; N, 4.41. Found: C, 52.79; H, 6.43; N 4.45%.

***N*-[6-Chloro-2,2-dimethyl-3-hydroxychroman-4-yl]-*N*-methylmethanesulfonamide 5.** Mp 167 °C; ^{1}H NMR ($CDCl_3$) δ [ppm] = 1.23 (s, 3H), 1.51 (s, 3H), 2.46 (d, *J* = 5.1 Hz, 1H), 2.70 (s, 3H), 3.13 (s, 3H), 3.80 (dd, *J* = 10 Hz und 5.1 Hz; 1H), 4.90 (d, *J* = 10 Hz, 1H), 6.75 (d, *J* = 8.5 Hz; 1H), 7.14 (dd, *J* = 8.5 Hz und 2.5 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 1H).

Anal. Calcd for $C_{13}H_{18}ClNO_4S$: C, 48.82; H, 5.67; N, 4.38. Found: C, 49.00; H, 5.59; N 4.46%.

***N*-[2,2-Dimethyl-3-hydroxy-6-propoxychroman-4-yl]-*N*-methylmethanesulfonamide 6.** Mp 150 °C; ^{1}H NMR ($CDCl_3$) δ [ppm] = 1.02 (t, *J* = 7.3 Hz, 3H), 1.21 (s, 3H), 1.50 (s, 3H), 1.77 (sext., *J* = 7.3 Hz, 2H), 2.4 (s br., 1H), 2.69 (s, 3H), 3.13 (s, 3H), 3.8 (d, *J* = 9.8 Hz, 1H), 3.86 (t, *J* = 7 Hz, 2H), 4.90 (d, *J* = 9.8 Hz, 1H), 6.7−6.82 (m, 3H).

Anal. Calcd for $C_{16}H_{25}NO_5S$: C, 55.96; H, 7.34; N, 4.08. Found: C, 56.05; H, 7.39; N 4.02%.

***N*-[6-Benzyloxy-2,2-dimethyl-3-hydroxychroman-4-yl]-*N*-methylmethanesulfonamide 7.** Mp 163 °C; ^{1}H NMR ($CDCl_3$) δ [ppm] = 1.2 (s, 3H), 1.48 (s, 3H), 2.36 (d, *J* = 5.5 Hz, 1H), 2.6 (s, 3H), 3.05 (s, 3H), 3.75 (dd, *J* = 11 Hz and 5.5 Hz, 1H), 4.85 (d, *J* = 11 Hz, 1H), 5.0 (s, 2H), 6.7−6.9 (m, 3H), 7.3−7.45 (m, 5H).

Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.27; H, 6.59; N 3.56%.

(3R,4S)-*N*-[6-Benzyloxy -2,2-dimethyl-3-hydroxychroman-4-yl]-*N*-methylethanesulfonamide 8a. Mp 166 °C; ^{1}H NMR ($CDCl_3$) δ [ppm] = 1.2 (s, 3H), 1.45 (t, *J* = 7.3 Hz, 3H), 1.49 (s, 3H), 2.59 (d, OH), 2.60 (s, 3H), 3.20 (q, *J* = 7.3 Hz, 2H), 3.76 (dd, *J* = 10 and 5.5 Hz, 1H), 4.80 (d, *J* = 10 Hz, 1H), 5.02 (s, 2H), 6.7−6.9 (m, 3H), 7.3−7.45 (m, 5H); [α] = + 40.5° (*c* = 2, MeOH).

Anal. Calcd for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45. Found: C, 62.17; H, 6.59; N 3.56%.

(3S,4R)-*N*-[6-Benzyloxy -2,2-dimethyl-3-hydroxychroman-4-yl]-*N*-methylethanesulfonamide 8b. Mp 173 °C. NMR see **8a**. [α] = − 41° (*c* = 2, MeOH).

Anal. Calcd for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45. Found: C, 62.27; H, 6.65; N 3.44%.

***N*-[6-Butoxy -2,2-dimethyl-3-hydroxychroman-4-yl]-*N*-methylmethanesulfonamide 9.** Mp 139 °C; ^{1}H NMR ($CDCl_3$) δ [ppm] = 0.96 (t, *J* = 7.2 Hz, 3H), 1.21 (s, 3H), 1.49 (s, 3H), 1.4−1.8 (m, 4H), 2.37 (s, br., 1H), 2.69 (s, 3H), 3.13 (s, 3H),

3.79 (d, $J = 9.8$ Hz, 1H), 3.89 (t, $J = 6.3$ Hz, 2H), 4.88 (d, $J = 9.8$ Hz, 1H), 6.70−6.80 (m, 3H).

Anal. Calcd for $C_{17}H_{27}NO_5S$: C, 57.12; H, 7.61; N, 3.92. Found: C, 57.07; H, 7.59; N 4.01%.

***N*-[3-Hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)-chroman-4-yl]-*N*-methylmethanesulfonamide 10.** Mp 162 °C. NMR see **10a**.

Anal. Calcd for $C_{17}H_{24}F_3NO_5S$: C, 49.63; H, 5.88; N, 3.40. Found: C, 49.54; H, 5.79; N 3.36%.

(3S, 4R)-(+)-*N*-[3-Hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-*N*-methylmethanesulfonamide 10b. Mp 179 °C. NMR see **10a**. $[\alpha] = -2.6°$ ($c = 2$, MeOH).

Anal. Calcd for $C_{17}H_{24}F_3NO_5S$: C, 49.63; H, 5.88; N, 3.40. Found: C, 49.64; H, 5.85; N 3.49%.

II. Pharmacological Methods. Heterologous expression of I_{Ks} in *Xenopus* oocytes.

Handling and injection of *Xenopus* oocytes has been described previously in detail.[40,41] *Xenopus laevis* were anaesthetized by immersion in 3-aminobenzoic acid ethyl ester (1 g/L) and put on ice. A small incision was made to retrieve sacs of oocytes, and then the incision was sutured with absorbable surgical thread. The ovaries of *Xenopus laevis* were cut into small pieces and the oocytes were first washed in a Ca^{2+}-free Or-2 solution containing (mM): 82.5 NaCl, 2 KCl, 1 $MgCl_2$, 5 HEPES, pH 7.4, and subsequently digested with the same Or-2 solution to which 1 mg mL^{-1} collagenase A (Worthington, type II) was added until no follicle was detectable on the surface of the oocytes. Oocytes were stored in recording solution ND-96 containing (mM) 96 NaCl, 2 KCl, 1.8 $CaCl_2$, 1 $MgCl_2$, 5 HEPES, pH 7.4) with additional Na-pyruvate (275 mg/L), theophylline (90 mg/L), and gentamycin (50 mg/L) at 18 °C. The oocytes were individually injected with cRNA encoding for the human potassium channel β-subunit of K_vLQT1 (hminK). From 12 h on after the injection, two-microelectrode voltage-clamp recordings were carried out using a GeneClamp amplifier (Axon Instruments, Foster City, USA) and MacLab A/D converter and software for data acquisition and analysis (ADInstruments, Castle Hill, Australia). The microelectrodes were filled with 3 M KCl solution and had resistances between 0.5 and 1 MΩ. During the electrophysiological experiments the oocytes were continuously superfused with ND96 at room temperature. The test compounds were dissolved in DMSO at a concentration of 10 mM. This solution was added to ND96 shortly before the experiment.

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References

(1) Roden, D. M. Antiarrhythmic drugs. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Gilman, A. G., Eds.; McGraw-Hill: New York, 1996; pp 839−874.

(2) Vaughan Williams, E. M. Classifying antiarrhythmic actions: by fact or speculation. *J. Clin. Pharmacol.* **1992**, *32*, 964−977.

(3) Charlier, R.; Deltour, G.; Baudine, A.; Chaillet, F.; Pharmacology of amiodarone, an antianginal drug with a new biological profile. *Arzneim-Forsch.* **1968**, *18*, 1408−1417.

(4) Mason, J. W.; Amiodarone. *N. Engl. J. Med.* **1987**, *316*, 455−466.

(5) CAST investigators: Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression After Myocardial Infarction. *N. Eng. J. Med.* **1989**,*321*, 406−412.

(6) Echt, D. S.; Liebson, M. D.; Mitchell, L. B.; et al. Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo-The Cardiac Arrhythmia Supression Trial. *N. Engl. J. Med.* **1991**, *324*, 781−788.

(7) (a) Woosley, R. L. CAST: Implications for Drug Development. *Clin. Pharmacol. Ther.* **1990**, *47*, 553−556. (b) Pratt, C. M.; Moye, L. A. The Cardiac Arrhythmia Suppression Trial: background, interim results and implications. *Am. J. Cardiol.* **1990**, *65*(4), 20B−29B.

(8) Singh, B. N. The coming of Age of the Class III Antiarrhythmic Principle: Retrospective and Future Trends. *Am. J. Cardiol.* **1996**, *78 (suppl 4A)*, 17−27.

(9) Wellens, H. J.; Brugada, P.; Faber, J. Ventricular arrhythmias: Mechanisms and actions of antiarrhythmic drugs. *Am. Heart J.* **1984**, *107*, 1053−1057.

(10) Waldo, A. L.; Camm, A. J.; DeRuyter, H.; Friedman, P. L.; MacNeil, D. J.; Pauls, J. F.; Pitt, B.; Pratt, C. M.; Schwartz, P. J.; Veltri, E. P. for the SWORD Investigators. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* **1996**, *348*, 7−12.

(11) Torp-Pedersen, C.; Moller, M.; Bloch-Thomsen, P. E.; Kober, L.; Sandoe, E.; Egstrup, K.; Agner, E.; Carlsen, J.; Videbaek, J.; Marchant, B.; Camm, A. J., Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N. Engl. J. Med.* **1999,** *341*, 857−65.

(12) Hondeghem, L. M.; Snyders, D. J. Class III Antiarrhythmic Agents Have A Lot of Potential but a Long Way To Go: Reduced Effectiveness und Dangers of Reverse Use Dependence. *Circulation* **1990**, *81*, 686−690.

(13) Hohnloser, S. H. Proarrhythmia with class III antiarrhythmic drugs: types, risks, and management. *Am. J. Cardiol.* **1997**, *80*(8A), 82G−89G.

(14) Haverkamp, W.; Shenasa, M.; Borggrefe, M.; Breithardt, G. Torsade de Pointes. In *Cardiac Electrophysiology: from Cell to Bedside*, 2nd ed., Zipes D. P., Jalife, J., Eds.; Saunders: Philadelphia, 1995; pp 885−899.

(15) Jurkiewicz, N. K.; Sanguinetti, M. C. Rate Dependent Prolongation of Cardiac Action Potentials By a Methanesulfonanilide Class III Antiarrhythmic Agent: Specific Block of a Rapidly Activating Delayed Rectifier K+ Current By Dofetilide. *Circ. Res.* **1993**, *72*, 75−83.

(16) Sanguinetti, M. C.; Jurkiewicz, N. K.; Scott, A.; Siegl, P. K. S. Isoproterenol antagonizes prolongation of refractory period by the class III antiarrhythmic agent E−4031 in guinea pig myocytes. *Circ. Res.* **1991**, *68*, 77−84.

(17) Schreieck, J.; Wang, Y.; Gjini, V.; Korth, M.; Zrenner, B.; Schömig, A.; Schmitt, C. Differential Effect of β-Adrenergic Stimulation on the Frequency-Dependent Electrophysiologic Actions of the New Class III Antiarrhythmics Dofetilide, Ambasilide, and Chromanol 293B. *J. Cardiovasc. Electrophysiol.* **1997**, *8*, 1420−1430.

(18) (a) Sanguinetti, M. C.; Jurkiewicz, N. K. Two Components of Cardiac Delayed Rectifier K+ Current. *J. Gen. Physiol.* **1990**, *96*, 195−215. (b) Wang, Z.; Fermini, B.; Nattel, S. Rapid and slow components of delayed rectifier current in human atrial myocytes. *Cardiovasc. Res.* **1994**, *28*, 1540−1546. (c) Gintant, G. A. Two components of delayed rectifier current in canine atrium and ventricle. Does I_{Ks} play a role in the reverse rate dependence of class III agents? *Circ. Res.* **1996**, *78*, 26−37. (d) Lei, M.; Brown, H. F. Two components of the delayed rectifier potassium current, IK, in rabbit sino-atrial node cells. *Exp. Physiol.* **1996**, *81*, 725−741.

(19) (a) Yusuf, S.; Peto, R.; Lewis, J.; Collins, R.; Sleight, P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog. Cardiovasc. Dis.* **1985**, *27*, 335−371. (b) Freedman, R. A.; Swerdlow, C. D.; Echt, D. S.; Winkle, R. A.; Soderholm-Difatte, V.; Mason, J. W. Facilitation of ventricular tachyarrhythmia induction by isoproterenol. *Am. J. Cardiol.* **1984**, *54*, 765−770. (c) Reddy, C. P.; Gettes, L. S. Use of isoproterenol as an aid to electric induction of chronic recurrent ventricular tachycardia. *Am. J. Cardiol.* **1979**, *44*, 705−713.

(20) Jazayeri, M. R.; Van-Wyhe, G.; Avitall, B.; McKinnie, J.; Tchou, P.; Akhtar, M. Isoproterenol reversal of antiarrhythmic effects in patients with inducible sustained ventricular tachyarrhythmias. *J. Am. Coll. Cardiol.* **1989**, *14*, 705−711.

(21) Vanoli, E.; Priori, S. G.; Nakagawa, H.; Hirao-K.; Napolitano, C.; Diehl, L.; Lazzara, R.; Schwartz, P. J. Sympathetic activation, ventricular repolarization and Ikr blockade: implications for the antifibrillatory efficacy of potassium channel blocking agents. *J. Am. Coll. Cardiol.* **1995**, *25*, 1609−1624.

(22) Sager, P. T.; Follmer, C.; Uppal, P.; Pruitt, C.; Godfrey, R. The effects of beta-adrenergic stimulation on the frequency-dependent electrophysiologic actions of amiodarone and sematilide in humans. *Circulation* **1994**, *90*, 1811−1819.

(23) Busch, A. E.; Suessbrich, H.; Waldegger, S.; Sailer, E.; Greger, R.; Lang, H.-J.; Lang, F.; Gibson, K. J.; Maylie, J. G. Inhibition of I_{Ks} in guinea pig cardiac myocytes and guinea pig I_{sK} channels by the chromanol 293B. *Plügers Arch.* **1996**, *432*, 1094−1096.

(24) Suessbrich, H.; Bleich, M.; Ecke, D.; Rizzo, M.; Waldegger, S.; Lang, F.; Szabo, I.; Lang, H.-J.; Kunzelmann, K.; Greger, R.; Busch, A. E. Specific blockade of slowly activating I_{sK} channels by chromanols − impact on the role of I_{sK} channels in epithelia. *FEBS Lett.* **1996**, *396*, 271−275.

(25) (a) Bleich, M.; Briel, M.; Busch, A. E.; Lang, H. J.; Gerlach, U.; Goegelein, H.; Greger, R.; Kunzelmann, K. KVLQT channels are inhibited by the K+ channel blocker 293B. *Pflügers Arch.* **1997**, *434*, 499−501. (b) Lohrmann, E.; Burhoff, I.; Nitschke, R. B.; Lang, H. J.; Mania, D.; Englert, H. C.; Hropot, M.; Warth, R.; Rohm, W.; Bleich, M.; Greger, R. A new class of inhibitors of cAMP-mediated Cl^- secretion in rabbit colon, acting by the reduction of cAMP-activated K^+ conductance. *Pflügers Arch.* **1995**, *429*, 517−530.

(26) Bosch, R. F.; Gaspo, R.; Busch, A. E.; Lang, H. J.; Li, G. R.; Nattel, S. Effects of the chromanol 293B, a selective blocker of the slow, component of the delayed rectifier K^+ current, on repolarization in human and guinea pig ventricular myocytes. *Cardiovasc. Res.* **1998**, *38*, 441.

(27) Shiimizu, W.; Antzelevitch, C. Cellular Basis for the ECG Features of the LQT1 Form of the Long-QT Syndrome. *Ciruculation* **1998**, *98*, 2314−2322.

(28) (a) Bauer, A.; Müller, M.; Gerlach, U.; Lang, H. J.; Schoels, W. Frequency-dependent effect of the new I_{Ks} -blocker chromanol 293b in intact dog myocardium. *Z. Kardiol.* **1998**, *87* (suppl. 1), 283. (b) Bauer, A.; Becker, R.; Freigang, K. D.; Senges, J. C.; Voss, F.; Hansen, A.; Müller, M.; Lang, H. J.; Gerlach, U.; Kraft, P.; Kuebler, W.; Schoels, W. Rate- and Site-Dependent Effects of Propafenone, Dofetilide, and the New I_{Ks} −Blocking Agent Chromanol 293B on Individual Muscle Layers of the Intact Canine Heart, *J. Cardiovasc. Res.*, in press. (c) Bauer, A.; Becker, R.; Lang, H.-J.; Gerlach, U.; Hansen, A.; Mueller, M.; Kraft, P.; Senges, J. C.; Voss, F.; Freigang, K. D.; Schoels, W. Are there differential effects of the new I_{Ks} blocking agent chromanol 293b in normal and infarcted canine hearts? *J. Am. Coll. Cardiol.* **1999**, *33*, 152A.

(29) Selnick, H. G.; Liverton, N. J.; Baldwin, J. J.; Butcher, J. W.; Claremon, D. A.; Elliott, J. M.; Freidinger, R. M.; King, S. A.; Libby, B. E.; Mclntyre, C. J.; Pribush, D. A.; Remy, D. C.; Smith, G. R.; Tebben, A. J.; Jurkiewicz, N. K.; Lynch, J. J.; Salata, J. J.; Sanguinetti, M. C.; Siegl, P. K. S.; Slaughter, D. E.; Vyas, K. Class III Antiarrhythmic Activity in Vivo by Selective Blockade of the Slowly Activating Cardiac Delayed Rectifier Potassium Current I_{Ks}. by (R)-2-(2,4-Trifluoromethyl)-N-[2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-III-benzo[*e*][1,4]diazepin-3-yl-lacetamide. *J. Med. Chem.* **1997**, *40*, 3865−3868.

(30) Lloyd, J.; Schmidt, J. B.; Ahmad, S. et al. Design and synthesis of potent, selective, and orally bioavailable potassium (IKs) blockers. Book of Abstracts 220th ACS National Meeting, Washington, DC, August 20−24 2000, MEDI-327.

(31) Gerlach, U.; Brendel, J.; Brüggemann, A.; Gögelein, H,; Lang, H. J.; Weidmann, K.; Busch, A. Synthesis and SAR of novel I_{Ks} -channel blockers: From K(ATP)-channel opener to IKs-channel blocker. Book of Abstracts, 219th ACS National Meeting, San Francisco, March 26−30 1999, MEDI-159.

(32) Englert, H. C.; Wirth, K.; Gehring, D.; Fuerst, U.; Albus, U.; Scholz, W.; Rosenkranz, B.; Schoelkens, B. A. Airways pharmacology of the potassium channel opener, HOE 234, in guinea pigs: in vitro and in vivo studies. *Eur. J. Pharmacol.* **1992**, *210*, 69−75.

(33) (a) Barhanin, J.: Lesage, F.; Guillemare, E.; Fink, M.; Lazdunski, M.; Romey, G. KvLQT1 und IsK (min K) proteins Associate to Form the I_{Ks}. Cardiac Potassium Current. *Nature* **1996**, *384*, 78. (b) Sanguinetti, M. C.; Curran, M. E.; Zou, A.; Shen, J.; Spector, P. S.; Atkinson, D. L.; Keating, M. T. Coassembly of KvLQTI und mink (Isk) Proteins to Form Cardiac I_{Ks} Potassium Channel. *Nature* **1996**, *384*, 80.

(34) Paulus, E. F.; Burgard, A.; Lang, H. J.; Gerlach, U. (−)-N-[(3R,-4S)-6-Cyano-3-hydroxy-2,2-dimethyl-chroman-4-yl]-N-methyl-ethansulfonamide semihydrate. *Acta Crystallogr.* In review.

(35) Bell, D.; Davies, M. R.; Frances, J. L.; Geen, G. R.; Kincey, P. M.; Inderjit, S. M. The Effect of Catalyst Loading and Donor Ligands in the Mn(III)Salen Catalysed Chiral Epoxidationof Chromenes: Synthesis of BRL 55834. *Tetrahedron Lett.* **1996**, *37*, 3895−3898.

(36) (a) Gögelein, H.; Brüggemann, A.; Gerlach, U.; Brendel, J.; Busch, A. Inhibition of I_{Ks} Channels by HMR1556. Naunyn-Schmiedeberg's Arch. Pharmacol. **2000**, *362*, 480−488. (b) Brüggemann, A.; Gögelein, H.; Gerlach, U.; Busch, A. Charakterization of the I_{Ks}-channel blocker HMR 1556 on cardiomyocytes of guinea pig and *Xenopus* oocytes, Europace Suppl. April **2000**, B28. (c) Eckardt, L.; Kirchhof, P.; Gerlach, U.; Brendel, J.; Haverkamp, W. Regional unterschiedliche elektrophysiologische Effekte einer I_{Ks} −Blockade am isolierten Kaninchenherz, Z. Kardiol. **2000,** *89* (Suppl. 5), 1172. (d) Wirth, K. J.; Gerlach, U.; Brendel, J.; Busch, A. Wirkung des selektiven I_{Ks} −Kanalblockers HMR1556 auf die Refraktärzeit des Vorhofs und Ventrikels am Schwein, Z. Kardiol. **2000**, *89* (Suppl. 5), 735.

(37) (a) Kabbe, H. J. *Synthesis* **1978**, 886. (b) Kabbe, H. J.; Heitzer, H. *Synthesis* **1978**, 888.

(38) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. Enantioselective Epoxidation of Unfunctionalized Olefins by (Salen)manganese Complexes. *J. Am. Chem. Soc.* **1990**, *112*, 2801−2803.

(39) Sheldrick, G. M. SHELXTL-PLUS, Release 5.10. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data. Bruker Analytical Systems: Madison, WI, 1997.

(40) Methfessel, C.; Witzemann, V.; Takahashi, T.; Mishina, M.; Numa, S.; Sakmann, B. Patch clamp measurements on *Xenopus laevis* oocytes: currents through endogenous channels and implanted acetylcholine receptor. *Pflügers Arch.* **1986**, *407*, 577−588.

(41) Golding, A. L. Maintenance of *Xenopus laevis* and oocyte injection. *Methods Enzymol.* **1992**, *207*, 266−279.

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