Cardioselective K_{ATP} Channel Blockers Derived from a New Series of *m*-Anisamidoethylbenzenesulfonylthioureas

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Sulfonylthioureas exhibiting cardioselective blockade of ATP-sensitive potassium channels (K_{ATP} channels) were discovered by stepwise structural variations of the antidiabetic sulfonylurea glibenclamide. As screening assays, reversal of rilmakalim-induced shortening of the cardiac action potential in guinea pig papillary muscles was used to probe for activity on cardiac K_{ATP} channels as the target, and membrane depolarization in CHO cells stably transfected with hSUR1/hKir6.2 was used to probe for unwanted side effects on pancreatic K_{ATP} channels. Changing glibenclamide's *para*-arrangement of substituents in the central aromatic ring to a *meta*-pattern associated with size reduction of the substituent at the terminal nitrogen atom of the sulfonylurea moiety was found to achieve cardioselectivity. An additional change from a sulfonylurea moiety to a sulfonylthiourea moiety along with an appropriate substituent in the *ortho*-position of the central aromatic system was a successful strategy to further improve potency on the cardiac K_{ATP} channel. Among this series of sulfonylthioureas HMR1883, 1-[5-[2-(5-chloro-*o*-anisamido)ethyl]-2-methoxyphenyl]sulfonyl-3-methylthiourea, and its sodium salt HMR1098 were selected for development and represent a completely new therapeutic approach toward the prevention of life-threatening arrhythmias and sudden cardiac death in patients with coronary heart disease.

Introduction

Sudden cardiac death is a leading cause of mortality in western countries.[1] In the United States it annually accounts for 300 000 deaths and in Europe for 120 000 deaths. The majority of these victims suffer from coronary artery disease suggesting that myocardial ischemia may have triggered a lethal arrhythmia.[2,3] Thus far, conventional antiarrhythmic therapy has failed in the prevention of sudden cardiac death due to an inherent proarrhythmic potential as highlighted by large clinical trials such as CAST or SWORD.[4,5] An increase of extracellular potassium ions and a shortening of the cardiac action potential, well-established derangement seen soon after the onset of ischemia, set the stage for a re-entry movement of the cardiac excitation wave underlying ischemic ventricular tachycardias and fibrillation.[6] In this context the opening of K_{ATP} channels has been shown to play a pivotal role.[7−9] Among all ion channels controlling the shape of the cardiac action potential, the K_{ATP} channel is unique since it is activated only during myocardial ischemia but does not contribute to the shape in the absence of ischemia. Consequently, a blocker of this channel should have the unique property to be pharmacologically silent in the absence of ischemia, whereas it has the potential to abrogate ischemia-related electrophysiological derangements and, in turn, to prevent the formation of life-threatening arrhythmias. K_{ATP} channels can be blocked by antidiabetic sulfonylureas such as glibenclamide. Indeed, it was demonstrated that glibenclamide can ameliorate many of the electrophysiological derangements in early ischemia and prevented ischemic ventricular fibrillation (VF) in isolated hearts and in whole animals.[10,11] However, antidiabetic sulfonylureas cannot be regarded as an option for the prevention of severe arrhythmias in cardiovascular patients since they lack tissue selectivity. At least from animal experiments it can be concluded that antiarrhythmic doses of glibenclamide will be connected with the risk of severe metabolic and hemodynamic disturbances.[11]

Glibenclamide predominantly triggers insulin secretion via blockade of pancreatic K_{ATP} channels,[12,13] potently interferes with K_{ATP} channels in vascular smooth muscles,[14] and inhibits ischemic preconditioning[15] as a consequence of mitochondrial K_{ATP} channel blockade.[16] Recently, HMR1883, a member of the *m*-anisamidoethylbenzenesulfonylthioureas, was reported to block cardiac K_{ATP} channels more potently than pancreatic and vascular channels without affecting other types of cardiac potassium currents such as Ik_r and Ik_s.[17] This compound prevented sudden cardiac death in conscious dogs subjected to exercise and myocardial ischemia without the untoward side effects of glibenclamide such as hypoglycemia and a reduction in coronary flow.[18] Cardioselectivity of HMR1883 was also confirmed in rats with coronary ligation and reperfusion[19] where the compound exerted antifibrillatory effects at a dose range that showed no effects on insulin, while glibenclamide potently released insulin even at the lowest antifibrillatory dose. Also not optimized for this property, HMR1883 showed no interference with mitochondrial K_{ATP} channels in a model of diazoxide (100 μM)-induced flavoprotein oxidation.[20] This observation explains why HMR1883, in contrast

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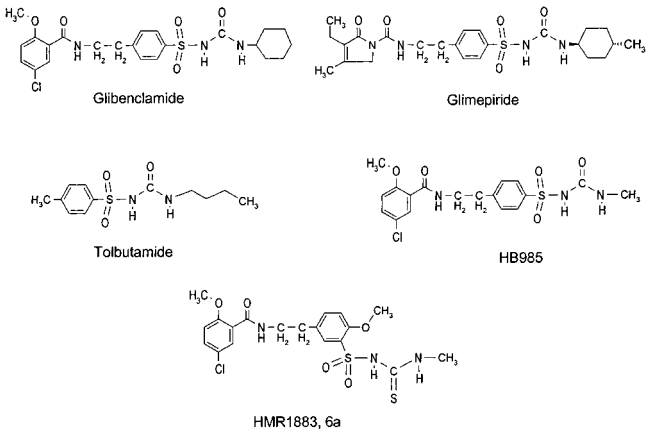
to glibenclamide, has no impact on myocardial preconditioning.[21] Thus, for the first time a sulfonylurea is available to safely explore the clinical potential of cardiac plasmalemmal K_{ATP} blockade as a new antifibrillatory approach in patients with coronary artery disease.

As predicted for a selective blocker of plasmalemmal cardiac K_{ATP} channel, HMR1883 was indeed shown in preclinical studies to have no effect on the ECG under nonischemic conditions but to prevent ECG abnormalities as soon as ischemia comes into play.[22] The well-established proarrhythmic potential of existing antiarrhythmics, however, is generally attributed to a continuous impact of these agents on the ECG. In this context HMR1883 should bear no proarrhythmic potential, and so far proarrhythmic effects could not be seen in any of the preclinical studies. Given this unique pharmacological profile, HMR1883 was selected for development as an agent for the prevention of malignant arrhythmias and sudden cardiac death.

In the present study the discovery of HMR1883 as well as a structure−activity relationship (SAR) among this new series of sulfonylthioureas regarding effects on plasmalemmal cardiac and pancreatic K_{ATP} channels will be elucidated. The design of new sulfonylureas with a cardioselective profile was based on observations among existing antidiabetic sulfonylureas such as glimepiride, glibenclamide, and tolbutamide.



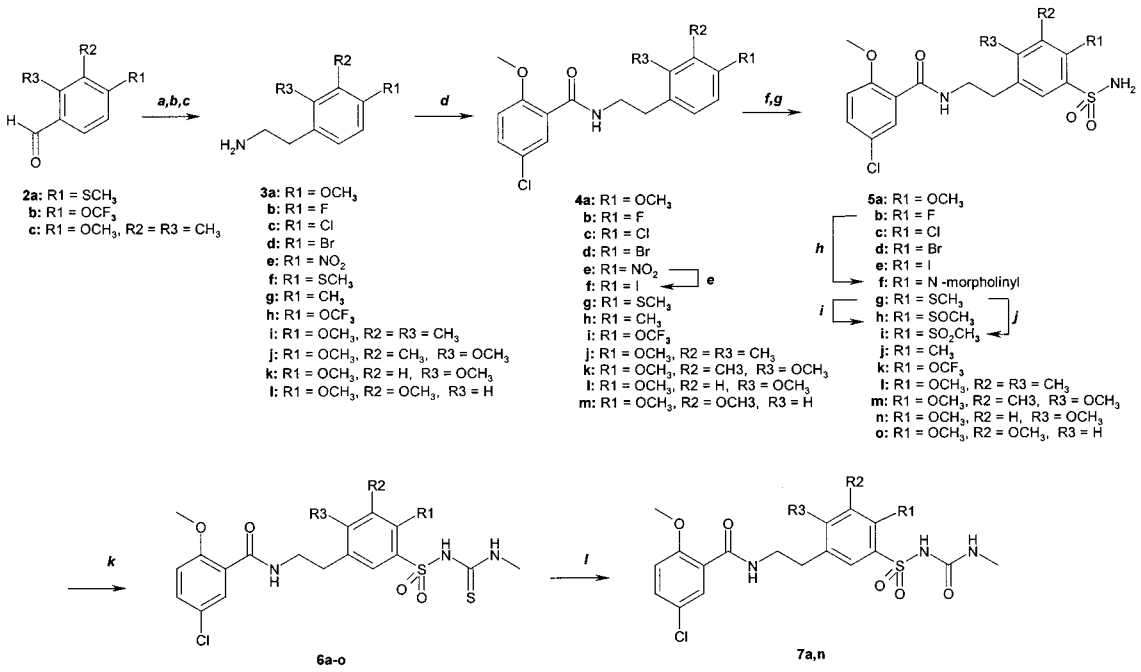
Tolbutamide, for example, exerts little if any effect on cardiac K_{ATP} channels while potently interfering with the pancreatic SUR1 component of K_{ATP} channels.[23] In contrast, glibenclamide acts on both types of K_{ATP} channels suggesting that the methoxychlorobenzamide moiety is a good option to achieve additional cardiac activity since tolbutamide lacks this structural feature. On the other hand, a bulky lipophilic substituent attached to the terminal nitrogen of the sulfonylurea moiety is present in both compounds and in addition is a key structural feature of all other antidiabetic sulfonylureas known so far.[24] In the following we focused on structural variations of glibenclamide-like molecules keeping the methoxychlorobenzamide moiety unchanged and, in addition, tried to reduce the size of the lipophilic substituent at the sulfonylurea moiety. However, this concept failed in the glibenclamide series itself. Replacing glibenclamide's *c*-hexyl group by methyl leads to the known compound HB985, an investigational tool used to probe for pancreatic K_{ATP} channels.[25] HB985, however, displayed no cardioselectivity. This prompted us to include regioisomers of glibenclamide which might be more sensitive to this kind of structural variation.

Chemistry

Scheme 1 describes the synthesis of the majority of the sulfonylthioureas starting from appropriately substituted and in most cases readily available phenylethylamines **3** as the key intermediates. These amines were coupled either with 5-chloro-2-methoxybenzoic acid using standard coupling reagents such as *N*,*N*′-carbonyldiimidazole or with 5-chloro-2-methoxybenzoic acid chloride in pyridine as solvent. Introduction of the sulfonamide group into amides **4** was achieved by chlorosulfonic acid and subsequent treatment of the resulting sulfonyl chloride intermediates with aqueous ammonia in acetone. Sulfonamides **5** are readily transformed into sulfonylthioureas **6** by treatment with isothiocyanates in the presence of an appropriate base such as K_2CO_3. Phenethylamines **3f**,**h**−**j** were prepared via known procedures starting from 4-substituted benzaldehydes, which were treated with Meldrum's acid in tetraethylammonium formiate (TEAM) to give 4-substituted phenylpropionic acids.[26] Treatment of these acids with azidodiphenylphosphate in *tert*-butanol afforded amines **3** via their *tert*-butoxycarbonyl-protected derivatives. The amide **4e** was transformed into its iodo derivative **4f** via reduction of the nitro group in **4e** using $SnCl_2$ and subsequent Sandmeyer reaction of the intermediate amine in approximately 50% yield. The *N*-morpholino derivative **5f** was obtained by refluxing the fluoro derivative **5b** in morpholine. The yield, however, was only 10%. Cleavage of the methoxy ethers was observed as the main reaction. 2-Methylsulfinyl and 2-methylsulfonyl derivatives **5h**,**i** were obtained from the corresponding methylmercapto precursor **5g** by oxidation with aqueous H_2O_2 in acetic acid at either 0 or 80 °C. H_2O_2 in aqueous NaOH was the reagent of choice to obtain the sulfonylureas **7** from the corresponding sulfonylthioureas **6**.

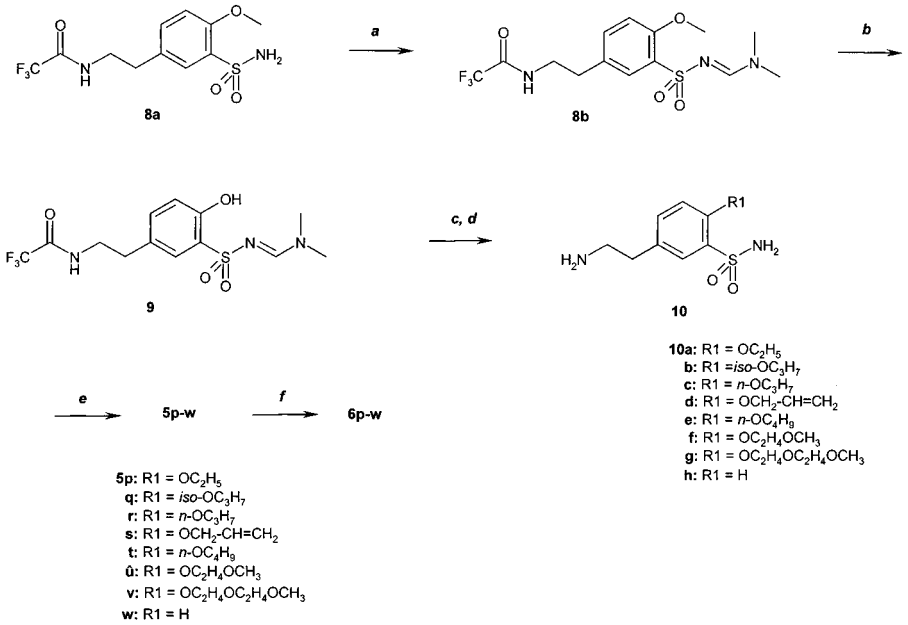
Scheme 2 shows the synthesis of sulfonylthioureas **6p**−**w.** Compounds **6p**−**v** are higher homologues of HMR1883 containing more than one carbon atom in the adjacent alkoxy group. In the preparation of these compounds via the route described in Scheme 1, the chlorosulfonation of the corresponding alkoxy amide analogues of **4** ended up with yields lower than 10%, apparently due to steric hindrance in the adjacent *ortho*-position by the bulky alkoxy substituents. To avoid these shortcomings, compound **8a**[27] was chosen as a convenient starting material in which the sulfamoyl group was already introduced in the presence of the methoxy group and the phenethylamino moiety was protected by trifluoroacetylation. The sulfamoyl group was additionally proteced by its corresponding *N*,*N*-dimethylformamidine derivative **8b**. The methoxy ether was cleaved using boron tribromide to give **9** as a versatile intermediate which was well-suited for *O*-alkylation by standard procedures. Deprotected compounds **10a**−**g** were subsequently converted via amides **5p**−**v** into corresponding sulfonylthioureas **6p**−**v** as described in Scheme 1. Compound **6w** is the "demethoxy" derivative of HMR1883. It was analoguously synthesized from the already known intermediate **10h**.[27]

Scheme 1. Synthesis of Sulfonylthioureas **6a**−**o** and Sulfonylureas **7a,n**[a]



[a] Reagents: (a) Meldrum's acid, TEAF; (b) azidodiphenylphosphate, TEA, *tert*-butanol; (c) 2 N HCl, MeOH; (d) (i) *N*,*N*′-carbonyldiimidazole, TEA, 5-chloro-2-methoxybenzoic acid, (ii) 5-chloro-2-methoxybenzoic acid chloride, pyridine; (e) $SnCl_2$, HCl, $NaNO_2$, KJ; (f) $ClSO_3H$; (g) NH_4OH, acetone; (h) morpholine; (i) AcOH, H_2O_2, 0 °C; (j) AcOH, H_2O_2, reflux; (k) CH_3NCS, KO*t*Bu, DMF; (l) NaOH, H_2O_2.

Scheme 2. Synthesis of Sulfonylthioureas **6p**−**w** with Modified Alkoxy Substituents in Position 2 of the Central Aromatic Ring[a]

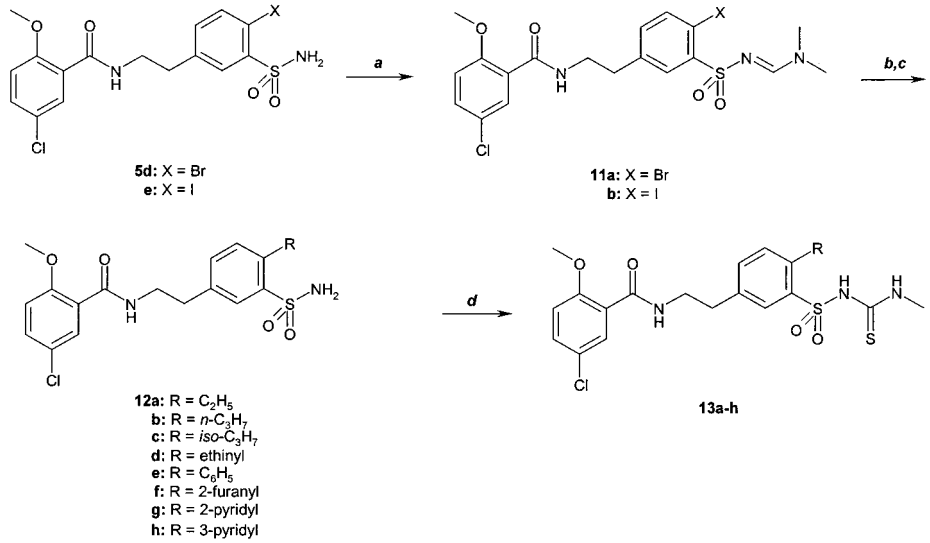


[a] Reagents: (a) *N*,*N*-dimethylformamide dimethylacetal, DMF; (b) BBr_3; (c) R′$_1$-Hal (R′$_1$ = 1-deoxy-R$_1$), K_2CO_3; (d) 5.5 N HCl, reflux; (e) *N*,*N*-carbonyldiimidazole, TEA, 5-chloro-5-methoxybenzoic acid; (f) CH_3NCS, KO*t*Bu, DMF.

Compounds **5j** (Scheme 1) and **13a**−**h** (Scheme 3) are "deoxy" derivatives of HMR1883 bearing substituents attached via a carbon atom in position 2 of the central aromatic ring. Except for the methyl derivative **5j**, which is readily available via the synthetic path described in Scheme 1, the higher homologues **13a**−**h** were more favorably synthesized via a different synthetic route as depicted in Scheme 3 with transition metal-mediated C−C bond formations in the presence of the already introduced sulfonamide group as the key synthetic step, thus avoiding again sluggish chlorosulfonation in the presence of large size substituents R (Table 3).

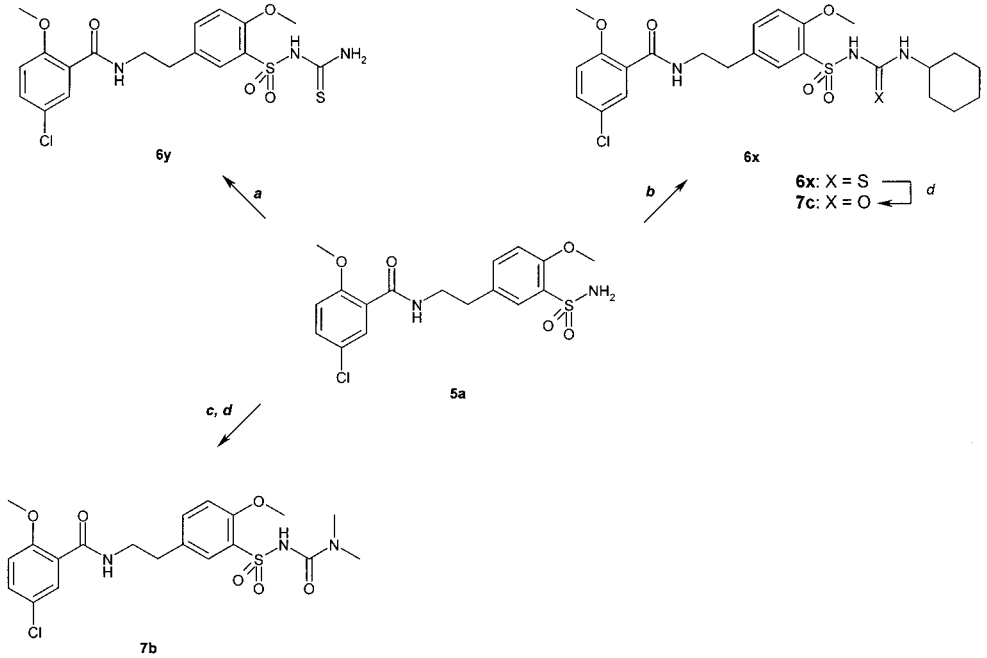
Key intermediates in the synthesis of these sulfonylureas are the *N*,*N*-dimethylformamidino-protected 2-bromo or 2-iodo sulfonamides **11a**,**b**, which were readily available by treatment of the sulfonamides **5d**,**e** with *N*,*N*-dimethylformamide dimethylacetal in DMF.[28] The alkyl-substituted sulfonamides **12a**−**c** were prepared via a Pd(0)-catalyzed Nigishi-Kumada-type cross-cou-

Scheme 3. Synthesis of Sulfonylthioureas **13a**−**h** via Pd(0)-Catalyzed Cross-Coupling Reactions[a]



[a] Reagents: (a) $(CH_3O)_2CHN(CH_3)_2$, DMF, 20 °C; (b) **12a**−**c:** RMgBr, $ZnCl_2$, Pd(dppf)Cl_2, CuI, THF, **12d,f,i:** $RSnBu_3$, Pd$(PPh_3)_2Cl_2$, THF, **12g,h:** $RSnMe_3$, Pd$(PPh_3)_2Cl_2$, THF, **12e,h:** $RB(OH)_2$, Pd$(PPh_3)_4$, Cs_2CO_3, toluene/EtOH; (c) concd HCl, MeOH; (d) CH_3NCS, KO*t*Bu, DMF.

Scheme 4. Synthesis of Sulfonylthioureas **6x,y** and Sulfonylureas **7b,c**[a]



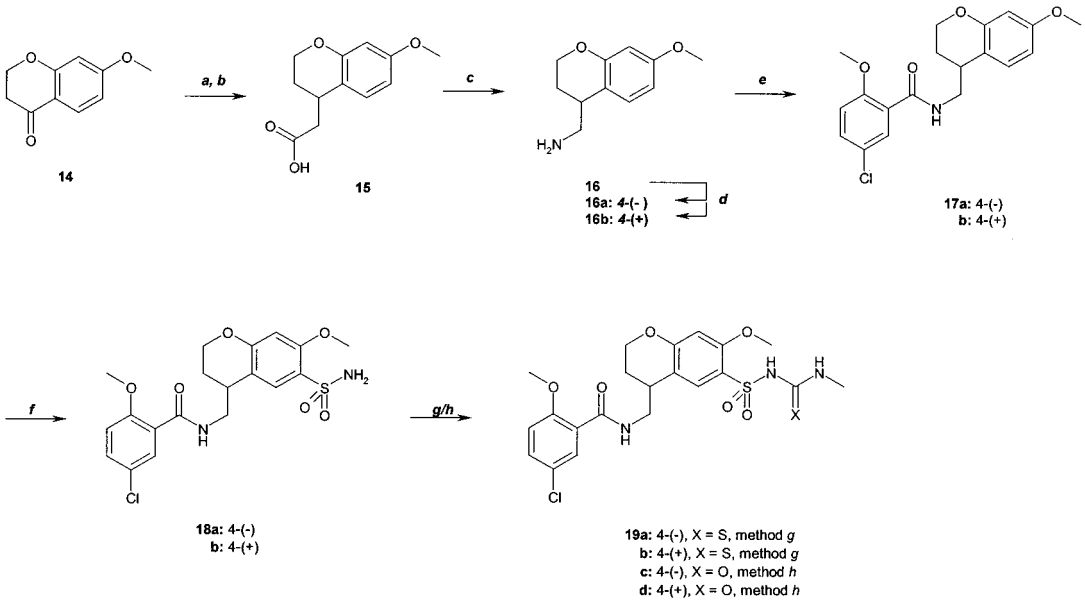
[a] Reagents: (a) CS_2, $ClCOOC_2H_5$, NH_3; (b) *c*-$C_6H_{11}NCS$, KO*t*Bu, DMF; (c) CS_2, $ClCOOC_2H_5$, $(CH_3)_2NH$; (d) 1 N NaOH, H_2O_2.

pling reaction[29] of the iodide **11b** with the appropriate alkylzinc reagent and copper(I) as cocatalyst followed by removal of the amidino protecting group. The acetylene, the 2-furyl, and the 2- and 3-pyridyl substituents of **12d,f**−**h** were introduced by a Pd(0)-catalyzed Stille-type cross-coupling reaction of the appropriate trialkylstannanes with either the bromide or the iodide **11a,b**.[30] It is noteworthy that the introduction of pyridyl residues could only be achieved in satisfactory yields by using freshly prepared 2- or 3-(trimethylstannyl)pyridine, respectively.[31] Subsequent cleavage of the amidino protecting group yielded the corresponding sulfonamides **12d,f**−**h**. The 2-phenyl-substituted sulfonamide **12e** was finally derived from a Pd(0)-catalyzed Suzuki-type cross-coupling reaction[32] of bromide **11a** with benzeneboronic acid and subsequent removal of the amidino protecting group.

Treatment of likewise thus obtained sulfonamides with methyl isothiocyanate finally gave the desired sulfonylthioureas **13a**−**h**.

Compound **6y** (Scheme 4) is a HMR1883 derivative with the unsubstituted terminal nitrogen of the sulfonylthiourea moiety. This compound could not be obtained by using potassium or sodium isothiocyanate in a protic solvent, although corresponding reactions with benzenesulfonamides without adjacent substituents were found in our laboratory to proceed smoothly. Therefore, we chose the rather complicated route via a sulfonyl isothiocyanate intermediate that readily reacts with ammonia to give **6y**. To this end the sulfonamide

Scheme 5. Synthesis of Chromane-Derived Sulfonyl(thio)ureas **19a**−**d** with a Chromane Framework[a]



[a] Reagents: (a) phosphonoacetic acid trimethyl ester, NaH, THF; (b) (1) Pd/C (10%), H_2, (2) 2 N NaOH, EtOH; (c) (1) azidodiphenylphosphate, TEA, *t*BuOH, (2) 2 N HCl, MeOH; (d) (+)- or -(−)-mandelic acid, EtOH; (e) *N*,*N*′-carbonyldiimidazole, TEA, 5-chloro-2-methoxybenzoic acid; (f) $ClSO_3H$, NH_4OH; (g) CH_3NCS, K_2CO_3, DMSO; (h) $CCl_3CONHCH_3$, NaOH (powder), DMSO.

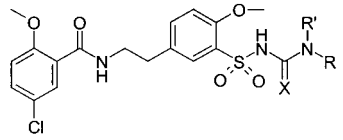
5a was reacted with carbon disulfide to give a dipotassium salt of a dithioxanthogenate which was subsequently treated with ethyl chloroformate to enable the formation of an intermediate sulfonyl isothiocyanate. This intermediate was then treated with aqueous ammonia to provide **6y**. The *N*-cyclohexyl derivatives of HMR1883, **6x** and **7c**, were obtained as described in Scheme 1 using H_2O_2 in 2 N NaOH. The dimethyl derivative **7b** was obtained in the same way as **6y** by reaction of aqueous dimethylamine instead of aqueous ammonia with the sulfonyl isothiocyanate and subsequent oxidation of the thiosulfonylurea.

The sulfonyl(thio)ureas **19a**−**d** with a chromane framework instead of the central aromatic ring were synthesized according to Scheme 5. Starting material was 7-methoxy-4-chromanone (**14**)[33] which was subjected to Wittig reaction with phosphonoacetic acid trimethyl ester to yield the carboxy derivative **15** after hydrogenation and alkaline hydrolysis. This acid **15** was converted to a racemic mixture of amine **16** as described for phenethylamines **3f,h**−**j** in Scheme 1 using azidodiphenylphosphate in *tert*-butanol which provides **16** via its *tert*-butoxycarbonyl-protected derivative. Enantiomeric separation was achieved via fractional crystallization following salt formation with either (*S*)-(+)- or (*R*)-(−)-mandelic acid. The further transformation into thioureas **18a**−**b** follows nearly the same pattern as given by steps d, f, g, k of Scheme 1. In step k the base used to introduce the thiourea moiety from isothiocyanate was K_2CO_3 in DMSO. In contrast to phenylethylamine-derived sulfonylureas **7**, the chromane sulfonylureas **19c**−**d** were directly obtained from the sulfamoylchromanes **18** using *N*-methyltrichloroacetamide in DMSO/NaOH. During the whole sequence from **16** to **19** a (+)-educt yielded allways a (+)-product whereas (−)-educts gave consistently (−)-products. As checked by HPLC, enantiomeric purity was >98% at the stage of the amine **16** and >99% at the stage of the final products **19a**−**d**.

Results and Discussion

Our final goal was to provide a compound that prevents ischemic arrhythmias without affecting metabolic parameters for at least up to the 10-fold minimally effective antiarrhythmic dose level in a given species. However, animal models that are available for this purpose are rather sophisticated and, hence, cannot be used for compound screening. As a surrogate for insulin secretion we chose membrane depolarization in hSUR1/hKir6.2 (the cloned components of the pancreatic K_{ATP} channel) transfected CHO cells. As indicated by the potency of glibenclamide, this testing system can be regarded as a validated model with respect to results obtained in native pancreatic tissue and, hence, is well-suited for evaluations of new sulfonylureas. It is important to keep in mind that insulin secretion in native tissue is triggered only when depolarization reaches a certain threshold of membrane potential. Unfortunately such an accepted model with a proven equivalence to native tissue was not available for the cloned cardiac SUR2A/Kir6.2 K_{ATP} channel. The poor potency described in this system for glibenclamide is at variance with our own observations showing a high potency of glibenclamide in native cardiac tissue, such as isolated cardiomyocytes[34] or papillary muscles. This indicates that the presently available SUR2a/Kir6.2 system still lacks some important intrinsic modulators. Therefore, we decided to use a native tissue preparation to avoid these shortcomings. The reversal of action potential shortening in the isolated papillary muscle subjected to the specific K_{ATP} channel opener rilmakalim (HOE 234[34,35]) can be taken as an indirect measure of the antifibrillatory the potency on the cardiac K_{ATP} channel. However, HMR1883, inducing a 71% reversal of the shortening at 2 μM (Table 1), significantly reduced the incidence of VF by 50% already at 0.1 μM.[14] This indicates that already slight effects on action potential shortening are sufficient to completely prevent VF. Therefore, results from our screening assay may un-

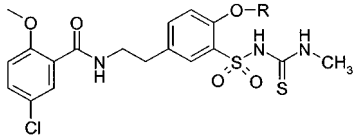
Table 1. Physical Data and Effects on K_{ATP} Channels for Sulfonylthioureas and Sulfonylureas



compd	X	R, R′	mp (°C)	formula	anal.	pancreatic[c] K_{ATP} (% inhib)	cardiac[e] K_{ATP} (% inhib)
glib[a]						24, 73.3, 92.7[d]	0.0, 76, 87[f]
HB985						−0.7, 62.8, 86.3	nd,[g] 31, 96
7c	O	H, *c*-C_6H_{11}	164−167	$C_{24}H_{30}ClN_3O_6S$	C, H, N	65.5, 92.8, 81.7	nd, 45, 77
7a	O	H, CH_3	201−203	$C_{19}H_{22}ClN_3O_6S$	C, H, N	−2.8, −1.3, 43.9	nd, 35, 68
7b	O	CH_3, CH_3	205−208	$C_{20}H_{24}ClN_3O_6S$	C, H, N	−3.6, −3.2, 25.0	nd, 0, nd
6a[b]	S	H, CH_3	190−193	$C_{19}H_{22}ClN_3O_5S_2$	C, H, N	5, 24.3, 83.8	3, 71, 117
6y	S	H, H	177−178	$C_{18}H_{20}ClN_3O_5S_2$	C, H, N	1.6, 11.2, 64.7	nd, 29, nd
6x	S	H, *c*-C_6H_{11}	167−169	$C_{24}H_{30}ClN_3O_5S_2$	C, H, N	20.5, 87.6, 121.5	nd, 60, nd

[a] glib, glibenclamide. [b]HMR1883. [c]h-SUR1/Kir6.2 activated by diazoxide; test compound concentrations 0.1, 1, and 10 μM. [d]Glibenclamide concentrations 1, 3, and 10 nM. [e]Guinea pig papillary muscle, % reversal of action potential shortening due to rilmakalim; test compound concentrations 0.2, 2, and 20 μM. [f]Glibenclamide concentrations 0.02, 0.2, and 2 μM. [g]nd, not determined.

Table 2. Physical Data and Effects on K_{ATP} Channels for Sulfonylthioureas: Variations of the Oxo Substituent



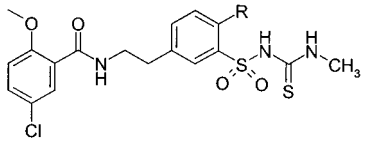
compd	R	mp (°C)	formula	anal.	pancreatic[c] K_{ATP} (% inhib)	cardiac[e] K_{ATP} (% inhib)
glib[a]					24, 73.3, 92.7[d]	0.0, 76, 87[f]
6a[b]	CH_3				5, 24.3, 83.8	3, 71, 117
6k	CF_3	180−182	$C_{19}H_{19}ClF_3N_3O_5S_2$	C, H, N	0.8, 6.0, 64.9	nd,[g] 58, nd
6p	C_2H_5	185−187	$C_{20}H_{24}ClN_3O_5S_2$	C, H, N	−2.7, 16.3, 75.4	14, 100, nd
6q	*i*-C_3H_7	164−166	$C_{21}H_{26}ClN_3O_5S_2$	C, H, N	−4.7, 27.4, 81.1	24, 95, nd
6r	C_3H_7	179−182	$C_{21}H_{26}ClN_3O_5S_2$	C, H, N	4.2, 63.6, 103.26	40, 114, nd
6s	C_3H_5	170−173	$C_{21}H_{24}ClN_3O_5S_2$	C, H, N	1.7, 31.8, 94.0	nd, 79, 96
6u	C_2H_4-O-CH_3	134−135	$C_{21}H_{26}ClN_3O_6S_2$	C, H, N	12.5, 26.2, 49.5	61, 98, nd
6v	C_2H_4-O-C_2H_4-OCH_3	105−108	$C_{23}H_{30}ClN_3O_7S_2$	C, H, N	1,0, 45.5, 96.4	14, 97, nd

[a] glib, glibenclamide. [b]HMR1883. [c]h-SUR1/Kir6.2 activated by diazoxide; test compound concentrations 0.1, 1, and 10 μM. [d]Glibenclamide concentrations 1, 3, and 10 nM. [e]Guinea pig papillary muscle, % reversal of action potential shortening due to rilmakalim; test compound concentrations 0.2, 2, and 20 μM. [f]Glibenclamide concentrations 0.02, 0.2, and 2 μM. [g]nd, not determined.

derestimate antifibrillatory potency of our compounds. With glibenclamide and HMR1883, two compounds are available that allow correlation of effects in our screening models with the in vivo situation measuring antifibrillatory potency and insulin release. As already mentioned HMR1883 in rats is antifibrillatory at a dose range of 1−10 mg/kg iv without having significant effects on plasma insulin.[19] This correlates perfectly with approximately 70% inhibition of the action potential shortening at 2 μM (Table 1) with almost no effect (<30% inhibition) on the pancreatic β-cell membrane potential at this concentration. In the rat only at 30 mg/kg iv did HMR1883 increase serum insulin, which has to be correlated with a 80% inhibition at 10 μM of pancreatic K_{ATP} channels (Table 1). Vice versa, glibenclamide is antifibrillatory at doses of 0.1−1 mg/kg iv, while it already induces significant insulin secretion at 0.01 mg/kg iv without having any effect on VF. Again, this is completely in line with the data of our screening assays showing no effect at 20 nM in the cardiac preparation whereas the pancreatic K_{ATP} channel was almost completely inhibited already at 10 nM (see Table 1). Using these two marker compounds, glibenclamide and HMR1883, for comparison the amount of cardioselectivity achieved with any other compound of our series can be easily estimated.

Compound **7c** (Table 1), a *meta*-derivative of glibenclamide with an adjacent methoxy group in the central aromatic ring, was considered to be an attractive lead compound since pancreatic activity, despite an intact cyclohexyl substituent, was already reduced by approximately 2 orders of magnitude whereas cardiac activity was much less affected. When we replaced its cyclohexyl moiety by the much smaller methyl group of HB985 we identified for the first time a K_{ATP} blocker, **7a**, with a greater inhibitory effect in heart than in the pancreatic system. However, the moderate potency of **7a** rendered this compound less attractive in terms of drug development. This shortcoming could be overcome by replacement of the sulfonylurea group by a sulfonylthiourea moiety. Starting from compound **7a**, this important structural change increased activity in the heart as well as in the pancreas, to a similar extent, thereby providing HMR1883 (**6a**) with sufficient cardiac potency and an acceptable cardioselectivity profile. In an attempt to further improve the cardiac potency, a cyclohexyl moiety was reintroduced. However, the resulting compound **6x** was found to have less cardiac potency than HMR1883, indicating that in the series of sulfonylthioureas cardiac activity benefits from a small substituent and is less compatible with larger alkyl substituents. Regarding pancreatic activity **6x** behaved "normal" since the large *c*-hexyl moiety increased activity by more than 1 order of magnitude. In **7b** a further methyl group was attached to the terminal *N* of **7a**. Since this variation resulted in a complete loss

Table 3. Physical Data and Effects on K_{ATP} Channels of Sulfonylthioureas: Influence of Various Substituents



compd	R	mp (°C)	formula	anal.	pancreatic[c] K_{ATP} (% inhib)	cardiac[e] K_{ATP} (% inhib)
glib[a]					24, 73.3, 92.7[d]	0.0, 76, 87[f]
6a[b]	OCH_3				5, 24.3, 83.8	3, 71, 117
6w	H	173−175	$C_{18}H_{20}ClN_3O_4S_2$	C, H, N	−4.1, 1.9, 52.7	nd,[g] 11, nd
6b	F	197−199	$C_{18}H_{19}ClFN_3O_4S_2$	C, H, N	−3.9, −1.3, 18.1	nd, 7, nd
6c	Cl	194−196	$C_{18}H_{19}Cl_2N_3O_4S_2$	C, H, N	2.3, 2.8, 40.1	nd, 14, nd
6d	Br	amorph	$C_{18}H_{19}BrClN_3O_4S_2$	C, H, N	3.3, 2.2, 67.7	nd, 37, nd
6e	J	181	$C_{18}H_{19}ClIN_3O_4S_2$	C, H, N	1.7, 19.2, 89.2	nd, 22, nd
6g	SCH_3	186−187	$C_{19}H_{22}ClN_3O_4S_3$	C, H, N	−2.1, 15.2, 81.4	nd, 34, nd
6h	$SOCH_3$	174−176	$C_9H_{22}ClN_3O_5S_3$	C, H, N	1.9, 2.4, 17.6	nd, 0, nd
6i	SO_2CH_3	205−207	$C_{19}H_{22}ClN_3O_6S_3$	C, H, N	1.8, 1.1, 16.4	nd, 0, nd
6f	*N*-morpholinyl	195	$C_{22}H_{27}ClN_4O_5S_2$	C, H, N	−1.6, 26.7, 89.1	30, 92, nd
6j	CH_3	183	$C_{19}H_{22}ClN_3O_4S_2$	C, H, N	1.9, 21.0, 74.8	nd, 22, nd
13a	C_2H_5	155	$C_{20}H_{24}ClN_3O_4S_2$	C, H, N	1.3, 20.5, 92.9	nd, 29,nd
13b	C_3H_7	156−160	$C_{21}H_{26}ClN_3O_4S_2$	C, H, N	2.3, 41.5, 97.1	nd, 52, nd
13c	*i*-C_3H_7	180	$C_{21}H_{26}ClN_3O_4S_2$	C, H, N	12.01, 29.3, 92.4	nd, 30, nd
13d	ethynyl	225	$C_{20}H_{20}ClN_3O_4S_2$	C, H, N	3.3, 3.4, 27.6	nd, 10, nd
13e	C_6H_5	192−194	$C_{24}H_{24}ClN_3O_4S_2$	C, H, N	9.4, 33.0, 67.7	nd, 52, nd
13f	2-furanyl	144−145	$C_{22}H_{22}ClN_3O_5S_2$	C, H, N	−2.6, 16.0, 82.7	nd, 33, nd
13g	2-pyridyl	85−86	$C_{23}H_{23}ClN_4O_4S_2$	C, H, N	6.6, 24.4, 91.4	43, 80, nd
13h	3-pyridyl	amorph	$C_{23}H_{23}ClN_4O_4S_2$	C, H, N	4.4, 10.2, 62.3	nd, 20, nd

[a] glib, glibenclamide. [b]HMR1883. [c]h-SUR1/Kir6.2 activated by diazoxide; test compound concentrations 0.1, 1, and 10 μM. [d]Glibenclamide concentrations 1, 3, and 10 nM. [e]Guinea pig papillary muscle, % reversal of action potential shortening due to rilmakalim; test compound concentrations 0.2, 2, and 20 μM. [f]Glibenclamide concentrations 0.02, 0.2, and 2 μM. [g]nd, not detemined.

of activity this structural pattern was not further explored. Attempts to further improve cardioselectivity by removing the *N*-methyl group of **6a** leading to compound **6y** were not successful.

Table 2 shows the influence of alkoxy substituents adjacent to the *N*-methylsulfonylthiourea moiety. All compounds in this subseries showed excellent cardioselectivity. Apparently, trifluoromethyl (**6k**) displayed a slightly less pronounced cardiac potency than HMR1883 whereas ethoxy, propoxy, and isopropoxy (**6p**−**r**) all had increased cardiac potency while cardioselectivity was roughly not changed. A double bond is well-tolerated as indicated by allyloxy derivative **6s**. A highly potent compound with excellent cardioselectivity was obtained using methoxyethoxy substitution (**6u**). This compound is apparently superior to HMR1883, whereas its homologue **6v** was found to be slightly less potent than HMR1883.

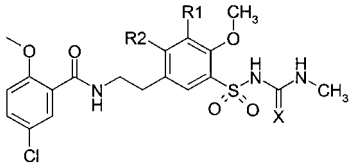
Table 3 shows the effect of further variations in the 2-position of the central aromatic ring. Halogen (**6b**−**e**) instead of alkoxy is usually associated with less cardiac activity as compared to the methoxy derivative **6a**. The same is true for hydrogen in the 2-position (**6w**) and for the thioether **(6g**). The sulfoxide (**6h**) and sulfone (**6i**) showed almost no cardiac activity at 2 μM indicating that electron-withdrawing groups are less favorable in this position. In contrast, excellent cardioselectivity and cardiac potency were found for the electron-donating *N*-morpholinyl residue (**6f**). Among various substituents attached via a C atom to the central aromatic system (**6j, 13a**−**h**), only the 2-pyridyl derivative (**13g**), despite its electron-withdrawing properties, turned out to have a HMR1883-like profile.

As can be seen from Table 4, the central aromatic ring does not tolerate additional substituents in positions 3 and 4 of the central aromatic ring as exemplified by methyl and methoxy groups (compounds **6l**−**o**).

If the 4-methoxy group and the aminoethyl group of **6n** were incorporated into a ring system, an almost inactive compound was transformed to the rather potent enatiomeric chromane derivatives **19a**,**b** with the (+)-compound being more cardioselective, the (−)-enantiomer being more potent. Rather unexpected, compound **19c**, the sulfonylurea derivative of **19a**, displayed a highly favorable cardioselectivity associated with a slightly better potency than the parent sulfonylthiourea **19a**. In this case the enantiomeric counterpart **19d** is much less potent on both channels. It is tempting to speculate that in particular **19c** interacts with a different binding site of the cardiac K_{ATP} channel as compared to "open chain" sulfonylthioureas such as HMR1883. These results promoted us also to investigate the "des-3-C" analogue of **19c**, **7n**. Again, much to our surprise, **7n** had almost no activity in the dose range investigated (Table 4), indicating that in the "open chain" series a 4-methoxy group cannot restore activity as might be expected from **19c**. Hence, we speculated that it is not the additional electron-donating group introduced by the chromane oxygen to the central aromatic ring, rather it is the overall changed geometry that causes chromanes such as **19** to target a different binding site on the cardiac K_{ATP} channel.

Pharmacological Profile of HMR1883. As already mentioned HMR1883 was shown to have potent antifibrillatory effects in a canine model of sudden cardiac death without the untoward side effects of a nonselective K_{ATP} channel blocker such as glibenclamide.[15] In contrast to the present investigations the opening of K_{ATP} channels was induced in this canine model by ischemia due to coronary ligation in the presence of exercise instead of rilmakalim. As shown by Gögelein et al. HMR1883 has significant effects at 2 μmol on action potential shortenings due to either hypoxia or rilmakalim in papillary muscles of guinea pigs[17] suggest-

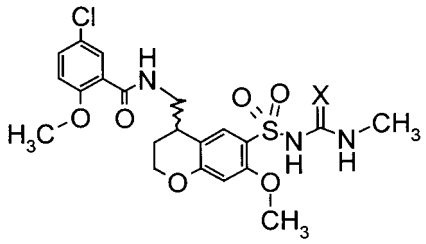
Table 4. Physical Data and Effects on K_{ATP} Channels for Sulfonylthioureas: Influence of Additional Substituents



compd	R1, R2	X	mp (°C)	formula	anal.	pancreatic[c] K_{ATP} (% inhib)	cardiac[e] K_{ATP} (% inhib)
glib[a]						24, 73.3, 92.7[d]	0, 76, 87[f]
6a[b]	H, H	S				5, 24.3, 83.8	3, 71, 117
6o	OCH_3, H	S	166−168	$C_{20}H_{24}ClN_3O_6S_2$	C, H, N	−3.8, −2.12, −2.34	nd,[h] 0, nd
6n	H, OCH_3	S	105−107	$C_{20}H_{24}ClN_3O_6S_2$	C, H, N	−1.0, 0.7, 30.5	nd, 7, nd
7n	H, OCH_3	O	128	$C_{20}H_{24}ClN_3O_7S$	C, H, N	−0.6, 2.8, 13.5	nd, 0, nd
6m	CH_3, OCH_3	S	75−80[g]	$C_{21}H_{26}ClN_3O_6S_2$	C, H, N	−2.0, 6.7, 47.8	nd, 12, nd
6l	CH_3, CH_3	S	202−204	$C_{21}H_{26}ClN_3O_5S_2$	C, H, N	0.8, 6.1, 64.9	nd, 2, nd

[a] glib, glibenclamide. [b]HMR1883. [c]h-SUR1/Kir6.2 activated by diazoxide; test compound concentrations 0.1, 1, and 10 μM. [d]Glibenclamide concentrations 1, 3, and 10 nM. [e]Guinea pig papillary muscle, % reversal of action potential shortening due to rilmakalim; test compound concentrations 0.2, 2, and 20 μM. [f]Glibenclamide concentrations 0.02, 0.2, and 2 μM. [g]Decomposition point. [h]nd, not determined.

Table 5. Physical Data and Effects on K_{ATP} Channels for Chromane-Derived Sulfonylthioureas



compd	opt. rotation	X	mp (°C)	formula	anal.	pancreatic[c] K_{ATP} (% inhib)	cardiac[e] K_{ATP} (% inhib)
glib[a]						24, 73.3, 92.7[d]	0, 76, 87[f]
6a[b]						5, 24.3, 83.8	3, 71, 117
19a	(−)	S	201−203	$C_{21}H_{24}ClN_3O_6S_2$	C, H, N	6.8, 63.0, 75.7	27, 86, nd[g]
19c	(−)	O	238−240	$C_{21}H_{24}ClN_3O_7S$	C, H, N	2.5, 14.2, 105.4	32, 116, nd
19b	(+)	S	200−202	$C_{21}H_{24}ClN_3O_6S_2$	C, H, N	−3.9, 3.6, 70.7	nd, 52, 98
19d	(+)	O	241−243	$C_{21}H_{24}ClN_3O_7S$	C, H, N	2.0, 1.0, 0.3	nd, nd, 14

[a] glib, glibenclamide. [b]HMR1883. [c]h-SUR1/Kir6.2 activated by diazoxide; test compound concentrations 0.1, 1, and 10 μM. [d]Glibenclamide concentrations 3 and 10 nM. [e]Guinea pig papillary muscle, % reversal of action potential shortening due to rilmakalim; test compound concentrations 0.2, 2, and 20 μM. [f]Glibenclamide concentrations 0.02, 0.2, and 2 μM. [g]nd, not determined.

ing that both protocols of channel opening are equivalent to predict antifibrillatory potency of a blocker.

A more recent study in rats shed some light on the amount of cardioselectivity that can be achieved with HMR1883 in vivo. Wirth et al. showed in a rat model that doses of 1, 3, and 10 mg/kg iv dose-dependently reduced VFs following an ischemia reperfusion protocol without significantly affecting insulin secretion.[29] Glibenclamide, though 1 order of magnitude more potent in this model, increased insulin at all antiarrhythmic doses. This suggests that a therapeutic width of roughly 10 for HMR1883, as estimated from our in vitro data, translates into an acceptable in vivo cardioselectivity.

Glibenclamide has been used to demonstrate that blockade of myocardial K_{ATP} channels interferes with ischemic preconditioning of the hearts.[16] However, the channel responsible for ischemic preconditioning differs from the channel being connected with VF and is located within the mitochondria while plasmalemmal K_{ATP} channels account for action potential shortening and subsequently for VF. HMR1883 specifically adresses the plasmalemmal channel[20,36] and hence does not bear the risk of interfering with ischemic preconditioning. Of course, this unique property of HMR1883 could not be predicted from our data. It is tempting to speculate that the reduction of effects on pancreatic K_{ATP} channels might run in parallel with the decreased potency on the cardiac mitochondrial channels. In this regard, other members of our series have to be investigated for their potency on the cardiac mito-K_{ATP} channel.

Conclusion

We could demonstrate that by structural modifications of the antidiabetic glibenclamide, a predominant blocker of pancreatic K_{ATP} channels, new compounds with selectivity for the cardiac plasmalemmal K_{ATP} channel can be obtained. The following key modifications were identified: *meta*-arrangement of the sulfonylurea group and the ethylamino side chain in the central aromatic ring and size reduction of the lipophilic substituent attached to the terminal sulfonylurea nitrogen. In addition it could be demonstrated that cardiac inhibitory potency and/or cardioselectivity is further increased by replacement of the sulfonylurea by a sulfonylthiourea moiety and by an additional substituent adjacent to the sulfonylthiourea group, the chemical nature of which may vary to a considerable extent. These structural modifications led to the new class of *m*-anisamidoethylbenzenesulfonylthioureas, among which HMR1883 was selected for development as a new and preventive therapeutic agent against malignant arrhythmias and sudden cardiac death.

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 was carried out on TLC glass sheets with silica gel 60 F 254, 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 apparatus B-540 and are not corrected. Enantiomeric purity was determined by a ThermoQuest-HPLC device, using chiral DNBPG-Bakerbond following Mosher derivatization of enantiomeric **16a** or **16b** in the presence of *N*-ethylmorpholine or using a CSP S Whelk-01 column from Daicel for enantiomeric **19a**−**d**.

Typical Procedure for the Preparation of Phenethylamines 3. 4-(Methylmercapto)phenylethylamine Hydrochloride (3f). 4-(Methylmercapto)benzaldehyde (**2a**; 1.52 g, 10.0 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid; 1.44 g, 10.0 mmol) and tetraethylammonium formiate (5 mL) were combined and the solution stirred at 95−100 °C for 5 h. After adding of ice−water (50 mL) and acidification to pH 1 by 2 N HCl crystals were obtained, removed by suction and dried. The material was crystallized from petroleum ether to yield 3-(4-(methylmercapto)phenyl)propionic acid (1.23 g, 63%) as a white solid: mp 97−98 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H), 2.77 (t, 2H, J = 6 Hz), 3.33 (br s, 2H, 7.17 (s, 4H); MS (DCI) *m/e* 197 (M + H$^+$). This material (1.2 g, 6.0 mmol) was added to azidodiphenylphosphate (1.7 g, 6.1 mmol) and triethylamine (0.62 g, 6.1 mmol) in *tert*-butanol (20 mL) and refluxed for 24 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (silica gel, ethyl acetate/methanol) to give *N*-(*tert*-butoxycarbonyl)-4-(methylmercapto)phenylethylamine, mp 97−98 °C, which was refluxed in methanol and 2 N HCl (1:1) for 2 h. Following removal of the solvent in vacuo, the residue was crystallized from diethyl ether to give **3a** as its hydrochloride (0.61 g, 50%): mp 243−248 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H), 2.82−3.05 (m, 4H), 7.15−7.25 (m, 4H); MS (DCI) *m/e* 204 (M + H$^+$).

The phenylethylamines **3b**,**c** were prepared in a similar manner.

Typical Procedure for the Preparation of *N*-(2-Phenylethyl)-5-chloro-2-methoxybenzamides 4 by Acylation of Phenethylamines 3. Method i: A solution of the 5-chloro-2 methoxybenzoic acid (1.00 mmol) and *N,N*′-carbonyldiimidazole (1.10 mmol) in dry THF (5 mL) was stirred at ambient temperature for 2h. Amine **3** (1.05 mmol) and triethylamine (1.00 mmol) was added and the reaction mixture stirred at ambient temperature for 12 h. After addition of 1 N HCl solution (20 mL) the product precipitated and was isolated by filtration, washing with water and drying under reduced pressure. Alternatively, the product was obtained by extraction of the reaction mixture with EtOAc, drying of the combined extracts over Na_2SO_4, evaporation of the solvent and purification of the residue by chromatography on silica gel.

Method ii: The hydrochloride of amine **3** (10.0 mmol) was dissolved in pyridine (10 mL) and 5-chloro-2-methoxybenoic acid chloride (11.0 mmol) was added. After stirring for 1 h at ambient temperature. The solution was poored into ice−water (80 mL) and was slowly neutralized with concentrated HCl. The product precipitated and was isolated by filtration, washing with water and drying under reduced pressure. Alternatively, the product was obtained by extraction of the reaction mixture with ethyl acetate, drying of the combined extracts over Na_2SO_4, evaporation of the solvent and purification of the residue by chromatography on silica gel.

5-Chloro-2-methoxy-*N*-(2-(4-methoxyphenyl)ethyl)benzamide (4a). 4-Methoxyphenylethylamine (3.02 g, 20.0 mmol) was acylated with 5-chloro-2-methoxybenzoic acid chloride (4.3 g, 21.0 mmol) using method ii. The product was extracted with ethyl acetate and 6.4 g (99%) of **4a** was obtained: mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 2.86 (t, 2H, J = 6.0 Hz), 3.64−3.83 (m, 8H) 6.81−6.94 (m, 3H), 7.15−7.21 (m, 2H), 7.35−7.40 (m, 1H) 7.79 (bs, 1H), 8.19 (d, 1H); MS (DCI) *m/e* 320 (M + H$^+$).

The following compounds were prepared accordingly.

5-Chloro-2-methoxy-*N*-(2-(4-methylmercaptophenyl)ethyl)benzamide (4g), 5-Chloro-2-methoxy-*N*-(2-(4-trifluoromethoxyphenyl)ethyl)benzamide (4i), *N*-(2-(4-Bromophenyl)ethyl)-5-chloro-2-methoxybenzamide (4d), and 5-Chloro-*N*-(2-(4-iodophenyl)ethyl)-2-methoxybenzamide (4f). A suspension of the nitro derivative **4e** (13.7 g, 46.1 mmol) and $SnCl_2 \cdot 2H_2O$ (60.0 g, 0.27 mmol) in EtOAc (400 mL) was refluxed for 2 h. 10% aqueous $NaHCO_3$ (400 mL) was added to the reaction mixture and the resulting white precipitate was filtered off. The filtrate was extracted with EtOAc, the combined extracts dried over Na_2SO_4 and the solvent evaporated to give 12.1 g (86%) of the intermediate *N*-(2-(4-aminophenyl)ethyl)-5-chloro-2-methoxybenzamide as an amorphous foam: R_f = 0.23 (EtOAc/*n*-heptane 4:1); ^{1}H NMR ($CDCl_3$) δ 2.80 (t, 2H, J = 7.0 Hz), 3.68 (dt, 2H, J = 7.0 Hz), 3.78 (s, 3H), 6.70 (m, 2H), 6.85 (m, 1H), 7.05 (m, 2H), 7.35 (m, 1H), 7.78 (br t, 1H), 8.18 (m, 1H); MS (ESI) *m/e* 305 (M + H$^+$).

To a cooled (0 °C) suspension of the thus obtained intermediate (9.0 g, 29.6 mmol) in concentrated HCl (7.5 mL) and water (30 mL) a solution of $NaNO_2$ (2.1 g, 30.6 mmol) in water (6 mL) was added. After 5 min of stirring at 0 °C a solution of KI (5.0 g, 30.6 mmol) in water (7.5 mL) was added dropwise and the reaction mixture was stirred for 2 h at room temperature. Extraction with CH_2Cl_2, drying over Na_2SO_4, and evaporation of the solvent gave a residue which was purified by chromatography on silica gel (EtOAc/*n*-heptane 1:2) to yield 5.9 g (48%) of **4f** as a pale yellow foam: R_f = 0.48 (EtOAc/*n*-heptane 2:1); ^{1}H NMR (DMSO-d_6) δ 2.80 (t, 2H, J = 7.0 Hz), 3.52 (dt, J = 7.0 Hz), 3.82 (s, 3H), 7.05−7.18 (m, 3H), 7.44−7.72 (m, 3H), 8.22 (br t, 1H); MS (DCI) *m/e* 415 (M + H$^+$).

Typical Procedure for the Preparation of 2-Substituted 5-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulfonamides 5. The benzamide derivative **4** (1.00 mmol) was added in small portions to cooled (0−5 °C) chlorosulfonic acid (3.5 mL). After stirring at ambient temperature for 3 h the reaction mixture was poured on crushed ice (15 mL). The precipitated sulfochloride was filtered off and taken up in acetone (10 mL). Concentrated NH_4OH (2 mL) was added to the cooled (0−5 °C) solution and the reaction mixture stirred at ambient temperature for 1 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The product was isolated by extraction with EtOAc, drying of the extracts over Na_2SO_4, evaporation of the solvent, and purification either by crystallization or by chromatography on silica gel.

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-methoxybenzenesulfonamide (5a). The amide **4a** (6.6 g, 20.6 mmol) was treated with chlorosulfonic acid and afterward with aqueous ammonium hydroxide via the general procedure described above to yield 6.64 g (81%) of **5a** as a white solid: mp 220−221; ^{1}H NMR (DMSO-d_6) δ 2.82 (t, 2H, J = 6.0 Hz), 3.41−3.49 (m, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 7.01 (bs, 2H), 7.09−7.17 (m, 2H), 7.41−7.56 (m, 2H), 7.62−7.70 (m, 2H), 8.25 (br t, 1H); MS (DCI) *m/e* 399 (M + H$^+$).

The following compounds were prepared accordingly.

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-(methylmercapto)benzenesulfonamide (5g), 5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-(trifluoromethoxy)benzenesulfonamide (5k), 2-Bromo-5-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonamide (5d), and 5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-(methylsulfinyl)-benzenesulfonamide (5h). The sulfonamide **5g** (0.41 g, 1.0 mmol) was added to 0.2 mL 30% H_2O_2 (0.2 mL) in acetic acid (4 mL) and the resulting solution was allowed to stand at 0 °C for 2 days. The mixture was diluted with ice−water (20 mL) and the crystallized material was removed by suction to give 280 mg (65%) of **5h** as a white solid: mp 241−242 °C; ^{1}H

NMR (DMSO-d_6) δ 2.76 (s,3H) 2.98 (t, 2H, J = 6.5 Hz), 3.58 (dt, 2H, J = 6.5 Hz), 3.82 (s, 3H), 7.16 (d, 1H, J = 8 Hz), 7.48−7.84 (m, 5H), 8.10 (d, 1H, J = 8 Hz), 8.35 (br t, 1H); MS (DCI) *m/e* 431 ($M + H^+$).

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-(methylsulfonyl)benzenesulfonamide (5i). The sulfonamide **5g** (0.41 g, 1 mmol) was added to 30% H_2O_2 (0.4 mL) in acetic acid (4 mL) and the resulting solution was kept at 80 °C for 8 h. The mixture was diluted with ice−water (20 mL) and the crystallized material was removed by suction to give 310 mg (69%) of **5i** as a white solid: mp 241−242 °C; ^{1}H NMR (DMSO-d_6) δ 2.76 (s, 3H), 2.98 (t, 2H, J = 6.5 Hz), 3.54 (dt, 2H, J = 6.5 Hz), 3.83 (s, 3H), 7.17 (d, 1H, J = 8 Hz), 7.48−7.95 (m, 5H), 8.10 (d, 1H, J = 8 Hz), 8.35 (br t, 1H); MS (DCI) *m/e* 447 ($M + H^+$).

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-*N*-morpholinylbenzenesulfonamide (5f). The sulfonamide **5b** (500 mg, 1.29 mmol) was dissolved in 4.0 mL DMF and 0.11 mL morpholine (112 mg, 1.29 mmol). After addition of 357 mg (2.58 mmol) potassium carbonate the mixture was heated to reflux for 3h. The reaction was poured on ice/water and extracted with ethyl acetate followed by cromatography (EtOAc/*n*-heptane 2:1−4:1). The product (59 mg, 10%) was isolated as a colorless solid: mp 236 °C; ^{1}H NMR (DMSO-d_6) δ 2.81−2.98 (m, 6H), 3.42−3.58 (m, 2H), 3.71−3.84 (m, 7H), 6.92 (bs, 2H), 7.14−7.20 (m, 1H), 7.48−7.57 (m, 3H), 7.62−7.66 (m, 1H), 7.75 (bs, 1H), 8.30 (bt, 1H); MS (DCI) *m/e* 454 ($M + H^+$).

Typical Procedure for the Preparation of 2-Substituted 5-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulfonyl-*N*-methylthioureas from Benzenesulfonamides. A solution of the sulfonamide (1.00 mmol) and KO*t*Bu (1.20 mmol) was stirred at ambient temperature for 15 min. A 1 M solution of the isothiocyanate in dry DMF (1.10 mmol) was added and stirring was continued at 80 °C for 1 h. The reaction mixture was acidified by addition of 1 N HCl and the product was isolated either by filtering off the precipitate or extraction with CH_2Cl_2.

2-Bromo-5-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonyl-3-methylthiourea (6d). The sulfonamide **5d** (184 mg, 0.41 mmol) was treated with methyl isothiocyanate via general procedure described above. Chromatography with EtOAc/methanol (20:1) yielded 152 mg (71%) of **6d** as an amorphous white foam: R_f = 0.13 (EtOAc/*n*-heptane 2:1); ^{1}H NMR (DMSO-d_6) δ 2.85 (d, 3H, J = 4.0 Hz), 2.92 (t, 2H, J = 7.0 Hz), 3.55 (dt, 2H, J = 7.0 Hz), 3.80 (s, 3H), 7.16 (m, 1H), 7.42−7.80 (m, 4H), 8.02 (m, 1H), 8.26 (br t, 1H); MS (ESI) *m/e* 520/522 ($M + H^+$).

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-methoxybenzenesulfonyl-3-methylthiourea (6a). The sulfonamide **5a** (1.2 g, 3.0 mmol) was treated with methyl isothiocyanate via the typical procedure described above. Trituration with 1 N HCl yielded 1.3 g (92%) of **6a** as a white solid: mp 190−193 °C; ^{1}H NMR (DMSO-d_6) δ 2.85 (t, 2H, J = 5.0 Hz), 2.93 (d, 3H, J = 5.0 Hz), 3.49 (q, 2H, J = 5.0 Hz), 3.85 (s, 3H), 3.88 (s, 3H), 7.11−7.25 (m, 2H), 7.45−7.61 (m, 2H),), 7.63−7.75 (m, 2H), 8.25 (br t, 1H); 8.40 (q, 1H, J = 5.0 Hz), 11.21 (s, 1H); MS (ESI) *m/e* 472 ($M + H^+$).

The following compounds were prepared accordingly: **5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-isopropoxybenzenesulfonyl-3-methylthiourea (6q), 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-(methylmercapto)-benzenesulfonyl-3-methylthiourea (6g), 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-(trifluoromethoxy)benzenesulfonyl-3-methylthiourea (6k), 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-(2-methoxyethoxy)benzenesulfonyl-3-methylthiourea (6u), 2-(allyloxy)-5-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonyl-3-methylthiourea (6s), 5-[2-(5-chloro-2-methoxybenzamido)-ethyl]-2-phenylbenzenesulfonyl-3-methylthiourea (13e), 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-ethynylbenzenesulfonyl-3-methylthiourea (13d), 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-(2-pyridyl)benzenesulfonyl-3-methylthiourea (13g),** and **5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-(3-pyridyl)benzenesulfonyl-3-methylthiourea (13h).**

Synthesis of Intermediates. 4-(2-(Trifluoroacetamido)-ethyl)-2-*N,N*-dimethylaminomethyleneaminosulfonylanisol (8b). The sulfonamide **8a** (32.6 g, 100 mmol) was dissolved in DMF (70 mL) and *N,N*-dimethylformamide dimethylacetal (16 mL, 14.3 g, 120 mmol) was added. After 3 h stirring at room temperature the mixture was poured into an ice/$NaHSO_4$ solution (5%). The precipitate was filtered, washed with water and dried. 32.5 g (85%) of **8b** was obtained as a white solid: mp 143−144 °C; ^{1}H NMR (DMSO-d_6) δ 2.75−2.82 (m, 2H), 2.88 (s, 3H), 3.11 (s, 3H), 3.12−3.24 (m, 2H), 3.79 (s, 3H), 7.05−7.11 (m, 1H), 7.26−7.31 (m, 1H), 7.40−7.45 (m, 1H), 8.18 (s, 1H), 9.45 (br t, 1H); MS (ESI) *m/e* 382 ($M + H^+$).

4-(2-(Trifluoroacetamido)ethyl)-2-dimethylaminomethylaminosulfonylphenol·HBr (9). 4-(2-(Trifluoroacetamido)ethyl)-2-*N,N*-dimethylaminomethyleneaminosulfonylanisol (**8b**; 32.5 g, 85 mmol) was dissolved in CH_2Cl_2 (450 mL) and BBr_3 solution (100 mL, 100 mmol, 1 M in CH_2Cl_2) was added slowly. After additional 5 h stirring at room temperature the mixture was diluted with methanol (150 mL). The mixture was poured into diisopropyl ether (2 L) and the precipitate was filtered off. 36.0 g (95%) of the hydrobromide **9** was obtained as a colorless solid: mp 160−161 °C; ^{1}H NMR (DMSO-d_6) δ 2.73 (t, 2H, J = 7.0 Hz), 2.90 (s, 3H), 3.16 (s, 3H), 3.38 (q, 2H, J = 7.0 Hz), 3.79 (s, 3H), 6.79−6.84 (m, 1H), 7.17−7.23 (m, 1H), 7.55−7.60 (m, 1H), 8.21 (s, 1H), 9.43 (br t, 1H); 10.0−10.4 (m, 1H); MS (ESI) *m/e* 368 ($M + H^+$).

Typical Procedure for the Preparation of 2-(4-Alkoxy-3-sulfamoylphenyl)ethylamine Hydrochlorides 10. To a mixture of the phenol (1 mmol) and 2.5 mmol of potassium carbonate in dry DMF (40 mL) was added alkyl halide (2.0 mmol). The mixture was heated for 3 h at 80 °C. After dilution with ethyl acetate, the organic layer was washed with sodium chloride solution, dried and the solvent evaporated. The resulting product was chromatographed, if necessary, or directly used in the next reaction. The alkylated compound (1 mmol) was heated to reflux in a mixture of methanol (10 mL) and 5.5 N HCl (10 mL) for 8 h. The mixture was concentrated and the residue stirred with ethanol. The precipitate was filtered and washed with ethanol.

2-(4-Ethoxy-3-sulfamoylphenyl)ethylamine Hydrochloride (10a). Phenol **9** (5.4 g, 12 mmol) was treated with ethyl iodide and the resulting product was deprotected with HCl as described in the general procedure above. Precipitation with ethanol resulted in 2.9 g (86%) of the product as a colorless solid: mp 254−247 °C; ^{1}H NMR (DMSO-d_6) δ 1.39 (t, 3H, J = 7.0 Hz), 2.80−3.06 (m, 4H), 4.22 (q, 2H, J = 7.0 Hz), 6.90 (bs, 2H), 7.13−7.22 (m, 1H), 7.40−7.49 (m, 1H), 7.61−7.65 (m, 1H), 8.11 (bs, 3H); MS (ESI) *m/e* 245 ($M + H^+$).

2-(4-Allyloxy-3-sulfamoylphenyl)ethylamine Hydrochloride (10d). Phenol **9** (4.5 g, 10 mmol) was alkylated with allyl bromide and the resulting product deprotected with HCl as described in the general procedure given above. The precipitated compound (2.4 g, 82%) was filtered and dried: mp 247−248 °C; ^{1}H NMR (DMSO-d_6) δ 2.81−3.04 (m, 4H), 4.71−4.82 (m, 2H), 5.19−5.45 (m, 2H), 5.96−6.17 (m, 1H), 7.00 (bs, 2H), 7.10−7.20 (m, 1H), 7.39−7.43 (m, 1H), 7.61- − 7.65 (m, 1H), 8.05 (bs, 3H); MS (ESI) *m/e* 257 ($M + H^+$).

2-(4-Methoxyethoxy-3-sulfamoylphenyl)ethylamine Hydrochloride (10f). Phenol **9** (2.7 g, 6 mmol) was alkylated with bromoethyl methyl ether and the resulting product deprotected with HCl as given in the general procedure described above. Precipitation with ethanol resulted in 1.2 g (65%) of the desired product as a colorless solid: mp 195−197 °C; ^{1}H NMR (DMSO-d_6) δ 2.81−3.10 (m, 4H), 3.36 (s, 3H), 3.64−3.78 (m, 2H), 4.21−4.30 (m, 2H), 6.81 (bs, 2H), 7.10−7.16 (m, 1H), 7.41−7.52 (m, 1H), 7.61- − 7.64 (m, 1H), 8.08 (bs, 3H); MS (ESI) *m/e* 275 ($M + H^+$).

Typical Procedure for the Preparation of *N*-(2-Phenylethyl)-5-chloro-2-methoxybenzamides 12a−h by Pd(0)-Catalyzed Cross-Coupling Reactions and Removal of the Protecting Group. 5-[2-(5-Chloro-2-methoxybenzamido)-ethyl]-2-*n*-propylbenzenesulfonamide (12b). Under an

argon atmosphere a 0.5 M solution of $ZnCl_2$ in THF (5.5 mL) were added dropwise to a suspension of the iodide **11b** (500 mg, 0.91 mmol), Pd(dppf)Cl_2 (37.5 mg, 0.05 mmol) and CuI (10.2 mg, 0.05 mmol) in THF (5 mL). A 2 M solution of *n*-propylmagnesium chloride (1.2 mL) in diethyl ether was added slowly and the reaction mixture was refluxed for 6 h. After cooling to room temperature and evaporation of the solvents and the obtained residue was dissolved in a solution of EtOAc and 1 N HCl. The separated organic layer was washed with 1 N HCl, aqueous $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent and purification of the obtained residue by chromatography on silica gel with EtOAc/*n*-heptane (3:1) gave 307 mg (73%) of 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-*n*-propyl-*N*-(dimethylaminomethylene)benzenesulfonamide as an amorphous foam: $R_f = 0.40$ (EtOAc/*n*-heptane 8:1); ^{1}H NMR (DMSO-d_6) δ 0.95 (t, 3H, $J = 7.5$ Hz), 1.60 (m, 2H), 2.84 (t, 2H, $J = 6.5$ Hz), 2.90 (s, 3H), 2.95 (t, 2H, $J = 7.0$ Hz), 3.10 (s, 3H), 3.50 (dt, 2H, $J = 7.0$ Hz), 3.82 (s, 3H), 7.14 (m, 1H), 7.35 (m, 2H), 7.50 (m, 1H), 7.64 (m, 1H), 7.72 (m, 1H), 8.14 (m, 1H), 8.25 (br t, 1H); MS (DCI) *m/e* 466 ($M + H^+$).

A solution of the amidine (300 mg, 0.56 mmol) in methanol (10 mL) and concentrated HCl (1.7 mL) was refluxed for 3 h. After evaporation of the methanol the pH of the remaining aqueous solution was adjusted to 5, the precipitate filtered off and dried under reduced pressure to yield 237 mg (89%) of **12b** as a white solid: mp 177−181 °C; $R_f = 0.76$ (EtOAc/*n*-heptane 8:1); ^{1}H NMR (DMSO-d_6) δ 0.96 (t, 3H, $J = 7.0$ Hz), 1.64 (m, 2H), 2.88 (m, 4H), 3.50 (dt, 2H, $J = 6.5$ Hz), 3.82 (s, 3H), 7.15 (m, 1H), 7.35 (m, 2H), 7.50 (m, 1H), 7.68 (m, 1H), 7.75 (m, 1H), 8.28 (br t, 1H); MS (DCI) *m/e* 411 ($M + H^+$).

According to this procedure using a Nigishi-Kumada-type cross-coupling reaction as the key step, also the sulfonamides **12a**,**c** were synthesized.

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-ethynylbenzenesulfonamide (12d). A solution of the iodide **11b** (800 mg, 1.46 mmol), ethynyl tri-*n*-butylstannane (477 μL, 1.65 mmol) and Pd(PPh_3)$_2Cl_2$ (80 mg, 0.01 mmol) in dry THF (15 mL) was refluxed for 20 h. After cooling to ambient temperature EtOAc (20 mL) was added to to reaction mixture. Filtration, evaporation of the solvents and finally purification of the obtained residue by chromatography on silica gel with EtOAc/*n*-heptane (4:1) yielded 420 mg (64%) of 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-ethynyl-*N*-(dimethylaminomethylene)benzenesulfonamide as an amorphous foam: $R_f = 0.10$ (EtOAc/*n*-heptane 4:1); ^{1}H NMR (DMSO-d_6) δ 2.88 (s, 3H), 2.92 (t, 2H, $J = 6.0$ Hz), 3.15 (s, 3H), 3.54 (dt, 2H, $J = 6.0$ Hz), 7.14 (m, 1H), 7.44−7.64 (m, 4H), 7.86 (m, 1H), 8.24 (m, 1H), 8.28 (br t, 1H); MS (FAB) *m/e* 448 ($M + H^+$).

This amidine (210 mg, 0.47 mmol) was deprotected applying the procedure described for compound **12b** to yield 90 mg (48%) of **12d** as an amorphous solid: $R_f = 0.23$ (EtOAc/*n*-heptane 4:1); ^{1}H NMR (DMSO-d_6) δ 3.05 (t, 2H, $J = 6.5$ Hz), 3.60 (dt, 2H, $J = 6.5$ Hz), 3.84 (s, 3H), 7.12 (m, 1H), 7.48 (m, 1H), 7.58 (m, 1H), 7.75 (m, 1H), 7.95 (m, 1H), 8.05 (m, 1H), 8.28 (br t, 1H); MS (DCI) *m/e* 393 ($M + H^+$).

According to this procedure using a Stille-type cross-coupling reaction as the key step, the sulfonamide **12f** was synthesized.

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-phenylbenzenesulfonamide (12e). A solution of benzeneboronic acid (488 mg, 3.98 mmol) in ethanol (20 mL) was added to a suspension of the bromide **11a** (2.0 g, 3.98 mmol) and Pd(PPh)$_4$ (142 mg, 0.11 mmol) in toluene (20 mL). After 15 min of stirring at ambient temperature a 2 M Cs_2CO_3 solution (4.6 mL) was added and the reaction mixture refluxed for 6 h. The mixture was concentrated under reduced pressure and the remaining residue taken up in CH_2Cl_2 (50 mL). Washing with water, drying over Na_2SO_4, evaporation of the solvent and purification of the residue by chromatography on silica gel with EtOAc/toluene (8:1) gave 1.44 g (72%) of 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-phenyl-*N*-(dimethylaminomethylene)benzenesulfonamide as a white amorphous foam: $R_f =$ 0.40 (CH_2Cl_2/methanol 20:1); ^{1}H NMR (DMSO-d_6) δ 2.64 (s, 3H), 2.72 (s, 3H), 2.96 (t, 2H, $J = 6.0$ Hz), 3.58 (dt, 2H, $J =$ 6.0 Hz), 3.85 (s, 3H), 7.00 (s, 1H), 7.12−7.26 (m, 5H), 7.38 (m, 2H), 7.50 (m, 2H), 7.66 (m, 1H), 7.96 (m, 1H), 8.30 (br t, 1H); MS (DCI) *m/e* 500 ($M + H^+$).

This amidine (1.43 g, 2.88 mmol) was deprotected applying the procedure described for compound **12b** to yield 1.05 g (82%) of **12e** as a pale yellow solid: mp 134−136 °C; $R_f = 0.73$ (EtOAc/*n*-heptane 5:1); ^{1}H NMR (DMSO-d_6) δ 2.95 (t, 2H, $J =$ 7.5 Hz), 3.60 (dt, 2H, $J = 7.5$ Hz), 3.84 (s, 3H), 7.10 (m, 1H), 7.26 (m, 1H), 7.38 (m, 5H), 7.50 (m, 2H), 7.68 (m, 1H9, 7.95 (m, 1H), 8.35 (br t, 1H); MS (FAB) *m/e* 445 ($M + H^+$).

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-(2-pyridyl-)benzenesulfonamide (12g). A suspension of the iodide **11b** (400 mg, 0.73 mmol), freshly prepared 2-(trimethylstannyl)-pyridine (199 mg, 0.82 mmol), 10 mg LiCl, 10 mg CuI and Pd-(PPh_3)$_2Cl_2$ (32 mg, 0.004 mmol) in dry THF (10 mL) was refluxed for 10 h. After cooling to ambient temperature EtOAc (10 mL) was added to reaction mixture. Filtration, evaporation of the solvents and subsequent purification of the obtained residue by chromatography on silica gel with CH_2Cl_2/EtOAc (4:1) yielded 265 mg (73%) of 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-(2-pyridyl)-*N*-(dimethylaminomethylene)benzenesulfonamide as an amorphous white foam: $R_f = 0.05$ (CH_2-Cl_2/EtOAc 4:1); ^{1}H NMR (DMSO-d_6) δ 2.66 (s, 3H), 2.90 (s, 3H), 3.00 (t, 2H, $J = 6.5$ Hz), 3.58 (dt, 2H, $J = 6.5$ Hz), 3.84 (s, 3H), 7.15 (m, 1H), 7.30−7.58 (m, 6H), 7.66 (m, 1H), 7.82 (m, 1H), 7.95 (m, 1H), 8.32 (br t, 1H), 7.58 (m, 1H); MS (DCI) *m/e* 501 ($M + H^+$).

This amidine (250 mg, 0.50 mmol) was deprotected applying the procedure described for compound **12b** to give 161 mg (72%) of **12g** as a white solid: mp 202−203 °C; $R_f = 0.29$ (CH_2-Cl_2/EtOAc 4:1); ^{1}H NMR (DMSO-d_6) δ 2.96 (t, 2H, $J = 7.0$ Hz), 3.58 (dt, 2H, $J = 7.0$ Hz), 3.84 (s, 3H), 7.16 (m, 1H), 7.42−7.70 (m, 6H), 7.94 (m, 2H), 8.35 (br t, 1H), 8.65 (m, 1H); MS (DCI) *m/e* 446 ($M + H^+$).

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-(3-pyridyl)-benzenesulfonamide (12h). The iodide **11b** (200 mg, 0.36 mmol) was coupled with freshly prepared 3-(trimethylstannyl)-pyridine (100 mg, 0.41 mmol) following the procedure described for compound **12g** to yield 60 mg (32%) of 5-[2-(5-chloro-2-methoxybenzamido)ethyl]-2-(3-pyridyl)-*N*-(dimethylaminomethylene)benzenesulfonamide as an amorphous solid: $R_f =$ 0.26 (CH_2Cl_2/EtOAc/methanol 8:4:1); ^{1}H NMR (DMSO-d_6) δ 2.66 (s, 3H), 2.84 (s, 3H), 2.98 (t, 2H, $J = 6.5$ Hz) 3.56 (dt, 2H, $J = 6.5$ Hz), 3.84 (s, 3H), 7.18 (m, 1H), 7.30 (m, 2H), 7.50 (m, 4H), 7.65 (m, 1H), 7.70 (m, 1H), 7.96 (m, 1H), 8.16 (m, 1H), 8.34 (br t, 1H); MS (ESI) *m/e* 501 ($M + H^+$).

This amidine (55 mg, 0.11 mmol) was deprotected applying the procedure described for compound **12b** to give 34 mg (65%) of **12h** as an amorphous solid; $R_f = 0.32$ (CH_2Cl_2/EtOAc/methanol 8:4:1); ^{1}H NMR (DMSO-d_6) δ 3.00 (t, 2H, $J = 6.5$ Hz) 3.52 (dt, 2H, $J = 6.5$ Hz), 3.84 (s, 3H), 7.20 (m, 1H), 7.34 (m, 2H), 7.44−7.52 (m, 3H), 7.60 (m, 1H), 7.72 (m, 1H), 7.92 (m, 1H), 8.16 (m, 1H), 8.30 (br t, 1H); MS (ESI) *m/e* 446 ($M + H^+$).

General Procedure for Protection of a Sulfamoyl Group. 5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-iodo-*N*-(dimethylaminomethylene)benzenesulfonamide (11b). A solution of the sulfonamide **5e** (4.3 g, 8.70 mmol) and *N*,*N*-dimethylformamide dimethylacetal (1.4 mL, 10.4 mmol) in dry DMF (32 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated, the obtained residue dissolved in water and in aqueous $NaHSO_4$ (100 mL) and the precipitate was filtered off. Chromatography of the precipitate on silica gel with EtOAc/*n*-heptane (2:1) yielded 3.4 g (70%) of **11b** as a white solid: mp 183−186 °C; $R_f = 0.13$ (EtOAc/*n*-heptane 4:1); ^{1}H NMR (DMSO-d_6) δ 2.88 (t, 2H, $J = 7.0$ Hz), 2.95 (s, 3H), 3.18 (s, 3H), 3.50 (dt, 2H, $J = 7.0$ Hz), 3.82 (s, 3H), 7.15 (m, 2H), 7.50 (m, 1H), 7.64 (m, 1H), 7.96 (m, 2H), 8.26 (m, 2H); MS (DCI) *m/e* 550 ($M + H^+$).

General Procedure for Oxidation of Sulfonylthiourea to Sulfonylurea. 1 mmol of sulfonythiourea **6** was dissolved in 3 mL 1 N NaOH and 0.6 mL hydrogen peroxide (30%) was

added. After 1 h stirring at room temperature the mixture was acidified with 2 N HCl and the precipitate filtered off and dried.

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-methoxybenzenesulfonyl-3-methylurea (7a). 470 mg (1.0 mal) of **6a** was oxidized according to the general procedure described above and the sulfonylurea **7a,** 420 mg (92%), was obtained as colorless solid: mp 201−203 °C; ^{1}H NMR (DMSO-d_6) δ 2.88−2.91 (m, 2H), 3.42−3.58 (m, 2H), 3.83 (s, 3H), 3.88 (s, 3H), 7.12−7.24 (m, 2H), 7.41−7.73 (m, 4H), 8.21−8.33 (m, 1H), 10.38 (s, 1H); MS (ESI) *m/e* 456 (M + H$^+$).

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-methoxybenzenesulfonylthiourea (6y). The sulfonamide **5a** (2.0 g, 5.0 mmol) was dissolved in DMF (15 mL) and carbon disulfide (0.4 mL) and powdered KOH (280 mg, 5.0 mmol) were added. After stirring at room temperature for 20 h, ethyl acetate (25 mL) was added. The precipitated intermediate was filtered, dried and directly used in the following step. 550 mg (1.0 mmol) of the intermediate was suspended in CH_2Cl_2 and ethyl chloroformate (0.18 mL, 2.2 mmol) was added. After stirring for 48 h ammonia gas was bubbled through the mixture for 30 min. The solvent was evaporated, the residue dissolved in DMF and 1 N HCl added. The product **6y** precipitated as colorless solid and was recrystallized from methanol to yield 100 mg (22%): mp 177−178 °C; ^{1}H NMR (DMSO-d_6) δ 2.78−2.93 (m, 2H), 3.41−3.56 (m, 2H), 3.85 (s, 3H), 3.91 (s, 3H), 7.11−7.28 (m, 2H), 7.32−7.78 (m, 5H), 8.28 (t, 1H, J = 5.0 Hz), 8.95 (bs, 1H), 11.33 (s, 1H); MS (ESI) *m/e* 458 (M + H$^+$).

5-[2-(5-Chloro-2-methoxybenzamido)ethyl]-2-methoxybenzenesulfonyl-3,3-dimethylurea (7b). The title compound was prepared by oxidation (see general method for **7a**) with H_2O_2 in 1 N NaOH following the procedure described above for thiourea **6y** using 40% aqueous dimethylamine instead of aqueous ammonia. **7b** was obtained in an overall yield of 18% from 2.0 g (5.0 mmol) sulfonamide **5a** as colorless solid: mp 205−208 °C; ^{1}H NMR (DMSO-d_6) δ 2.93 (s, 6H), 2.95 (t, 2H, J = 6.0 Hz), 3.73 (q, 2H, J = 5.0 Hz), 3.88 (s, 3H), 3.96 (s, 3H), 6.83−7.03 (m, 2H), 7.30−7.53 (m, 3H), 7.82−7.96 (m, 2H), 8.11−8.19 (m, 1H); MS (ESI) *m/e* 470 (M + H$^+$).

Synthesis of Chromanes 19a−d. (−)-*N*-[[4-[(5-Chloro-2-methoxybenzamido)methyl]-7-methoxy-6-chromanyl]-sulfonyl]-*N*′-methylthiourea (19a). (−)-5-Chloro-2-methoxy-*N*-[(7-methoxy-6-sulfamoylchroman-4-yl)methyl]benzamide (**18a**; 1.76 g, 4.0 mmol), K_2CO_3 (1.65 g) and methyl isothiocyanate (0.35 g, 4.8 mmol) were heated in DMSO (15 mL) at 80 °C for 2 h. The reaction mixture was poured into ice−water and acidified with 2 N HCl. The resulting precipitate was removed, dried at ambient temperature and recrystallized from ethanol containing traces of DMF to give 0.62 g (30%) of **19a**: mp 202 °C; $[\alpha]_D^{20} = -64.5°$ (c = 1, DMF); ^{1}H NMR (DMSO-d_6) δ 1.84−1.99 (m, 2H), 2.93 (d, 3H), 3.04, (m, 1H), 3.40−3.65 (m, 2H), 3.80 (s, 3H), 3.88 (s, 3H), 4.18−4.35 (m, 2H), 6.62 (s, 1H), 7.18 (d, 1H, J = 10 Hz), 7.55 (dd, 1H, J_1 = 10 Hz, J_2 = 2 Hz), 7.70−7.78 (m, 2H), 8.36 (br q, 1H), 8.46 (br t, 1H), 11.04 (s, 1H); MS (ESI) *m/e* 515 (M + H$^+$); HPLC (CSP S, S-Whelk-0 1, *n*-hexane/ethanol/CH_2Cl_2 4:1:1.1% AcOH) ee 97.9%.

(+)-*N*-[[4-[(5-Chloro-2-methoxybenzamido)methyl]-7-methoxy-6-chromanyl]sulfonyl]-*N*′-methylurea (19d). (+)-5-Chloro-2-methoxy-*N*-[(7-methoxy-6-sulfamoylchroman-4-yl)-methyl]benzamide (**18b**; 3.5 g, 8.0 mmol), powdered NaOH (0.8 g) and *N*-methyltrichloracetamide (2.1 g, 12.0 mmol) were heated in DMSO for 0.5 h. The mixture was poured into ice−water and acidified with 2 N HCl. The resulting precipitate, dried at ambient temperature, was purified by chromatography with CH_2Cl_2/acetic acid (29:1). Recrystallization from ethanol yielded 1.12 g (28%) of **19d**: mp 242 °C; $[\alpha]_D^{20} = +63.4°$ (c = 1, DMF); HPLC ee = 100%; ^{1}H NMR (DMSO-d_6) δ 1.85−1.96 (m, 2H), 2.53 (s, 3H), 3.03, (m, 1H), 3.40−3.57 (m, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 4.18−4.34 (m, 2H), 6.22, (br q, 1H, J = 2,5 Hz), 7.58, (s, 1H), 7.18 (d, 1H, J = 10 Hz), 7.55 (dd, 1H, J_1= 10 Hz, J_2 = 2 Hz) 7.68−77.4, m, 2H), 8.46 (br t, 1H), 11.2 (s, 1H); MS (ESI) *m/e* 498 (M + H$^+$); HPLC (CSP S, S-Whelk-0 1, *n*-hexane/ethanol/CH_2Cl_2 4:1:1.1% AcOH) ee 99.0%.

(+)-*N*-[[4-[(5-Chloro-2-methoxybenzamido)methyl]-7-methoxy-6-chromanyl]sulfonyl]-*N*′-thiourea (19b). This urea was prepared in the same manner as the (−)-derivative **19a** from (+)-5-chloro-2-methoxy-*N*-[(7-methoxy-6-sulfamoylchroman-4-yl)methyl]benzamide (**18b**): mp 201 °C; $[\alpha]_D^{20}$ = +59.1° (c = 1, DMF); HPLC (CSP S, S-Whelk-01, *n*-hexane/ethanol/CH_2Cl_2 4:1:1.1% AcOH) ee 98.0%.

(−)-*N*-[[4-[(5-Chloro-2-methoxybenzamido)methyl]-7-methoxy-6-chromanyl]sulfonyl]-*N*′-urea (19c). This urea was prepared in the same manner as the (+)-derivative from (−)-5-chloro-2-methoxy-*N*-[(7-methoxy-6-sulfamoylchroman-4-yl)methyl]benzamide (**18a**): mp 239 °C; $[\alpha]_D^{20} = -59.8°$ (c = 1, DMF); HPLC (CSP S, S-Whelk-01, *n*-hexane/ethanol/CH_2Cl_2 4:1:1.1% AcOH) ee 98.5%.

(+)-5-Chloro-2-methoxy-*N*-[(7-methoxy-6-sulfamoylchroman-4-yl)methyl]benzamide (18b) and (−)-5-Chloro-2-methoxy-*N*-[(7-methoxy-6-sulfamoylchroman-4-yl)-methyl]benzamide (18a). This compounds were prepared from (+)-5-chloro-2-methoxy-*N*-[(7-methoxychroman-4-yl)-methyl]benzamide (**17b**) and (−)-5-chloro-2-methoxy-*N*-[(7-methoxychroman-4-yl)methyl]benzamide (**17a**), respectively, according to the procedure described for benzenesulfonamides **5** (Scheme 1) using chlorosulfonic acid at ambient temperature and subsequently aqueous ammonia in acetone.

(+)-5-Chloro-2-methoxy-*N*-[(7-methoxychroman-4-yl)-methyl]benzamide (17b) and (−)-5-Chloro-2-methoxy-*N*-[(7-methoxychroman-4-yl)methyl]benzamide (17a). These compounds were prepared from (+)- and (−)-4-aminomethyl-7-methoxychromanes **16b**,**a**, respectively, according to method i for the preparation of amides **4** in Scheme 1.

(−)-4-Aminomethyl-7-methoxychromane (16a). Enantiomeric Separation of 16. (*R*)-(−)-Mandelic acid (82.1 g, 0.54 mol) and 4-aminomethyl-7-methoxychromane (**16**; 103.1 g, 0.534 mol) were fractionally crystallized from absolute ethanol (1200 mL) at ambient temperature. After 3 crystallizations 29.8 g of the (*R*)-(−) mandelic acid salt of **16a** were obtained with $[\alpha]_D^{20} = -59.5°$ (c = 1, H_2O); mp 147−148 °C; HPLC ee >99%. From this salt the free base of 4-aminomethyl-7-methoxychromane was obtained by treatment with aqueous NaOH and extraction with CH_2Cl_2 as a viscous oil.

(+)-4-Aminomethyl-7-methoxychromane (16b) was obtained in the same manner as the (−)-enantiomer **16a** using (*S*)-(+)-mandelic acid instead of the *R*-(−)-isomer. The purity of the (*S*)-(+)-mandelic salt **16b** was >98.2%.

4-Aminomethyl-7-methoxychromane (16). To NaH (30 g, 95% in oil, 1.2 mol) in THF (1 L) was added phosphonoacetic acid trimethyl ester (240 mL, 1.2 mol) dropwise under a N_2 atmosphere. The mixture was cooled to 0 °C and 7-methoxychroman-4-one (**14**; 116 g, 0.65 mol) in THF (200 mL) was added dropwise. The mixture was allowed to stand overnight. After removal of the solvent, the residue was taken up with water (2 L) and CH_2Cl_2 (1 L). The organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the resulting gum purified by column chromatography with silica gel (petroleum ether/ethyl acetate 5:1) to give a pale yellow oil, 98 g, (61%) consisting of a mixture of steroisomeric 7-methoxychromanylideneacetic acid methyl esters. This oil was completely dissolved in acetic acid (800 mL) and subjected to hydrogenation at ambient temperature with 12 g Pd/C (10%). The catalyst was filtered off and the solvent removed in vacuo to give the crude 7-methoxy-4-chromaneacetic acid ethyl ester as an oil which was dissolved in 2 N NaOH (320 mL) and ethanol (120 mL). After reflux for 1.5 h ethanol was removed in vacuo and the resulting clear aqueous solution was acidified to pH 1−2 (concentrated HCl). The precipitate was removed by suction and air-dried to give 7-methoxy-4-chromaneacetic acid: 71.6 g (61%); mp 82−83 °C; MS (DCI) *m/e* 223 (M + H$^+$). This material (18.9 g, 85 mmol) was added to azidodiphenylphosphate (18.88 mL, 85 mmol) and triethylamine (11.96 mL, 85 mmol) in *tert*-butanol (200 mL) and refluxed for 24 h. The solvent was removed in vacuo, the residue was purified by flash chromatography on silica gel (ethyl acteate/CH_2Cl_2 1:19) to give *N*-(*tert*-butoxycarbonyl)-4-aminomethyl-7-chromane: 23.3 g (95%); mp 83−85 °C; ^{1}H

NMR (DMSO-d_6) δ 1.38 (s, 9H), 1.70−1.97 (m, 2H), 2.70−2.82 (m, 1H), 2.88−3.06 (m, 1H), 3.14−3.30 (m, 1H), 3.68 (s, 3H), 3.97−4.20 (m, 2H), 6.30 (d, 1H, J = 2 Hz), 6.42 (dd, 1H, J_1 = 10 Hz, J_2 = 2 Hz), 7.02 (br d, 2H, J = 10 Hz); MS (DCI) *m/e* 294 (M + H^+), which was refluxed in methanol and 2 N HCl (1:1) for 2 h. Following removal of the solvent in vacuo, the residue was triturated with ether to give 4-aminomethyl-7-methoxychromane **16** as its hydrochloride (15 g, 82%): mp 191−193 °C; MS (DCI) *m/e* 194 (M + H^+).

II. Pharmacological Methods. Membrane Potential Measurement of CHO Cells Expressing SUR1 and Kir6.2. CHO cells stably expressing SUR1/Kir6.2 and SUR2A/Kir 6.2, respectively, were seeded in black-walled 96-well microtiter plates the day before measurement. On the experimental day plates were washed three times with PBS. The final washing step left 90 μL in each well. Cells were loaded with $DiBAC_4$ (3) (Molecular Probes, Portland, OR) by adding 90 μL of a 10 μM $DiBAC_4$ (3) solution in PBS and 90 μL of a 400 μM diazoxide solution in PBS into each well; cells were incubated for 30 min at 37 °C before transfer to the fluorescent microtiter plate reader (FLIPR, Molecular Devices, Sunnyvale, CA). Excitation was at 488 nm with an argon laser (Innova 90, Coherent, Santa Clara, CA) and fluorescence emission was monitored by a CCD camera. The membrane potential measurement was initiated after 4 min by the addition of 20 μL compound or control solution to each well and measurements were taken for 20 min every 20 s. Data are the mean of at least four experiments.

Method Cardiac Action Potential. Experiments with papillary muscles: Guinea pigs of either sex (Marioth, animal breeding Hoechst, Frankfurt/Main, Germany), weighing 300−500 g, were killed by cervical dislocation and exsanguination. The hearts were rapidly removed and the right or left papillary muscles were excised and mounted in an organ bath which contained the following bathing solution (in mM): 136 NaCl, 3.3 KCl, 2.5 $CaCl_2$, 1.2 KH_2PO_4, 1.1 $MgSO_4$, 5 glucose, 10 HEPES, pH adjusted to 7.4 with NaOH, gassed with 100% O_2.

The muscles were stimulated with rectangular pulses of 1 V and 1 ms duration at a rate of 1 Hz. The following parameters were determined: the cell's resting potential, the action potential duration at 90% repolarization (APD_{90}), the upstroke velocity, and the amplitude of the action potential.

To obtain the action potential, a standard microelectrode technique was used. Briefly, a glass microelectrode containing 3 M KCl was inserted into the cell, and the obtained signal was amplified (microelectrode amplifier type 309, Hugo Sachs, March-Hugstetten, Germany) and recorded with a computer system. When the right muscle was used, the contractile force was recorded by means of a strain-gage (GIC, Bodenheim, Germany) and the signal was displayed on a chart recorder.

Experiments with the channel opener rilmakalim: After a 30-min equilibration period, the channel opener rilmakalim (HOE234)[27,28] was applied. The test compound was added 30 min after the channel opener, and APD_{90} was recorded after an additional 60 min. As the shortening of the APD_{90} by rilmakalim and its subsequent prolongation by K_{ATP} channel blockers was highly reproducible, the number of experiments per concentration was one in most cases.

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