# 4,6-Disubstituted 2,2-Dimethylchromans Structurally Related to the $K_{ATP}$ Channel Opener Cromakalim: Design, Synthesis, and Effect on Insulin Release and Vascular Tone

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Five series (ureas, thioureas, carbamates, sulfonylureas, and amides) of 4,6-disubstituted-2,2-dimethylchromans structurally related to cromakalim were prepared and evaluated, as putative ATP-sensitive potassium channel activators, on rat pancreatic islets and rat aorta rings. The biological data indicate that most compounds were, like the reference molecule cromakalim, more active on the vascular smooth muscle tissue (myorelaxant effect on 30 mM KCl induced contractions of rat aorta rings) than on the pancreatic tissue (inhibition of 16.7 mM glucose induced insulin release from rat pancreatic islets). However, some drugs (**8h**, **8i**, **9f**, **9g**, **9h**, and **9i**) markedly inhibited insulin release and exhibited an activity equivalent or greater than that of diazoxide. Compounds **9h** and **9i** were also found to be more active on pancreatic $\beta$-cells than on vascular smooth muscle cells. Last, the amide **6b** was selected in order to examine its mechanism of action on vascular smooth muscle cells. Pharmacological results suggest that the compound acted as a $K_{ATP}$ channel opener. In conclusion, the present data indicate that appropriate structural modifications can generate dimethylchromans with pharmacological profiles different from that of cromakalim.

## Introduction

Among the wide variety of potassium channels so far described, the ATP-sensitive potassium channels ($K_{ATP}$ channels) are of particular interest because they couple cell metabolism to cell excitability. Such ionic channels are present in multiple cell types including endocrine cells,[1] skeletal and smooth muscle cells,[2−3] cardiac cells,[4] and central neurons.[5] $K_{ATP}$ channels are involved in main physiological processes such as hormone secretion, smooth muscle cell contractile activity, myocardial protection, and neurotransmitters release.[6] According to their tissue localization, $K_{ATP}$ channels do not exhibit the same sensitivity toward modulators (openers and blockers), which suggests the existence of several subtypes of channels. Recent progresses in molecular biology revealed that the $K_{ATP}$ channel consists of an octameric complex of two unrelated subunits: a pore-forming subunit ($K_{IR}6.x$) and the sulfonylurea receptor (SUR$x$). The latter regulatory subunit is expected to be the receptor protein, via multiple and distinct binding sites, for most channel activators and blockers.[7] The diversity of $K_{ATP}$ channels results from assembly of SURx and $K_{IR}6.x$ subunits in multiple combinations.[7] For example, the assembly of SUR1 and $K_{IR}6.2$ subunits forms the pancreatic (insulin-secreting) $\beta$-cell $K_{ATP}$ channel whereas the SUR2B with either $K_{IR}6.1$ or $K_{IR}6.2$ subunits generates the smooth muscle $K_{ATP}$ channel. Such a feature is a key element for the design of new $K_{ATP}$ channel modulators. Indeed, one main challenge in the development of $K_{ATP}$ modulators as therapeutic agents is to search out compounds with the best selectivity for a single $K_{ATP}$ channel subtype.

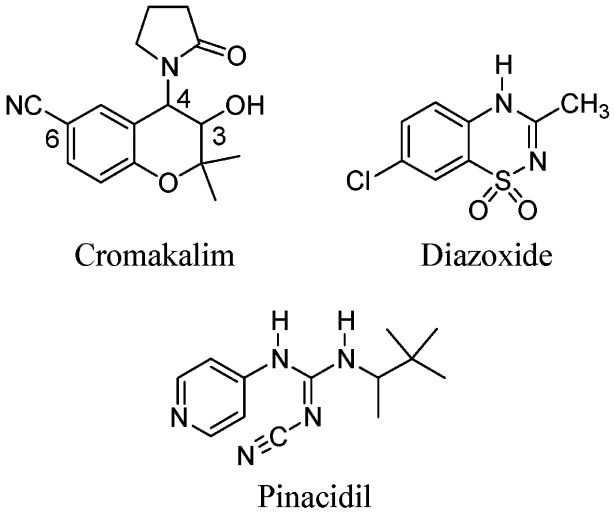


**Figure 1.** Chemical stucture of cromakalim, diazoxide and pinacidil.

Several compounds are known to activate $K_{ATP}$ channels and have been named "potassium channel openers" (PCOs).[8] Cromakalim is an example of such compounds (Figure 1). The drug exhibits a marked myorelaxant activity resulting from the activation of smooth muscle $K_{ATP}$ channels.[9] Cromakalim, however, is poorly active as an inhibitor of insulin secretion.[10,11]

To discover new potent and pancreatic $\beta$-cell selective PCOs, a series of 4,6-disubstituted-2,2-dimethylchromans structurally related to cromakalim were prepared

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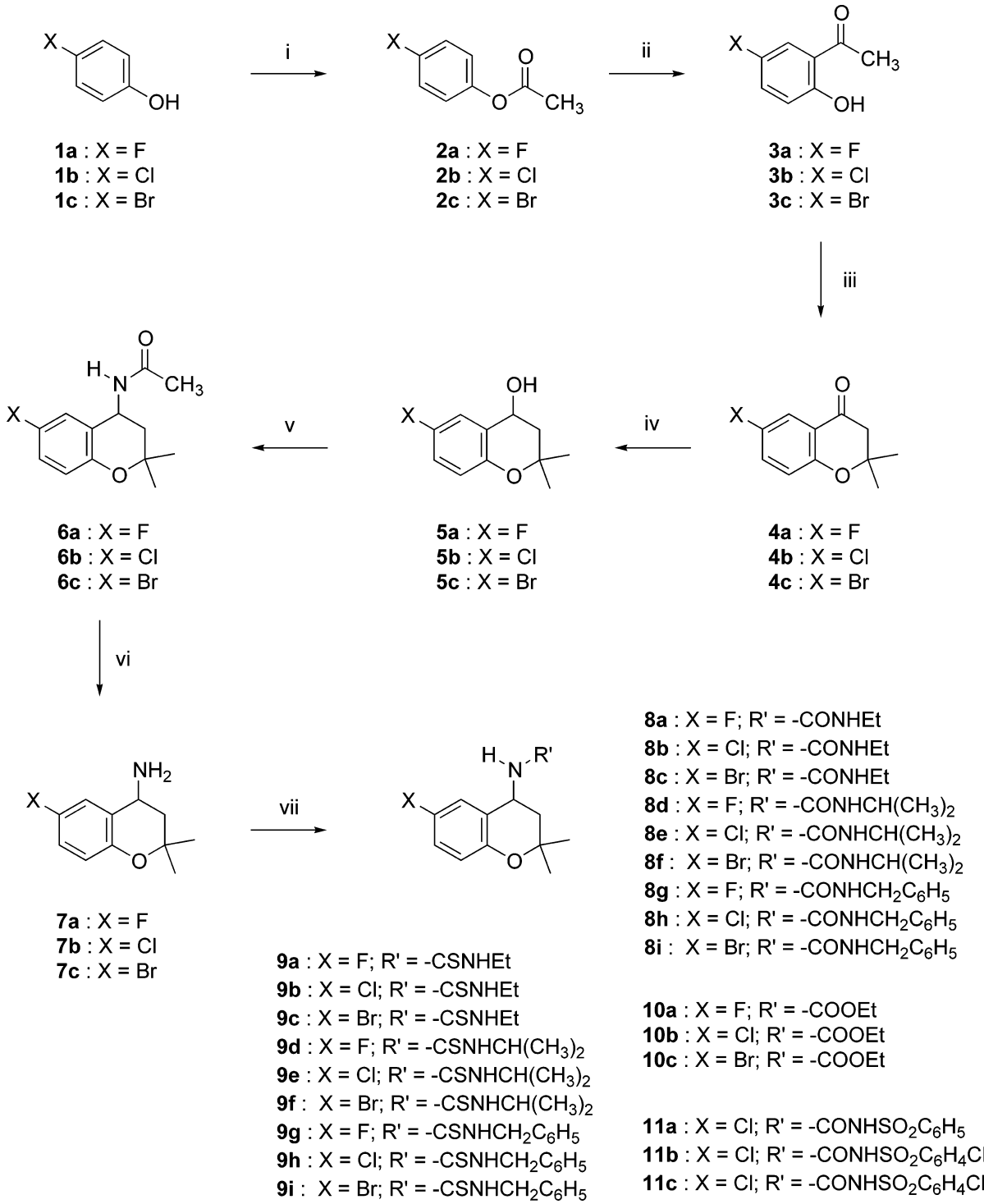
**Scheme 1.** Synthesis of Cromakalim Analogues[a]




[a] Reagents: (i) $(CH_3CO)_2O$, $H_2SO_4$; (ii) $AlCl_3$; (iii) acetone, pyrrolidine; (iv) $NaBH_4$, $CH_3OH$; (v) $CH_3CN$, $H_2SO_4$; (vi) HCl 37%; (vii) RNCO (**8a**−**i**), RNCS (**9a**−**i**), ClCOOEt (**10a**−**c**), or $RSO_2NCO$ (**11a**−**c**).

and evaluated on two different tissues: rat pancreatic islets and rat aorta rings.

The present work can be considered as the first one that aimed at developing original cromakalim analogues activating the pancreatic $\beta$-cell $K_{ATP}$ channels.

## Chemistry

Seven steps are needed to obtain the four series of cromakalim analogues (ureas (**8a**−**i**), thioureas (**9a**−**i**), carbamates (**10a**−**c**), and sulfonylureas (**11a**−**c**)) (Scheme 1).

The *R*/*S*-4-amino-3,4-dihydro-2,2-dimethyl-6-halogeno-2*H*-1-benzopyrans (**7 a**−**c**) are the key intermediates of this synthetic process, giving, in the last step, access to the target compounds. The fluoro and the bromo derivatives (**7a** and **7c**) are prepared according to the literature,[12] starting from the appropriate parahalogenophenols (**1a** and **1c**).

The *R*/*S*-4-(alkylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-halogeno-2*H*-1-benzopyrans (ureas **8a**−**f**), the *R*/*S*-4-(aralkylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-halogeno-2*H*-1-benzopyrans (ureas **8g**−

**i**), the *R*/*S*-4-(alkylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-halogeno-2*H*-1-benzopyrans (thioureas **9a**−**f**), and the *R*/*S*-4-(aralkylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-halogeno-2*H*-1-benzopyrans (thioureas **9g**−**i**) are obtained by reaction of the appropriate isocyanate or isothiocyanate with the amine function of compounds **7 a**−**c**.

Treatment of intermediates **7a**−**c** with ethyl chloroformate in the presence of pyridine leads to the carbamates **10a**−**c**.

Compound **7b** also gives access to the *R*/*S*-4-(arylsulfonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-chloro-2*H*-1-benzopyrans (sulfonylureas **11a**−**c**) after reaction with the appropriate arylsulfonyl isocyanate.

## Results and Discussion

We have synthesized simplified analogues of cromakalim in order to obtain compounds with reduced relaxant activity on smooth muscle cells. The electron-withdrawing cyano group of cromakalim, favorable to the myorelaxant activity,[13,14] was replaced with a halogen atom, and the hydroxy group, which appears also important for activity on smooth muscle cells,[15,16] was removed. The synthesis of the compounds lacking the C-3 hydroxy group was straightforward. Moreover, to preserve the hydrogen bonding site at C-4 leading to the $K_{ATP}$ channel opening properties of benzopyrans,[13,17] the 2-oxopyrrolidin-1-yl substituent in the 4 position of cromakalim was replaced by an urea, a thiourea, a sulfonylurea, a carbamate, or an amide group.

The newly synthesized analogues of cromakalim (ureas **8a**−**i**, thioureas **9a**−**i**, carbamates **10a**−**c**, sulfonylureas **11a**−**c**, and amides **6a**−**c**) have been evaluated as putative potassium channel openers on two in vitro pharmacological models: rat pancreatic islets and rat aorta rings.

In such models, PCOs such as diazoxide, pinacidil, and cromakalim have been reported to reduce the glucose-induced insulin output or to exhibit myorelaxant activity.[18]

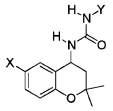
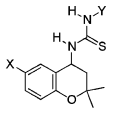
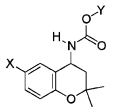
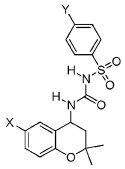
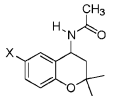
Table 1 depicts the biological data obtained with the newly synthesized dimethylchromans. Cromakalim, diazoxide, and pinacidil were used as reference compounds.

Results obtained on rat pancreatic islets indicated that, except for **8h**, **8i**, **9f**, **9g**, **9h**, and **9i**, none of the chroman derivatives markedly inhibited (>30%) insulin secretion.

According to the chemical structure of the drugs, the nature of the substituent in the 4 position appeared to be important for the inhibitory effect on insulin release. Indeed, compounds with a benzyl group in this position (benzylaminocarbonylamino (**8h** and **8i**) and benzylaminothiocarbonylamino groups (**9g**, **9h**, and **9i**)) were found to be more active than the other molecules on pancreatic $\beta$-cells.

However, most derivatives exhibited myorelaxant properties. Among the tested ureas, compounds **8b** and **8c** were found to be the most potent on the vascular smooth muscle. They are substituted by a chlorine or a bromine atom as the X substituent and by an ethylaminocarbonylamino group in the 4 position. Compounds **8d**, **8e**, **8f**, **8h**, and **8i** are less potent as myorelaxants.

**Table 1.** Effects of Original Dimethylchromans on Insulin Secretion from Rat Pancreatic Islets and on the Contractile Activity of Rat Aorta Rings[d]

| Compounds | | X | Y | Residual insulin secretion (%) [10 μM] | Myorelaxant activity $ED_{50}$ (μM) |
|---|---|---|---|---|---|
|  | **8 a** | F | $CH_2CH_3$ | 106.2 ± 4.5 (24) | 42.9 ± 7.0 (4) |
| | **8 b** | Cl | $CH_2CH_3$ | 89.5 ± 4.0 (15) | 6.8 ± 0.9 (4) |
| | **8 c** | Br | $CH_2CH_3$ | 91.5 ± 4.6 (15) | 7.6 ± 0.8 (4) |
| | **8 d** | F | $CH(CH_3)_2$ | 98.4 ± 4.2 (22) | 109.3 ± 8.1 (4) |
| | **8 e** | Cl | $CH(CH_3)_2$ | 86.8 ± 3.8 (23) | 144.1 ± 19.1 (5) |
| | **8 f** | Br | $CH(CH_3)_2$ | 79.1 ± 3.4 (31) | > 300 (4) |
| | **8 g** | F | $CH_2C_6H_5$ | 80.8 ± 3.1 (36) | nd[a] |
| | **8 h** | Cl | $CH_2C_6H_5$ | 67.1 ± 2.7 (32) | 15.3 ± 2.0 (7) |
| | **8 i** | Br | $CH_2C_6H_5$ | 58.5 ± 2.5 (31) | > 300 (4) |
|  | **9 a** | F | $CH_2CH_3$ | 82.5 ± 4.8 (21) | 17.6 ± 2.5 (5) |
| | **9 b** | Cl | $CH_2CH_3$ | 96.5 ± 4.9 (22) | 8.2 ± 0.5 (4) |
| | **9 c** | Br | $CH_2CH_3$ | 80.8 ± 4.1 (21) | 3.7 ± 0.6 (4) |
| | **9 d** | F | $CH(CH_3)_2$ | 88.7 ± 4.4 (21) | 18.5 ± 1.0 (5) |
| | **9 e** | Cl | $CH(CH_3)_2$ | 83.3 ± 4.2 (22) | 10.9 ± 1.6 (4) |
| | **9 f** | Br | $CH(CH_3)_2$ | 58.9 ± 2.8 (24) | 8.7 ± 1.2 (5) |
| | **9 g** | F | $CH_2C_6H_5$ | 54.4 ± 2.6 (24) | 4.3 ± 0.4 (5) |
| | **9 h** | Cl | $CH_2C_6H_5$ | 45.4 ± 2.3 (31) | 20.2 ± 6.6 (8) |
| | **9 i** | Br | $CH_2C_6H_5$ | 51.8 ± 2.8 (30) | 24.8 ± 5.9 (4) |
|  | **10 a** | F | $CH_2CH_3$ | 100.8 ± 5.4 (24) | 72.4 ± 5.4 (5) |
| | **10 b** | Cl | $CH_2CH_3$ | 83.3 ± 4.5 (21) | 38.5 ± 2.2 (4) |
| | **10 c** | Br | $CH_2CH_3$ | 88.8 ± 3.5 (22) | 25.7 ± 2.8 (4) |
|  | **11 a** | Cl | H | 94.7 ± 4.7 (14) | 210.5 ± 9.6 (4) |
| | **11 b** | Cl | $CH_3$ | 103.5 ± 4.4 (15) | 63.6 ± 4.6 (4) |
| | **11 c** | Cl | Cl | 89.2 ± 4.7 (16) | 51.0 ± 4.3 (4) |
|  | **6 a** | F | - | 83.8 ± 6.3 (31) | 46.5 ± 3.5 (4) |
| | **6 b** | Cl | - | 100.8 ± 5.6 (15) | 6.6 ± 0.5 (10) |
| | **6 c** | Br | - | 94.2 ± 4.4 (15) | 6.4 ± 2.0 (5) |
| **(±)-Cromakalim** | - | - | - | 94.7 ± 4.3 (24) | 0.13 ± 0.01 (7) |
| **Diazoxide** | - | - | - | 71.7 ± 2.8 (38)[b] | 23.8 ± 2.4 (10)[b] |
| **(±)-Pinacidil** | - | - | - | 96.0 ± 4.2 (20)[c] | 0.35 ± 0.02 (11) |

[a] nd: not determined. [b] Reference 19. [c] Reference 20. [d] Results are expressed as means ± sem; *n* refers to the number of samples.

They are substituted in the 4 position by a bulkier group, i.e., an isopropyl or a benzyl group.

Vascular results obtained with thioureas derivatives indicated that, except for the fluoro-substituted compound **9g**, drugs that are substituted by a chlorine or a bromine atom in the 6 position exhibited a higher vasorelaxant activity than the fluoro-substituted drugs (compare compounds **9b** and **9c** with **9a**, **9 e** and **9 f** with **9d**). Such a feature was also exhibited by the ethylureas, the carbamates, and the amides (see below).

The carbamates (**10a**−**c**) and the sulfonylureas (**11a**−**c**) were less active on precontracted rat aorta rings, but as discussed above, the rank order of potency for the carbamates was again F < Cl < Br. The chlorinated and brominated amides (**6b** and **6c**) induced a more marked myorelaxation and these halogenoderivatives were again more potent than the fluoro-substituted compound.

It was also found that many compounds were more potent than diazoxide ($IC_{50}$ = 23.8 $\mu$M) although all drugs were less active than pinacidil ($IC_{50}$ = 0.35 $\mu$M) or cromakalim ($IC_{50}$ = 0.13 $\mu$M) on the vascular smooth muscle tissue.

**Table 2.** Myorelaxant Effects of **6b** and Cromakalim on 30 and 80 mM Induced Contraction of Rat Aorta Rings Incubated in the Absence or the Presence of 1 and 10 $\mu$M Glibenclamide[a]

| compounds | rat aorta rings, 30 mM KCl $ED_{50}$ ($\mu$M) | | | rat aorta rings, 80 mM KCl $ED_{50}$ ($\mu$M) |
|---|---|---|---|---|
| | 0 $\mu$M glibenclamide | 1 $\mu$M glibenclamide | 10 $\mu$M glibenclamide | |
| **6b** | 6.3 ± 0.7 (5) | 33.8 ± 6.0 (5) | 44.6 ± 3.0 (5) | 84.2 ± 11.5 (5) |
| (±)-cromakalim | 0.14 ± 0.01 (4) | 1.8 ± 0.1 (4) | 15.2 ± 1.0 (4) | > 300 (4) |

[a] Results are expressed as mean ± sem; number in parentheses refers to the number of samples.

All together, these results indicate that the capacity of dimethylchromans to provoke a myorelaxant activity was related to the nature of the halogen atom in the 6 position; the preferred substituents appeared to be a chlorine or a bromine atom rather than a fluorine atom. Moreover, for those compounds bearing a chlorine or a bromine atom at the 6 position, the presence in the 4 position of small groups such as the ethylaminocarbonylamino, the ethylaminothiocarbonylamino, or the acetamido group further enhanced their myorelaxant effect.

Our new drugs present a stereogenic center. The tissue selectivity (pancreatic versus cardiovascular) of the individual optical isomers remains to be determined.

Inhibition of insulin secretion from rat pancreatic $\beta$-cells and relaxation of rat aorta rings may be dependent on the activation of $K_{ATP}$ channels but may also be related to the direct inhibition of $Ca^{2+}$ channels.[21]

Among the different compounds tested, **6b** was proved to be an effective myorelaxant ($ED_{50}$ = 6.6 $\mu$M) devoid of inhibitory effect on insulin secretion (% of residual insulin secretion at 10 $\mu$M = 100%). This drug was selected for further pharmacological evaluation in order to identify its mechanism of action.

First, the compound was tested on 30 mM $K^+$ depolarized rat aorta rings incubated in the absence and the presence of 1 or 10 $\mu$M glibenclamide, a blocker of $K_{ATP}$ channels.[9,20] If the drug **6b** acted as a potassium channel opener, then a reduction in myorelaxant activity should be observed in the presence of glibenclamide.[22] As shown in Table 2, a dose-dependent decrease of the vasorelaxant effect of **6b** was observed when increasing the glibenclamide concentration in the bathing medium. Under the same experimental conditions, the relaxant potency of the reference compound cromakalim was also markedly reduced (Table 2).

Second, the myorelaxant activity of **6b** versus cromakalim was examined on rat aorta rings precontracted by a 80 mM KCl solution (Table 2). Under the latter condition, the vasodilator potency of $K^+$ channel openers should be reduced, compared to their activity on 30 mM KCl induced contractions.[23,24] Conversely, drugs interfering directly at the level of $Ca^{2+}$ channels, such as $Ca^{2+}$ entry blockers, are expected to express the same myorelaxant efficacy on 30 and 80 mM KCl precontracted aorta rings.[23−25] Table 2 indicates that the myorelaxant activity of the selected compound (expressed as the $ED_{50}$ value) was strongly reduced in aorta rings bathed in 80 mM KCl solution, as expected for a $K^+$ channel opener.[23,24] Cromakalim also exhibited a less pronounced myorelaxant activity on 80 mM KCl depolarized rat aorta rings (Table 2).

Third, the effect of **6b** was further characterized on the rate of $^{86}Rb$ ($^{42}K$ substitute) outflow from rat aortic rings perifused in the absence and the presence of glibenclamide (10 $\mu$M). Compound **6b** provoked a rapid, sustained, and reversible increase in $^{86}Rb$ outflow from prelabeled and perifused rat aorta rings (Figure 2). When the same experiment was repeated in the presence of 10 $\mu$M glibenclamide in the perifusate, the cationic response to **6b** was markedly reduced. The increment in $^{86}Rb$ outflow represented 27.1 ± 3.0% of that recorded in the control conditions. Incidentally, cromakalim has previously been reported to provoke a sustained, glibenclamide-sensitive, and rapidly reversible increase in $^{86}Rb$ outflow from prelabeled and perifused rat aortic rings.[22]

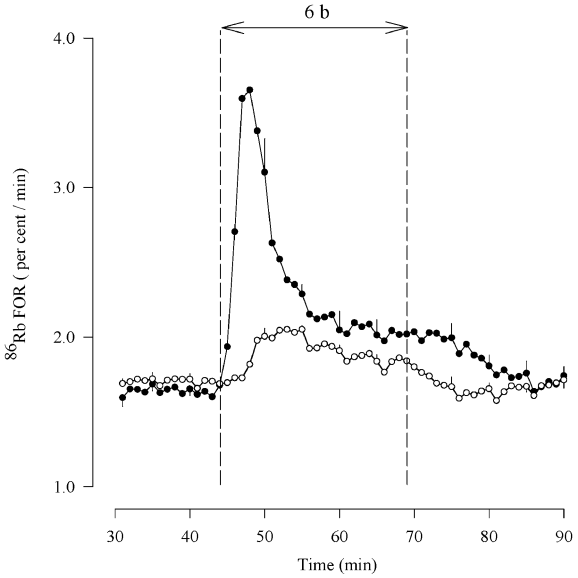



**Figure 2.** Effect of **6b** (100 $\mu$M) on $^{86}Rb$ outflow from aortic rings perifused in the absence (●) and presence (○) of glibenclamide (10 $\mu$M) throughout. The perifusate contained 30 mM $K^+$. Mean values (± sem) refer to four individual experiments.

Taken as a whole, the present findings suggest that *R*/*S*-4-(*N*-acetylamino)-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (**6b**) behaves as a $K_{ATP}$ channel opener expressing a pharmacological profile similar to that of cromakalim.

## Conclusion

The present work explored original compounds structurally related to the potassium channel opener cromakalim.

Our pharmacological data indicate that most compounds, although more active than the reference drug cromakalim, did not express a pronounced inhibitory effect on insulin secretion from rat pancreatic islets. Some drugs substituted in the 4 position with a benzylaminocarbonylamino (**8h** and **8i**), an isopropylaminothiocarbonylamino (**9f**), or a benzylaminothiocarbonylamino group (**9g**, **9h**, and **9i**) exhibited, however, a biological activity equivalent or greater than that of diazoxide. To our knowledge, this is the first report

describing cromakalim analogues with such an inhibitory potency on the insulin releasing process.

Drugs **9h** and **9i** were the most potent dimethylchromans at reducing the glucose-induced insulin release. These compounds, however, also presented a vasorelaxant activity. According to the fact that they were found to be more active on pancreatic $\beta$-cells than on vascular smooth muscle cells (estimated $ED_{50}$ on $\beta$-cells $<10$ $\mu$M (**9h**) and $\approx 10$ $\mu$M (**9i**), and $ED_{50}$ on vascular smooth muscle cells $=20.2$ $\mu$M (**9h**) and 24.8 $\mu$M (**9i**)), some pancreatic tissue selectivity can be detected. This feature should be noted because cromakalim, the parent molecule, is known to be only slightly effective as inhibitor of insulin release while being highly potent at reducing the vascular tone. Thus, it is tempting to speculate that these original dimethylchromans might serve as new leads for further developments to identify pharmacological entities with selective pancreatic $\beta$-cells activity.

Results obtained on vascular tissue indicated that molecules with a chlorine or a bromine atom in the 6 position and a small chain in the 4 position (ethylaminocarbonylamino (**8b** and **8c**), ethylaminothiocarbonylamino (**9b** and **9c**), isopropylaminothiocarbonylamino (**9e** and **9f**), or acetamido (**6b** and **6c**) exhibited a marked myorelaxant activity. These original compounds were, however, less potent than cromakalim as vasorelaxant.

Moreover, compounds **8b**, **8c**, **9b**, **9c**, **9e**, **6b**, and **6c** may be considered as rather selective for the vascular tissue because their inhibitory effect, if any, on the insulin releasing process was weak.

Last, measurements of $^{86}Rb$ outflow and contractile activity under different experimental conditions suggested that the myorelaxant properties of compound **6b**, an original dimethylchroman apparently selective for the vascular tissue, were related to the activation of $K_{ATP}$ channels.

In conclusion, we succeeded in developing novel dimethylchromans that are much more selective for insulin-secreting cells over vascular tissue than the reference molecule, cromakalim. Some compounds were even more potent than diazoxide at inhibiting the insulin-secretory process.

The design of these new $K_{ATP}$ channel openers calls for further structural modulation to identify original dimethylchromans with a powerful and selective activity on insulin-secreting cells.

## Experimental Section

**Chemistry.** Melting points were determined on a Büchi 530 capillary apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1000 FTIR spectrophotometer. The $^1H$ NMR spectra were recorded on a Bruker AW-80 (80 MHz) instrument using $d_6$-DMSO as solvent with HMDS as an internal standard; chemical shifts are reported in $\delta$ values (ppm) relative to internal HMDS. The abbreviations s = singulet, d = doublet, t = triplet, q = quadruplet, m = multiplet, and b = broad are used throughout. Elemental analyses (C, H, N, S) were realized on a Carlo-Erba EA 1108-elemental analyzer and were within $\pm 0.4\%$ of the theoretical values. All of the reactions were routinely checked by TLC on silica gel Merck 60 $F_{524}$.

**4-Chlorophenyl Acetate (2b).** 4-Chlorophenol (100 g, 0.78 mol) was dissolved in acetic anhydride (75 mL, 0.8 mol). Upon addition of 1 drop of concentrated sulfuric acid, the temperature raised to 120 °C. After being cooled, the mixture was poured into a solution of sodium hydrogenocarbonate (8 g in 1 L of water) and extracted with diethyl ether. The organic layer was washed with a saturated sodium hydrogenocarbonate solution, dried over magnesium sulfate, and evaporated under reduced pressure. The resulting oil (115 g, 87%) was used directly in the next step (Scheme 1, synthesis of **3b**).

**5-Chloro-2-hydroxyacetophenone (3b).** The crude ester **2b** (100 g, 0.59 mol) was heated together with aluminum chloride (132 g, 1 mol) at 160 °C for 2 h. The mixture was then poured on water and extracted with diethyl ether. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The product was dissolved in methanol. The solution was treated with charcoal and filtered, and water was added to the filtrate. The resulting precipitate was collected by filtration, washed with water, and dried (72 g, 72%).

**6-Chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-one (4b).** A solution of **3b** (50 g, 0.29 mol), acetone (33 mL, 0.45 mol), and pyrrolidine (37.5 mL, 0.45 mol) in methanol (1100 mL) was stirred at 25 °C overnight. On the next day, the mixture was concentrated to a red oil. Water was added, and the solution was adjusted to pH 1 with concentrated hydrochloric acid. The product was extracted with diethyl ether, and the organic layer was evaporated under reduced pressure. The residue was then dissolved in a small volume of methanol. The solution was treated with charcoal and filtered, and water was added to the filtrate. The resulting oil was extracted with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and evaporated under vacuum. The obtained oil (48 g, 79%; IR (KBr)) was used directly in the next step (Scheme 1, synthesis of **5b**).

***R/S*-6-Chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (5b).** Sodium borohydride (9.8 g, 0.26 mol) was added to a stirred suspension of **4b** (50 g, 0.24 mol) in methanol (700 mL) at 0 °C, and the mixture was maintained at this temperature for a further 30 min. After the mixture was stirred for an additional 30 min at ambient temperature, concentrated hydrochloric acid was added until acid and the solvent were evaporated under vacuum. Water was added to the residue, and the product was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The product was recrystallized in ether/petroleum ether (1:3). The resulting precipitate was collected by filtration, washed with petroleum ether, and dried (31 g, 61%). Mp: 98−101 °C. IR (KBr). Anal. ($C_{11}H_{13}ClO_2$) C, H.

***R/S*-4-(*N*-Acetylamino)-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (6b).** A suspension of **5b** (50 g, 0.23 mol) in acetonitrile (600 mL) was added dropwise to a stirred solution of acetonitrile (120 mL) in 98% sulfuric acid (30 mL) kept between −10 and 0 °C. Stirring was continued for 1 h at room temperature. The solution was poured into cold water, and the precipitate was collected by filtration, washed with water, and dried (50 g, 86%). Mp: 176−179 °C. IR (KBr). Anal. ($C_{13}H_{16}ClNO_2$) C, H, N.

***R/S*-4-Amino-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (7b).** A suspension of **6b** (20 g, 79 mmol) in concentrated hydrochloric acid (780 mL) was refluxed overnight. Hydrochloric acid was removed under vacuum, and the residue was dissolved in hot water (230 mL). The solution was filtered, and 10% aqueous sodium hydroxide was added to the filtrate until alkaline. The amine, which precipitated, was collected by filtration, washed with water, and dried under vacuum. This product (6.5 g, 39%; mp 70−73.5 °C; IR (KBr)) was used in the next steps (Scheme 1, synthesis of **8b**, **8e**, **8h**, **9b**, **9e**, **9h**, **10b**, **11a**, **11b**, and **11c**).

***R/S*-3,4-Dihydro-2,2-dimethyl-4-(ethylaminocarbonylamino)-6-fluoro-2*H*-1-benzopyran (8a).** Ethyl isocyanate (0.19 mL, 2.4 mmol) was added to a solution of **7a**[12] (0.4 g, 2 mmol) in methylene chloride (5 mL). After 20 min, the resulting precipitate was collected by filtration, washed with petroleum ether 40/60, and dried. The product was recrystallized in methanol/water (1:3) (0.34 g, 62%). Mp: 199−201 °C. IR (KBr). $^1H$ NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{14}H_{19}FN_2O_2$) C, H, N.

***R/S*-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(ethylaminocarbonylamino)-2*H*-1-benzopyran (8b).** The title compound was obtained as described for **8a** starting from **7b** (0.4 g, 1.9 mmol) and ethyl isocyanate (0.18 mL, 2.3 mmol) (0.44 g, 82%). Mp: 218−220 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 400 MHz). Anal. ($C_{14}H_{19}ClN_2O_2$) C, H, N.

***R/S*-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(ethylaminocarbonylamino)-2*H*-1-benzopyran (8c).** The title compound was obtained as described for **8a** starting from **7c**[12] (0.4 g, 1.6 mmol) and ethyl isocyanate (0.15 mL, 1.9 mmol) (0.45 g, 88%). Mp: 212−215 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{14}H_{19}BrN_2O_2$) C, H, N.

***R/S*-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(isopropylaminocarbonylamino)-2*H*-1-benzopyran (8d).** The title compound was obtained as described for **8a** starting from **7a** (0.4 g, 2 mmol) and isopropyl isocyanate (0.24 mL, 2.4 mmol) (0.39 g, 68%). Mp: 211−214 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{15}H_{21}FN_2O_2$) C, H, N.

***R/S*-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(isopropylaminocarbonylamino)-2*H*-1-benzopyran (8e).** The title compound was obtained as described for **8a** starting from **7b** (0.4 g, 1.9 mmol) and isopropyl isocyanate (0.23 mL, 2.3 mmol) (0.49 g, 96%). Mp: 225−227 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{15}H_{21}ClN_2O_2$) C, H, N.

***R/S*-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(isopropylaminocarbonylamino)-2*H*-1-benzopyran (8f).** The title compound was obtained as described for **8a** starting from **7c** (0.4 g, 1.6 mmol) and isopropyl isocyanate (0.18 mL, 1.9 mmol) (0.41 g, 77%). Mp: 225−227 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{15}H_{21}BrN_2O_2$) C, H, N.

***R/S*-4-(Benzylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran (8g).** The title compound was obtained as described for **8a** starting from **7a** (0.4 g, 2 mmol) and benzyl isocyanate (0.3 mL, 2.4 mmol) (0.55 g, 82%). Mp: 195−197 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{19}H_{21}FN_2O_2 \cdot {}^1/_2H_2O$) C, H, N.

***R/S*-4-(Benzylaminocarbonylamino)-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (8h).** The title compound was obtained as described for **8a** starting from **7b** (0.4 g, 1.9 mmol) and benzyl isocyanate (0.28 mL, 2.3 mmol) (0.50 g, 77%). Mp: 180−184 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{19}H_{21}ClN_2O_2$) C, H, N.

***R/S*-4-(Benzylaminocarbonylamino)-6-bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (8i).** The title compound was obtained as described for **8a** starting from **7c** (0.4 g, 1.6 mmol) and benzyl isocyanate (0.23 mL, 1.9 mmol) (0.56 g, 92%). Mp: 194−199 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{19}H_{21}BrN_2O_2$) C, H, N.

***R/S*-3,4-Dihydro-2,2-dimethyl-4-(ethylaminothiocarbonylamino)-6-fluoro-2*H*-1-benzopyran (9a).** Ethyl isothiocyanate (0.21 mL, 2.4 mmol) was added to a solution of **7a** (0.4 g, 2 mmol) in methylene chloride (5 mL). After 30 min, the solvent was removed under vacuum, and the crude product was triturated with ethyl acetate. The insoluble material was collected by filtration, and petroleum ether was added to the filtrate. The resulting precipitate was collected by filtration, washed with petroleum ether, and dried (0.31 g, 61%). Mp: 136−137 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{14}H_{19}FN_2OS$) C, H, N, S.

***R/S*-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(ethylaminothiocarbonylamino)-2*H*-1-benzopyran (9b).** The title compound was obtained as described for **8a** starting from **7b** (0.4 g, 1.9 mmol) and ethyl isothiocyanate (0.2 mL, 2.3 mmol) (0.33 g, 58%). Mp: 171−176 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 400 MHz). Anal. ($C_{14}H_{19}ClN_2OS$) C, H, N, S.

***R/S*-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(ethylaminothiocarbonylamino)-2*H*-1-benzopyran (9c).** The title compound was obtained as described for **8a** starting from **7c** (0.4 g, 1.6 mmol) and ethyl isothiocyanate (0.16 mL, 1.9 mmol) (0.23 g, 43%). Mp: 194−197 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{14}H_{19}BrN_2OS$) C, H, N, S.

***R/S*-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(isopropylaminothiocarbonylamino)-2*H*-1-benzopyran (9d).** The title compound was obtained as described for **9a** starting from **7a** (0.4 g, 2 mmol) and isopropyl isothiocyanate (0.26 mL, 2.4 mmol) (0.22 g, 36%). Mp: 143−145 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{15}H_{21}FN_2OS$) C, H, N, S.

***R/S*-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(isopropylaminothiocarbonylamino)-2*H*-1-benzopyran (9e).** The title compound was obtained as described for **9a** starting from **7b** (0.4 g, 1.9 mmol) and isopropyl isothiocyanate (0.24 mL, 2.3 mmol). The product was recrystallized in methanol/water (1:3) (0.33 g, 56%). Mp: 166−169 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{15}H_{21}ClN_2OS$) C, H, N, S.

***R/S*-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(isopropylaminothiocarbonylamino)-2*H*-1-benzopyran (9f).** The title compound was obtained as described for **9a** starting from **7c** (0.4 g, 1.6 mmol) and isopropyl isothiocyanate (0.2 mL, 1.9 mmol) (0.40 g, 71%). Mp: 174−176 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{15}H_{21}BrN_2OS$) C, H, N, S.

***R/S*-4-(Benzylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran (9g).** The title compound was obtained as described for **8a** starting from **7a** (0.4 g, 2 mmol) and benzyl isothiocyanate (0.33 mL, 2.4 mmol) (0.59 g, 84%). Mp: 169−171 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{19}H_{21}FN_2OS$) C, H, N, S.

***R/S*-4-(Benzylaminothiocarbonylamino)-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (9h).** The title compound was obtained as described for **8a** starting from **7b** (0.4 g, 1.9 mmol) and benzyl isothiocyanate (0.3 mL, 2.3 mmol) (0.58 g, 85%). Mp: 174−178 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{19}H_{21}ClN_2OS$) C, H, N, S.

***R/S*-4-(Benzylaminothiocarbonylamino)-6-bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (9i).** The title compound was obtained as described for **8a** starting from **7c** (0.4 g, 1.6 mmol) and benzyl isothiocyanate (0.25 mL, 1.9 mmol) (0.56 g, 88%). Mp: 186−191 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{19}H_{21}BrN_2OS$) C, H, N, S.

***R/S*-3,4-Dihydro-2,2-dimethyl-4-(*N*-ethoxycarbonylamino)-6-fluoro-2*H*-1-benzopyran (10a).** A solution of **7a** (0.2 g, 1 mmol) in pyridine (2 mL) was stirred at 0 °C. Ethyl chloroformate (0.2 mL, 2.09 mmol) was added to the mixture. After 30 min, the solvent was removed under vacuum, and water was added to the crude product. The crystalline solid was collected by filtration, washed with water, and dried (0.18 g, 64%). Mp: 106−111 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{14}H_{18}FNO_3$) C, H, N.

***R/S*-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(*N*-ethoxycarbonylamino)-2*H*-1-benzopyran (10b).** The title compound was obtained as described for **10a** starting from **7b** (0.2 g, 0.95 mmol) (0.17 g, 63%). Mp: 141−144 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 400 MHz). Anal. ($C_{14}H_{18}ClNO_3$) C, H, N.

***R/S*-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(*N*-ethoxycarbonylamino)-2*H*-1-benzopyran (10c).** The title compound was obtained as described for **10a** starting from **7c** (0.2 g, 0.8 mmol). The product was recrystallized in methanol/water (1:3) (0.19 g, 75%). Mp: 140−142 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{14}H_{18}BrNO_3$) C, H, N.

***R*/S-4-(Benzenesulfonylaminocarbonylamino)-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (11a).** The title compound was obtained as described for **8a** starting from **7b** (0.4 g, 1.9 mmol) and benzenesulfonyl isocyanate (0.3 mL, 2.3 mmol) (0.51 g, 68%). Mp: 205−206 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{18}H_{19}ClN_2O_4S$) C, H, N, S.

***R/S*-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-methylbenzenesulfonylaminocarbonylami-no)-2*H*-1-benzopyran (11b).** The title compound was obtained as described for **8a** starting from **7b** (0.4 g, 1.9 mmol) and 4-methylbenzenesulfonyl isocyanate (0.35 mL, 2.3 mmol) (0.35 g, 45%). Mp: 219−222 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 400 MHz). Anal. ($C_{19}H_{21}ClN_2O_4S$) C, H, N, S.

***R/S*-6-Chloro-4-(4-chlorobenzenesulfonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (11c).** The title compound was obtained as described for **8a** starting from **7b** (0.4 g, 1.9 mmol) and 4-chlorobenzenesulfonyl isocyanate (0.34 mL, 2.3 mmol) (0.63 g, 77%). Mp: 210−216 °C. IR (KBr). $^1$H NMR (DMSO-$d_6$, 80 MHz). Anal. ($C_{18}H_{18}Cl_2N_2O_4S$) C, H, N, S.

**Biological Assays.** Cromakalim (Beecham Pharmaceutical, U.K.), diazoxide (Sigma Chemical, U.S.A.), and pinacidil (Therabel Pharma, Belgium) were tested as reference compounds.

**Measurement of Insulin Release from Incubated Rat Pancreatic Islets.** Experiments were performed with pancreatic islets isolated from adult fed Wistar rats (Iffa-Credo, Belgium).

Groups of 10 islets, each derived from the same batch of islets, were preincubated for 30 min at 37 °C in 1 mL of a physiological salt medium (NaCl 115 mM, KCl 5 mM, $CaCl_2$ 2.56 mM, $MgCl_2$ 1 mM, $NaHCO_3$ 24 mM) supplemented with 2.8 mM glucose, 0.5% (w/v) dialyzed albumin (Sigma), and equilibrated against a mixture of $O_2$ (95%) and $CO_2$ (5%). The islets were then incubated at 37 °C for 90 min in 1 mL of the same medium containing 16.7 mM glucose and, in addition, the required chroman derivative.

The release of insulin was measured radioimmunologically using rat insulin as a standard.

Residual insulin secretion was expressed as a percentage of the value recorded in control experiments (100%), i.e., in the absence of drug and presence of 16.7 mM glucose.

**Measurement of Tension in Rat Aorta Rings.** Experiments were performed with aortae removed from adult fed Wistar rats (Iffa-Credo, Belgium).

A section of the thoracic aorta was cleared of adhering fat and connective tissue and was cut into transverse rings (3−4 mm long). The endothelium was removed, and the segments were suspended under 1.5 g tension in an organ bath containing 20 mL of a physiological solution (NaCl 118 mM, KCl 4.7 mM, $CaCl_2$ 2.5 mM, $NaHCO_3$ 25 mM, $KH_2PO_4$ 1.2 mM, $MgSO_4$ 1.2 mM, glucose 5 mM). The physiological solution was maintained at 37 °C and continuously bubbled with a mixture of $O_2$ (95%) and $CO_2$ (5%). Isometric contractions were measured with a force-displacement transducer. After 60 min of equilibration, the rings were exposed to KCl (30 or 80 mM). When the tension had stabilized, the chroman derivative was added to the bath at increasing concentrations until maximal relaxation (or until 300 $\mu$M). Some experiments were repeated in the continuous presence of 1 or 10 $\mu$M glibenclamide in the bathing medium.

The relaxation response was expressed as the percentage of the contractile response to KCl. The $ED_{50}$ values (concentration evoking 50% inhibition of the plateau phase induced by KCl) were assessed from dose−response curves using Datanalyst software (EMKA Technologies, France).

**Measurements of $^{86}$Rb Outflow from Rat Aorta Rings.** Experiments were performed with thoracic rat aorta rings (2 mm long) isolated from adult fed Wistar rats (Iffa-Credo, Belgium).

The aorta rings were preincubated for 30 min at 37 °C in a physiological solution (NaCl 115 mM, KCl 5 mM, $CaCl_2$ 2.56 mM, $MgCl_2$ 1 mM, $NaHCO_3$ 24 mM) equilibrated against a mixture of $O_2$ (95%) and $CO_2$ (5%). After preincubation, the aorta rings were incubated for 60 min at 37 °C in the same medium containing, in addition, $^{86}$Rb ion (0.15−0.25 mM, 50 $\mu$Ci mL$^{-1}$). After incubation, the segments were washed four times with nonradioactive medium and then placed in a perifusion chamber. The perifusate was delivered at a constant rate (1.0 mL min$^{-1}$). From the 31st to the 90th min, the effluent was continuously collected over successive periods of 1 min each and examined for its radioactive content by scintillation counting. At the end of the perifusion, the radioactive content of the aortic segments was also determined.

The experiments were conducted in the presence of 30 mM KCl in the perifusing medium to mimic the experimental conditions used to measure muscle tension.

The efflux of $^{86}$Rb was expressed as a fractional outflow rate (FOR: % of instantaneous aorta content per min).

The validity of $^{86}$Rb ($^{42}$K substitute) as a tracer for the study of $K^+$ handling in aorta rings has been previously assessed.[22,23]

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**Supporting Information Available:** IR spectra, $^1$H NMR spectra, and elemental analyses. This material is available free of charge via the Internet at http:/pubs.acs.org.

## References

(1) Cook, D. L.; Hales, C. N. Intracellular ATP directly blocks $K^+$ channels in pancreatic B-cells. *Nature* **1984**, *311*, 271−273.
(2) Spruce, A. E.; Standen, N. B.; Stanfield, P. R. Voltage-dependent ATP-sensitive potassium channels of skeletal muscle membrane. *Nature* **1985**, *316*, 736−738.
(3) Standen, N. B.; Quayle, J. M.; Davies, N. W.; Brayden, J. E.; Huang, Y.; Nelson, M. T. Hyperpolarizing vasodilators activate ATP-sensitive $K^+$ channels in arterial smooth muscle. *Science* **1989**, *245*, 177−180.
(4) Noma, A. ATP-regulated $K^+$ channels in cardiac muscle. *Nature* **1983**, *305*, 147−148.
(5) Bernardi, H.; Fosset, M.; Lazdunski, M. Characterization, purification and affinity labeling of the brain [$^3$H] glibenclamide-binding protein, a putative neuronal ATP-regulated $K^+$ channel. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9816−9820.
(6) Pirotte, B.; Fontaine, J.; Lebrun, P. Recent advances in the chemistry of potassium channel openers. *Curr. Med. Chem.* **1995**, *2*, 573−582.
(7) Babenko, A. P.; Aguilar-Bryan, L.; Bryan, J. A view of SUR/$K_{IR}6.x$ $K_{ATP}$ channels. *Annu. Rev. Physiol.* **1998**, *60*, 667−687.
(8) Longman, S. D.; Hamilton, T. C. Potassium channel activator drugs: mechanism of action, pharmacological properties and therapeutic potential. *Med. Res. Rev.* **1992**, *12*, 73−148.
(9) Edwards, G.; Weston, A.-H. The pharmacology of ATP-sensitive potassium channels. *Annu. Rev. Pharmacol. Toxicol.* **1993**, *33*, 597−637.
(10) Petit, P.; Hillaire-Buys, D.; Mir, A.-K.; Loubatieres-Mariani, M.-M. Differential effects of cromakalim on pancreatic vascular resistance and insulin secretion in vitro. *Fundam. Clin. Pharmacol.* **1992**, *6*, 185−190.
(11) Lebrun, P.; Antoine, M.-H.; Devreux, V.; Hermann, M.; Herchuelz, A. Paradoxical inhibitory effect of cromakalim on $^{86}$Rb outflow from pancreatic islets cells. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 948−954.
(12) Khelili, S.; Nguyen, Q.-A.; Lebrun, P.; Delarge, J.; Pirotte, B. Synthesis and pharmacological evaluation of $K_{ATP}$-channel openers related to cromakalim: introduction of arylsulfonylurea moieties. *Pharm. Pharmacol. Commun.* **1999**, *5*, 189−193.
(13) Atwal, K.-S. Modulation of potassium channels by organic molecules. *Med. Res. Rev.* **1992**, *12*, 569−591.
(14) Edwards, G.; Weston, A.-H. Structure−activity relationships of $K^+$ channel openers. *Trends Pharmacol.* **1990**, *11*, 417−422.
(15) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. Synthesis and antihypertensive activity of 4-(cyclic amido)-2*H*-1-benzopyrans. *J. Med. Chem.* **1986**, *29*, 2194−2201.
(16) Bergmann, R.; Gericke, R. Synthesis and antihypertensive activity of 4-(1,2-dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyrans and related compounds, new potassium channel activators. *J. Med. Chem.* **1990**, *33*, 492−504.
(17) Atwal, K.-S. Pharmacology and structure−activity relationships for $K_{ATP}$ modulators: tissue-selective $K_{ATP}$ openers. *J. Cardiovasc. Pharmacol.* **1994**, *24*, S12−S17.
(18) de Tullio, P.; Pirotte, B.; Lebrun, P.; Fontaine, J.; Dupont, L.; Antoine, M.-H.; Ouedraogo, R.; Khelili, S.; Maggetto, C.; Masereel, B.; Diouf, O.; Podona, T.; Delarge, J. 3- and 4-Substituted 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides as potassium channel openers: synthesis, pharmacological evaluation, and structure−activity relationships. *J. Med. Chem.* **1996**, *39*, 937−948.
(19) Becker, B.; Antoine, M.-H.; Nguyen, Q.-A.; Rigo, B.; Cosgrove, K. E.; Barnes, P. D.; Dunne, M. J.; Pirotte, B.; Lebrun, P. Synthesis and characterization of a quinolinonic compound activating ATP-sensitive $K^+$ channels in endocrine and smooth muscle tissues. *Br. J. Pharmacol.* **2001**, *134*, 375−385.
(20) Lebrun, P.; Antoine, M.-H.; Ouedraogo, R.; Kane, C.; Dunne, M.; Hermann, A.; Herchuelz, A.; Masereel, B.; Delarge, J.; de Tullio, P.; Pirotte, B. Activation of ATP-dependent $K^+$ channels and inhibition of insulin release: effect of BPDZ 62. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 156−162.
(21) Lebrun, P.; Antoine, M.-H.; Herchuelz, A. $K^+$ Channel openers and insulin release. *Life Sci.* **1992**, *51*, 795−806.

(22) Lebrun, P.; Fang, Z.-Y.; Antoine, M.-H.; Herchuelz, A.; Hermann, M.; Berkenboom, G.; Fontaine, J. Hypoglycemic sulfonylureas antagonize the effects of cromakalim and pinacidil on $^{86}Rb$ fluxes and contractile activity in the rat aorta. *Pharmacology* **1990**, *41*, 36−48.
(23) Antoine, M.-H.; Berkenboom, G.; Fang, Z.-Y.; Fontaine, J.; Herchuelz, A.; Lebrun, P. Mechanical and ionic response of rat aorta to diazoxide. *Eur. J. Pharmacol.* **1992**, *216*, 299−306.
(24) Pirotte, B.; Ouedraogo, R.; de Tullio, P.; Khelili, S.; Somers, F.; Boverie, S.; Dupont, L.; Fontaine, J.; Damas, J.; Lebrun, P. 3-Alkylamino-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides structurally related to diazoxide and pinacidil as potassium channel openers acting on vascular smooth muscle cells: design, synthesis, and pharmacological evaluation. *J. Med. Chem.* **2000**, *43*, 1456−1466.
(25) Ouedraogo, R.; Fontaine, J.; Antoine, M.-H.; Pirotte, B.; Lebrun, P. Effects of 3-alkylamino-7-chloro-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides on smooth muscle contraction. *Pharm. Pharmacol. Commun.* **2000**, *6*, 97−100.

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