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Synthesis and pharmacological evaluation of some *N*-arylsulfonyl-*N*-methyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas structurally related to cromakalim

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Abstract—Some *N*-arylsulfonyl-*N*-methyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas were prepared and evaluated as putative potassium channel openers on the vascular and uterine smooth muscle tissue (myorelaxant effect), as well as on insulin-secreting pancreatic islets (inhibition of insulin release). The pharmacological results indicated that these compounds exhibited a marked biological activity on these three tissues.

1. Introduction

A few years ago, we prepared a series of *N*-arylsulfonyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas[1] (**1**) (Fig. 1) structurally related to cromakalim (**4**) (Fig. 2) and BMS-180448 (**3**) (Fig. 1), and their biological activity was evaluated as putative potassium channel openers.

The compounds of general formula **1** exhibited some myorelaxant activity on vascular smooth muscle (rat aorta rings precontracted by 30 mM KCl) but did not show any inhibitory effect on the insulin releasing process from rat pancreatic β-cells.[1] In the present work, we describe the synthesis and pharmacological evaluation of N-methylated analogues (compounds of general formula **2**, Fig. 1) of these *N*-arylsulfonyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas. The compounds were tested as putative potassium channel openers on three different tissues, namely the rat aorta rings, the rat uterus, and the rat pancreatic islets. The aim of this study was to detect the effect of methylation of the nitrogen atom located between the sulfonyl and the carbonyl groups of these molecules on the biological efficacy and tissue selectivity. The presence of a methyl group on the sulfonylurea function is expected to avoid ionization of the molecules resulting from their deprotonation at physiological pH.

Figure 2 reports two examples of ATP-dependent potassium channel (K_{ATP} channel) openers belonging to two different chemical classes.[2–7]

Cromakalim (**4**) is a potent relaxant of the vascular smooth muscle as a result of its stimulating effect on vascular K_{ATP} channels[8], while BMS-180448 (**3**) (Fig. 1), a cardiac cell K_{ATP} channel opener, has been described as a cardioprotective agent.[9,10] Diazoxide (**5**), another potassium channel opener, is also known to act as a vasodilator but, in contrast to cromakalim, exerts an inhibitory effect on the insulin releasing process attributed to the opening of pancreatic β-cell K_{ATP} channels.[11,12] The original *N*-arylsulfonyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas reported here may be regarded as structural analogues of cromakalim (**4**) (Fig. 2) and BMS-180448 (**3**) (Fig. 1).

Keywords: Cromakalim derivatives; Potassium channel openers; Insulin secretion; Contractile activity.
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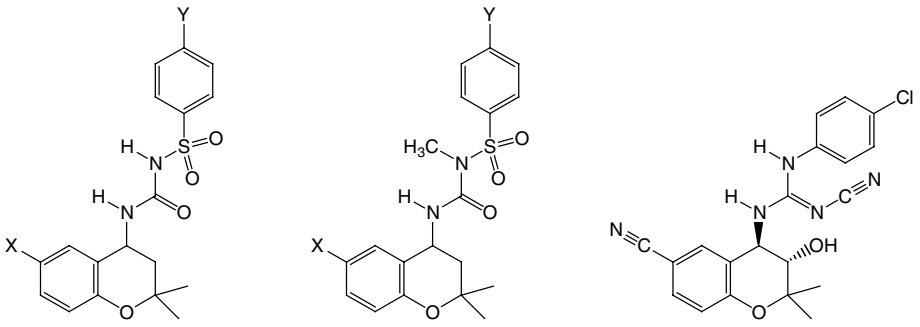


Figure 1. General structure of *N*-arylsulfonyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas (**1**) and *N*-arylsulfonyl-*N*-methyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas (**2**).

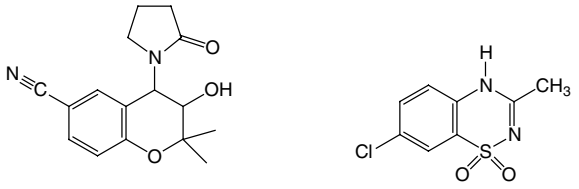


Figure 2. Two examples of openers of ATP-sensitive potassium channels.

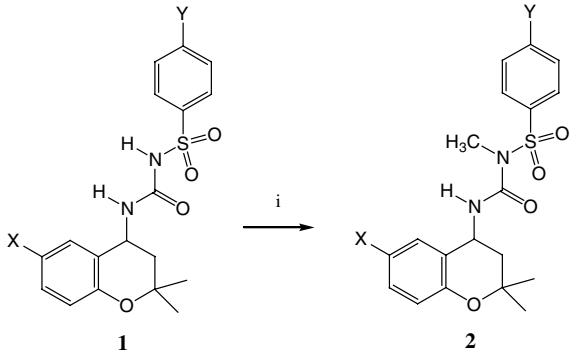
2. Results

2.1. Synthesis

The synthetic route used to prepare the novel compounds (**2**) consisted of methylation of *N*-arylsulfonyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas[1] (**1**) by using methyl iodide or dimethyl sulfate in acetonitrile, in the presence of sodium carbonate (Scheme 1). Compounds of general formula (**1**) were prepared according to a previously described method.[1]

2.2. Biological evaluation

2.2.1. Inhibitory activity on insulin secretion from rat pancreatic islets. Drugs acting as pancreatic β-cells K_{ATP} channel openers are able to inhibit the insulin releasing process.[5,11–15] Compounds **2a**–**f** were evaluated as inhibitors of insulin secretion from rat pancreatic islets incubated in the presence of an insulinotropic glucose concentration (16.7 mM). As observed in Table 1, at a 50 μM concentration, all compounds exhibited a marked inhibitory effect on the insulin releasing process. Except for **2c** (X = Br, Y = Cl) which was as potent as diazoxide, the others were found to be more active than this reference compound. All these drugs were also found to exhibit a lower but significant activity at a 10 μM concentration. Pinacidil, at a 50 μM concentration, failed to affect the glucose-induced insulin secretion. Cromakalim (50 μM) provoked a 23% reduction in the insulin secretory rate but the N-methylated analogues (**2a**–**f**) were always more potent than cromakalim (Table 1).



Scheme 1. Reagents: (i) CH_3I or $(CH_3O)_2SO_2$, Na_2CO_3, CH_3CN.

2.2.2. Myorelaxant effect on precontracted rat aorta rings. Potassium channel openers are known to be active as vasorelaxants, an effect linked to their ability to open vascular smooth muscle K_{ATP} channels.[2–7] The vasodilator effect of compounds **2a**–**f** was examined on rat aorta rings precontracted with 30 mM KCl. Table 1 reports the myorelaxant activity (ED_{50} in μM) of the different compounds. It can be observed that all compounds provoked marked vasorelaxant effects. They were more potent than diazoxide but less potent than pinacidil and cromakalim. Compound **2e** (X = F, Y = CH_3) was the most potent (ED_{50} = 1.9 μM) in this series.

As previously reported,[1] the myorelaxant activity of the non-methylated analogues **1a**–**i** was less pronounced than those of diazoxide and compounds **2a**–**f**, indicating that N-methylation, by avoiding deprotonation of the sulfonylurea function at physiological pH, was responsible for a marked increase of the activity on rat aorta rings.

2.2.3. Myorelaxant effects on rat uterus. The myorelaxant effect of compounds **2a**–**f** was also examined on rat uterus contracted by oxytocin. As shown in Table 2, at 10 μM, these compounds were found to have no marked effect on the contractile activity of rat uterus, as diazoxide, while pinacidil was significantly active at the same concentration. The non-methylated analogues **1a**–**i** previously synthesized

Table 1. Effects of compounds **2a–f** on insulin secretion from rat pancreatic islets and on the contractile activity of K^+ depolarized rat aorta rings (results expressed as means ± SEM (*n*))

Compound	X	Y	% Residual insulin secretion (rat islets)		Myorelaxant activity (rat aorta ring) ED_{50}[d] (μM)
			50 μM	10 μM	
2a	Br	H	13.1 ± 0.9 (14)	82.9 ± 5.1 (16)	6.4 ± 1.4 (6)
2b	Br	CH_3	12.5 ± 0.9 (14)	68.6 ± 3.5 (15)	5.5 ± 0.6 (4)
2c	Br	Cl	27.2 ± 2.5 (15)	82.5 ± 4.4 (16)	5.4 ± 1.0 (4)
2d	F	H	15.8 ± 1.0 (14)	65.8 ± 3.9 (23)	4.9 ± 0.3 (4)
2e	F	CH_3	10.7 ± 1.1 (14)	63.5 ± 3.8 (14)	1.9 ± 0.1 (4)
2f	F	Cl	14.8 ± 1.6 (13)	77.0 ± 5.2 (16)	4.5 ± 0.9 (6)
Diazoxide	—	—	27.9 ± 1.5 (37)[a]	71.7 ± 2.8 (38)[a]	23.8 ± 2.4 (10)[a]
±-Pinacidil	—	—	92.1 ± 5.5 (21)[b]	96.0 ± 4.2 (20)[b]	0.35 ± 0.02 (11)[c]
±-Cromakalim	—	—	77.2 ± 4.3 (22)	94.7 ± 4.3 (24)[c]	0.13 ± 0.01 (7)[c]

[a] Ref. 13.
[b] Ref. 14.
[c] Ref. 15.
[d] ED_{50}, drug concentration giving 50% relaxation of the 30 mM KCl induced contraction of rat aorta rings.

Table 2. Effects of compounds **1a–i** and **2a–f** on the contractile activity of rat uterus contracted by oxytocin (results expressed as means ± SEM (n))

Compound	X	Y	% Residual contractile activity of rat uterus		
			10 μM	50 μM	100 μM
1a	Br	H	87.3 ± 1.6 (4)	59.1 ± 2.2 (6)	46.3 ± 4.8 (4)
1b	Br	CH_3	95.7 ± 4.3 (4)	35.6 ± 2.6 (4)	12.8 ± 0.9 (4)
1c	Br	Cl	87.4 ± 3.0 (4)	42.6 ± 3,0 (4)	7.2 ± 3.1 (4)
1e	F	CH_3	89.3 ± 7.1 (4)	76.0 ± 5.4 (4)	54.2 ± 6.8 (4)
1f	F	Cl	101.8 ± 8.0 (4)	79.7 ± 16.3 (4)	51.9 ± 8.9 (4)
1g	NO_2	H	119.3 ± 8.9 (4)	113.7 ± 5.0 (4)	96.2 ± 5.7 (4
1h	NO_2	CH_3	107.5 ± 12.2 (4)	79.8 ± 9.4 (4)	60.8 ± 8.7 (4)
1i	NO_2	Cl	102.7 ± 1.1 (4)	91.9 ± 4.0 (4)	74.9 ± 3.3 (4)
2a	Br	H	130.8 ± 6.8 (4)	58.3 ± 4.0 (4)	18.5 ± 3.9 (4)
2b	Br	CH_3	91.8 ± 1.5 (4)	49.9 ± 8.7 (4)	21.4 ± 5.4 (4)
2c	Br	Cl	111.4 ± 9.0 (4)	46.7 ± 5.2 (4)	12.3 ± 2.6 (4)
2d	F	H	109.3 ± 6.7 (4)	57.8 ± 9.4 (4)	5.4 ± 1.0 (4)
2e	F	CH_3	75.2 ± 9.4 (4)	20.2 ± 5.3 (4)	1.2 ± 0.3 (4)
2f	F	Cl	98.2 ± 6.5 (4)	30.7 ± 4.8 (4)	7.1 ± 2.2 (4)
Diazoxide	—	—	93.8 ± 2.2 (4)	76.3 ± 4.9 (4)	67.7 ± 4.0 (4)
±-Pinacidil	—	—	58.1 ± 4.4 (4)	35.5 ± 2.9 (4)	38.1 ± 2.2 (4)

exhibited the same profile. At 50 μM, compounds **2a–f** were more active than diazoxide and **2e** even appear to be more potent than pinacidil. At the same concentration, the non-methylated analogues **1e**, **1f**, and **1h** appeared equipotent to diazoxide, while **1b** and **1c** were found to be roughly as active as pinacidil.

At 100 μM all methylated compounds **2a–f**, notably the 6-fluorinated analogues **2d–f**, appeared to be much more active than diazoxide or pinacidil. The myorelaxant effects of non-methylated compounds **1a–i** also increased at 100 μM, although to a lesser extent than methylated drugs **2a–f**. Compounds **1b** and **1c**, however, were found to be much more active than diazoxide and pinacidil. It should also be noted that, among the non-methylated derivatives, compound **1c** was previously found to be the most potent compound on rat aorta ring.[1]

3. Discussion and conclusion

The present results clearly revealed that the introduction of a methyl group on the nitrogen atom located between the sulfonyl and the carbonyl groups of *N*-arylsulfonyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas of general formula **1** dramatically increased their biological effects on rat pancreatic islets, on rat aorta, and rat uterine smooth muscles. Compared to *N*-arylsulfonyl-*N*′-(2,2-dimethyl-2*H*-1-benzopyran-4-yl)ureas **1a–f**, the N-methylated analogues **2a–f** are not able to be deprotonated at physiological pH and be present in solution as anionic structures. It is thus tempting to speculate that such a feature could account for the increasing activity of the methylated versus the non-methylated derivatives on the three pharmacological models used in the present study.

Another interesting observation on the uterine smooth muscle besides the marked myorelaxant activity of the N-methylated derivatives **2a–f** compared to those of K_{ATP} channel openers pinacidil and diazoxide. These two reference compounds were unable to completely suppress the contractions induced by 20 mU oxytocin even at high concentrations in contrast to compound **2e**.

In conclusion, such new types of drugs (compounds of general formula **2**) could constitute lead compounds

for the synthesis of original and potent therapeutic candidates. The relationship between the biological activity of these compounds and the modulation of potassium channels, particularly the ATP-sensitive potassium channels, needs to be further explored.

4. Experimental

4.1. Chemistry

Melting points were determined on a Büchi–Tottoli capillary apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1750 FT spectrophotometer. The ^{1}H NMR spectra were taken on a Bruker AW-80 (80 MHz) instrument in DMSO-d_6 or in $CDCl_3$ with hexamethyldisiloxane (HMDS) as an internal standard. Chemical shifts are reported in δ values (ppm) relative to internal HMDS. The abreviation s, singlet; d, doublet; t, triplet; q, quaduplet; m, multiplet; and b, broad are used throughout. Elemental analyses (C, H, N, and S) were realized on a Carlo-Erba EA 1108-elemental analyzer and were within ±0.4% of theoretical values. All reactions were routinely checked by TLC on silica gel Merck 60F 254.

4.1.1. General procedure. Methyl iodide or dimethyl sulfate (1 equiv) was added to a suspension of **1** (1 equiv) and sodium carbonate (1.2 equiv) in acetonitrile (15 mL). The mixture was stirred during 1 h and then poured on distilled water (15 mL). The obtained white precipitate was collected by filtration, washed twice with water, and dried under vacuum.

4.1.2. *N*-Benzenesulfonyl-*N*-methyl-*N*′-(6-bromo-2,2-dimethyl-2*H*-1-benzopyran-4-yl)urea (2a). White powder (85%); mp 190–193 °C; IR (KBr) *v*: 3340, (NH), 1660 (CO), 1290, 1170 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 1.20 (6H, 2s, $2CH_3$), 1.90 (2H, m, CH_2), 3.55 (3H, s, NCH_3), 4.6 (1H, m, CH), 7.25 (8H, m, CH_{arom}). Calculated for $C_{19}H_{21}BrN_2O_4S$: C, 50.33; H, 4.68; N, 6.18; S, 7.07. Found: C, 50.30; H, 4.65; N, 6.15; S, 7.04.

4.1.3. *N*-(4-Methylbenzenesulfonyl)-*N*-methyl-*N*′-(6-bromo-2,2-dimethyl-2*H*-1-benzopyran-4-yl)urea (2b). White powder (95%); mp 205–207 °C; IR (KBr) *v*: 3260 (NH), 1690 (CO), 1260, 1165 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 1.15 (6H, 2s, $2CH_3$), 1.90 (2H, m, CH_2), 2.35 (3H, s, CH_3), 3.50 (3H, s, NCH_3), 4.75 (1H, m, CH), 7.35 (7H, m, CH_{arom}). Calculated for $C_{20}H_{23}BrN_2O_4S$: C, 51.39; H, 4.97; N, 5.99; S, 6.86. Found: C, 51.37; H, 5.02; N, 6.03; S, 6.83.

4.1.4. *N*-(4-Chlorobenzenesulfonyl)-*N*-methyl-*N*′-(6-bromo-2,2-dimethyl-2*H*-1-benzopyran-4-yl)urea (2c). White powder (85%); mp 210–212 °C; IR (KBr) *v*: 3335 (NH), 1675 (CO), 1260, 1175 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 1.15 (6H, 2s, $2CH_3$), 1.80 (2H, m, CH_2), 3.60 (3H, s, NCH_3), 4.85 (1H, m, CH), 7.40 (7H, m, CH_{arom}). Calculated for $C_{19}H_{20}BrClN_2O_4S$: C, 46.78; H, 4.14; N, 5.74; S, 6.57. Found: C, 46.75; H, 4.11; N, 5.78; S, 6.60.

4.1.5. *N*-Benzenesulfonyl-*N*-methyl-*N*′-(2,2-dimethyl-6-fluoro-2*H*-1-benzopyran-4-yl)urea (2d). White powder (80%); mp 188–190 °C; IR (KBr) *v*: 3330, (NH), 1670 (CO), 1260, 1170 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 1.20 (6H, 2s, $2CH_3$), 1.90 (2H, m, CH_2), 3.55 (3H, s, NCH_3) 4.75 (1H, m, CH), 7.38 (8H, m, CH_{arom}). Calculated for $C_{19}H_{21}FN_2O_4S$: C, 58.14; H, 5.40; N, 7.14; S, 8.17. Found: C, 58.12; H, 5.36; N, 7.11; S, 8.15.

4.1.6. *N*-(4-Methylbenzenesulfonyl)-*N*-methyl-*N*′-(2,2-dimethyl-6-fluoro-2*H*-1-benzopyran-4-yl)urea (2e). White powder (85%); mp 185–187 °C; IR (KBr) *v*: 3330, (NH), 1695 (CO), 1250, 1185 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 1.20 (6H, 2s, $2CH_3$), 1.80 (2H, m, CH_2), 2.40 (3H, s, CH_3), 3.50 (3H, s, NCH_3), 4.70 (1H, m, CH), 7.20 (7H, m, CH_{arom}). Calculated for $C_{20}H_{23}FN_2O_4S$: C, 59.09; H, 5.72; N, 6.89; S, 7.89. Found: C, 59.04; H, 5.69; N, 6.85; S, 7.90.

4.1.7. *N*-(4-Chlorobenzenesulfonyl)-*N*-methyl-*N*-(2,2-dimethyl-6-fluoro-2*H*-1-benzopyran-4-yl)urea (2f). White powder (95%); mp 175–177 °C; IR (KBr) *v*: 3340 (NH), 1665 (CO), 1255, 1170 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 1.30 (6H, 2s, $2CH_3$), 1.90 (2H, m, CH_2), 3.60 (3H, s, NCH_3), 4.80 (1H, m, CH), 7.40 (7H, m, CH_{arom}). Calculated for $C_{19}H_{20}ClFN_2O_4S$: C, 53.45; H, 4.73; N, 6.56; S, 7.51. Found: C, 53.41; H, 4.71; N, 6.53; S, 7.69.

4.2. Rat pancreatic islets

Pancreatic islets were isolated by the collagenase method from fed Wistar rats (180–220 g). 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 (in mM: NaCl 115, KCl 5, $CaCl_2$ 2.56, $MgCl_2$ 1, and $NaHCO_3$ 24) 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 reference compound or the benzopyran derivative. The release of insulin was measured radioimmunologically using rat insulin as a standard. Residual insulin release[15,16] was expressed as a percentage of the value recorded in control experiments (100%), that is, in the absence of drug and presence of 16.7 mM glucose.

4.3. Rat aorta rings

All experiments were performed on aorta removed from fed Wistar rats (180–200 g), as previously described.[13,15,16] The ED_{50} was assessed for each dose–response curve as the concentration evoking 50% inhibition of the plateau phase induced by KCl 30 mM. Results are expressed as mean values (±SEM).

4.4. Rat uterus[16]

Fed Wistar rats (150–200 g) were treated the day before killing with diethylstilboestrol dipropionate [im injection of 0.1 mL/100 g of a 1 mg/mL oily solution of diethylstilboestrol dipropionate (Sigma)]. The rats were

anesthetized and then sacrificed. The two uterine horns were removed, cleared of adhering fat and connective tissue, and separated. Each horn was superfused with a Tyrode solution (in mM: NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.1, NaH_2PO_4 0.4, $NaHCO_3$ 11.9, and glucose 5.6) and bubbled continuously with a mixture of O_2 (95%) and CO_2 (5%). The superfusate was maintained at 37 °C. Injections of 20 mU oxytocin (200 μL of a 0.1 U/mL solution of the hormone in 0.9% NaCl) in the superfusion channel were repeated at 10-min intervals until the recorded contractions (AUC) were constant. The mean of the three last injections gave 100% of the contractile response to oxytocin. For each drug concentration added in the medium, injection of 20 mU oxytocin was repeated at least three times. The contractile responses (mean of three AUC) were expressed as a percent of the reference value (contractile response to oxytocin in the absence of drug).

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