Pharm. Pharmacol. Commun. 1999, 5: 189–193

Synthesis and Pharmacological Evaluation of K_{ATP}-channel Openers Related to Cromakalim: Introduction of Arylsulphonylurea Moieties

S. KHELILI, Q. -A. NGUYEN*, P. LEBRUN*, J. DELARGE AND B. PIROTTE

*Laboratoire de Chimie Pharmaceutique, Université de Liège, C.H.U., 1 Avenue de l'Hôpital, B-4000 Liège and *Laboratoire de Pharmacodynamie et de Thérapeutique, Université Libre de Bruxelles, 808, route de Lennik, B-1070 Bruxelles, Belgium*

Abstract

A series of 4-(arylsulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2 *H*-1-benzopyran derivatives were prepared and evaluated as potential ATP-sensitive potassium-channel activators.

Pharmacological studies showed that some compounds expressed vasodilator efficacy on vascular smooth muscle. The compounds had no inhibitory activity on insulin secretion from pancreatic β-cells.

ATP-sensitive potassium channels (K_{ATP} channels) attract considerable interest because of their essential role in diverse fundamental physiological processes. K_{ATP} channels are present in numerous cell types including endocrine cells (Cook & Hales 1984), smooth muscle cells (Standen et al 1989), cardiac cells (Noma 1983) and central neurons (Bernardi et al 1988). Several synthetic agents belonging to distinct chemical classes of molecules are activators of K_{ATP} channels and present interesting pharmacological and medical applications. Unfortunately, lack of tissue selectivity which is responsible for side effects has limited their use. Thus, the challenge is to find an agent exhibiting tissue selectivity, with even moderate activity. We describe here the synthesis and pharmacological evaluation of some 4-(arylsulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran derivatives (Figure 1), structurally related to cromakalim and other dihydrobenzopyran potassium-channel openers (Cho et al 1996; Rounyal et al 1997). The compounds were tested on pancreatic insulin secreting cells and on vascular smooth muscle cells.

Correspondence: S. Khelili, Laboratoire de Chimie Pharmaceutique, Université de Liège, C.H.U., 1 Avenue de l'Hôpital, B-4000 Liège, Belgium.

Materials and Methods

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 1000 FT-spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AW-80 (80 MHz) using d_6-DMSO as solvent. Chemical shifts (δ ppm) refer to hexamethyldisiloxane which was used as an internal reference. NH signal appeared as broad singlets exchangeable with D_2O. Key: t = triplet, s = singlet, d = doublet, q = quartet, m = multiplet. Elemental analyses (C, H, N or S) were performed on a Carlo-Erba EA 11008-elemental analyser.

*General procedure for preparing 4-(*N*-acetylamino)-3,4-dihydro-2,2-dimethyl-2*H *-1-benzopyrans (**7a–b**, **9**)*

A suspension of 3,4-dihydro-2,2-dimethyl-2 *H*-1-benzopyran-4-ols (**6a–b**, **8**) (77·8 mmol), obtained as previously described (Buckle et al 1990; Shawcross & Sard 1995), in acetonitrile (200 mL) was added dropwise to a stirred solution of acetonitrile (40 mL) in 98% sulphuric acid (10 mL) kept between −10 and 0°C. The mixture was allowed to warm to room temperature and stirring was continued for 1 h. The solution was poured into cold

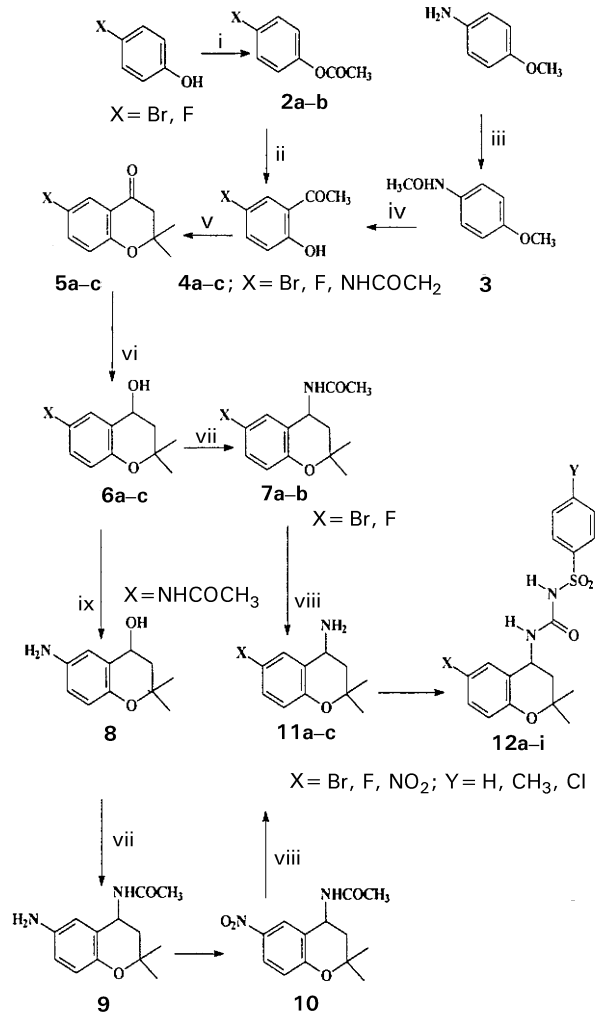


Figure 1. Synthesis of 4-(arylsulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran derivatives. Reagents: i. $(CH_3CO)_2O$, H_2SO_4; ii. $AlCl_3$; iii. CH_3COCl, pyridine; iv. CH_3COCl, $AlCl_3$, CS_2; v. acetone, pyrrolidine; vi. $NaBH_4$, CH_3OH; vii. CH_3CN, H_2SO_4; viii. HCl 37%; ix. NaOH 10%; x. CH_3CO_3H, CH_2Cl_2; xi. 4-Y-$C_6H_4SO_2NCO$, CH_2Cl_2.

water and the white precipitate collected by filtration, washed with water and dried. Compound **9**, a sulphate salt, was precipitated in its nonionic form by making the solution alkaline using sodium hydroxide. It was then collected by filtration, washed with water and dried.

*4-(*N*-Acetylamino)-6-bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (**7a**).* White powder (95% yield); mp 165–167°C; IR (KBr) *v*: 3287 (NH) cm^{-1}; 1647 (CO) cm^{-1}. ^{1}H NMR (d_6-DMSO) *δ*: 1·18 (6H, 2s, $2CH_3$), 1·85 (2H, m, CH_2), 2·00 (3H, s, CH_3), 5·19 (1H, m, CH), 6·7 (1H, m, CH_{arom}), 7·2 (2H, m, CH_{arom}), 8·33 (1H, d, NH). Calculated for $C_{13}H_{16}BrNO_2$: C, 52·36; H, 5·41; N, 4·70. Found: C, 52·48; H, 5·59; N, 4·85%.

*4-(*N*-Acetylamino)-3,4-Dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran (**7b**).* White powder (90% yield); mp 163–165°C; IR (KBr) *v*: 3282 (NH) cm^{-1}; 1639 (CO) cm^{-1}. ^{1}H NMR (d_6-DMSO) *δ*: 1·18 (6H, 2s, $2CH_3$), 1·86 (2H, m, CH_2), 1·93 (3H, s, CH_3), 5·16 (1H, m, CH), 7·13 (3H, m, CH_{arom}), 8·27 (1H, d, NH). Calculated for $C_{13}H_{16}FNO_2$: C, 65·81; H, 6·80; N, 5·90. Found: C, 66·04; H, 7·08; N, 6·02%.

*4-(*N*-Acetylamino)-6-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran monohydrate (**9**).* White powder (85% yield); mp 105–107°C; IR (KBr) *v*: 3362, 3274, (NH) cm^{-1}; 1629 (CO) cm^{-1}. ^{1}H NMR (d_6-DMSO) *δ*: 1·11 (6H, 2s, $2CH_3$), 1·58 (2H, m, CH_2), 2·00 (3H, s, CH_3), 4·41 (2H, s, NH_2), 4·85 (1H, m, CH), 6·40 (3H, s, CH_{arom}), 8·1 (1H, d, NH). Calculated for $C_{13}H_{18}N_2O_2.H_2O$: C, 61·88; H, 7·99; N, 11·10. Found: C, 62·07; H, 8·2; N, 11·25%.

*6-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (**8**).* 6-(*N*-Acetylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (**6c**) (10 g, 42·32 mmol), obtained as previously described (Buckle et al 1990; Shawcross & Sard 1995), was suspended in a solution of 10% sodium hydroxide (400 mL). The mixture was refluxed for 90 min. After cooling, the precipitate was collected by filtration, washed with cold water and dried. Brown powder (90% yield); mp 151–153°C; IR (KBr) *v*: 3348, 3284, 3200 (NH) cm^{-1}. ^{1}H NMR (d_6-DMSO) *δ*: 1·21 (6H, 2s, $2CH_3$), 1·75 (2H, m, CH_2), 4·48 (3H, m, CH + NH_2), 5·1 (1H, s, OH), 6·39 (2H, s, CH_{arom}), 6·67 (1H, s, CH_{arom}). Calculated for $C_{11}H_{15}NO_2$. C, 68·37; H, 7·82; N, 7·25. Found: C, 68·10; H, 8·01; N, 7·42%.

*4-(*N*-Acetylamino)-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1-benzopyran (**10**).* A solution of 4-(*N*-acetylamino)-6-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (**9**) (1 g, 4·27 mmol) in dichloromethane (20 mL) was added dropwise to a stirred cooled solution (−10 to 0°C) of peroxyacetic acid (5 mL; 32% weight in acetic acid) in dichloromethane (5 mL). Stirring was continued for 3 h and the temperature raised to room temperature. After dilution with dichloromethane (20 mL), the solution was washed with water, 5% sodium bicarbonate solution and finally brine. The organic layer was dried with magnesium sulphate and dichloromethane was removed under reduced pressure. The product was purified by flash chromatography using ethyl acetate as mobile phase and silica gel (60 F_{254}) as solid phase. White crystals (80% yield); mp 153–155°C; IR (KBr) *v*: 3242 (NH) cm^{-1}; 1631 (CO) cm^{-1}; 1·38 (6H, 2s,

$2CH_3$), 2·35 (2H, m, CH_2), 5·11 (1H, m, CH), 6·95 (1H, m, CH_{arom}), 8·03 (2H, m, $NH + CH_{arom}$), 8·38 (1H, d, CH_{arom}). Calculated for $C_{13}H_{16}N_2O_4$: C, 59·08; H, 6·10; N, 10·60. Found: C, 59·19; H, 6·28; N, 10·73%.

*General procedure for preparing 4-amino-3,4-dihydro-2,2-dimethyl-2*H *-1-benzopyrans (**11a–c**)*
A suspension of 4-(*N*-acetylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans (**7a–b**, **10**) (75·7 mmol) in 37% hydrochloric acid (250 mL) was refluxed for 10 h. Hydrochloric acid was removed under vacuum and the residue was dissolved in water (200 mL). The solution was cooled and 10% aqueous sodium hydroxide was added until alkaline. The amine, which precipitated from the solution, was collected by filtration, washed with water and dried under vacuum.

*4-Amino-6-bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (**11a**).* White powder (90% yield); mp 64–66°C; ^{1}H NMR (d_6-DMSO) δ: 1·3 (6H, 2s, $2CH_3$), 1·89 (2H, m, CH_2), 3·2 (2H, s, NH_2), 3·94 (1H, m, CH), 6·7 (1H, d, CH_{arom}), 7·25 (1H, d, CH_{arom}) 7·83 (1H, s, CH_{arom}). Calculated for $C_{11}H_{14}BrNO$: C, 51·58; H, 5·51; N, 5·47. Found: C, 51·47; H, 5·68; N, 5·51%.

*4-Amino-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran (**11b**).* White powder (90% yield); mp 59–61°C; ^{1}H NMR (d_6-DMSO) δ: 1·26 (6H, 2s, $2CH_3$), 1·83 (2H, m, CH_2), 2·85 (2H, s, NH_2), 3·85 (1H, m, CH), 6·81 (2H, m, CH_{arom}), 7·42 (1H, dd, CH_{arom}). Calculated for $C_{11}H_{14}FNO$: C, 67·67; H, 7·23; N, 7·17. Found: C, 67·53; H, 7·02; N, 7·10%.

*4-Amino-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1-benzopyran (**11c**).* White powder (90% yield); mp 84–86°C; ^{1}H NMR (d_6-DMSO) δ: 1·37 (6H, 2s, $2CH_3$), 2·18 (2H, m, CH_2), 2·85 (2H, s, NH_2), 4·74 (1H, m, CH), 7·06 (1H, m, CH_{arom}), 8·11 (1H, m, CH_{arom}), 8·79 (1H, m, CH_{arom}). Calculated for $C_{11}H_{14}N_2O_3$: C, 59·45; H, 6·35; N, 12·60. Found: C, 59·58; H, 6·63; N, 12·53%.

*General procedure for preparing 4-(arylsulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans (**12a–i**)*
To the solution of 4-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans (**11a–c**) (1·35 mmol) in anhydrous dichloromethane, the appropriate arylsulphonyl isocyanate (1·2 eq.) was added. After 20 min, the precipitate formed was collected by filtration, washed with petroleum ether 40/65 to eliminate excess arylsulphonyl isocyanate, and dried.

*4-(Benzenesulphonylaminocarbonylamino)-6-bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (**12a**).* White powder (85% yield); mp 209–211°C; IR (KBr) *v*: 3341, 3170 (NH), 1666 (CO), 1291, 1168 cm^{-1} (SO_2); ^{1}H NMR (d_6-DMSO) δ: 1·22 (6H, 2s, $2CH_3$), 1·9 (2H, m, CH_2), 4·7 (1H, m, CH), 7·3 (8H, m, CH_{arom}), 10·7 (1H, s, NH). Calculated for $C_{18}H_{19}BrN_2O_4S$: C, 49·21; H, 4·36; N, 6·38; S, 7·30. Found: C, 48·80; H, 4·55; N, 6·45; S, 7·69%.

*6-Bromo-3,4-dihydro-2,2-dimethyl-4-(4-methylbenzenesulphonylaminocarbonylamino)-2*H*-1-benzopyran (**12b**).* White powder (90% yield); mp 225–227°C; IR (KBr) *v*: 3261, 3164 (NH), 1693 (CO), 1261, 1166 cm^{-1} (SO_2); ^{1}H NMR (d_6-DMSO) δ: 1·10 (6H, 2s, $2CH_3$), 1·9 (2H, m, CH_2), 2·35 (3H, s, CH_3), 4·73 (1H, m, CH), 7·3 (7H, m, CH_{arom}), 10·65 (1H, s, NH). Calculated for $C_{19}H_{21}BrN_2O_4S$: C, 50·34; H, 4·67; N, 6·18; S, 7·07. Found: C, 50·37; H, 4·75; N, 6·45; S, 7·16%.

*6-Bromo-4-(4-chlorobenzenesulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (**12c**).* White powder (95% yield); mp 228–230°C; IR (KBr) *v*: 3341, 3160 (NH), 1669 (CO), 1262, 1169 cm^{-1} (SO_2); ^{1}H NMR (d_6-DMSO) δ: 1·11 (6H, 2s, $2CH_3$), 1·85 (2H, m, CH_2), 4·9 (1H, m, CH), 7·31 (7H, m, CH_{arom}), 10·9 (1H, s, NH). Calculated for $C_{18}H_{18}BrClN_2O_4S$: C, 45·63; H, 3·83; N, 5·91; S, 6·77. Found: C, 45·99; H, 4·01; N, 6·05; S, 6·70%.

*4-(Benzenesulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran (**12d**).* White powder (90% yield); mp 206–208°C; IR (KBr) *v*: 3334, 3171 (NH), 1675 (CO), 1255, 1171 cm^{-1} (SO_2); ^{1}H NMR (d_6-DMSO) δ: 1·22 (6H, 2s, $2CH_3$), 1·83 (2H, m, CH_2), 4·7 (1H, m, CH), 7·34 (8H, m, CH_{arom}), 10·77 (1H, s, NH). Calculated for $C_{18}H_{19}FN_2O_4S$: C, 57·13; H, 5·06; N, 7·40; S, 8·47. Found: C, 57·01; H, 5·22; N, 7·49; S, 7·93%

*3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(4-methylbenzenesulphonylaminocarbonylamino)-2*H*-1-benzopyran (**12e**).* White powder (85% yield); mp 192–194°C; IR (KBr) *v*: 3333, 3272 (NH), 1700 (CO), 1248, 1190 cm^{-1} (SO_2); ^{1}H NMR (d_6-DMSO) δ: 1·18 (6H, 2s, $2CH_3$), 1·85 (2H, m, CH_2), 2·4 (3H, s, CH_3), 4·72 (1H, m, CH), 7·21 (7H, m, CH_{arom}). Calculated for $C_{18}H_{19}FN_2O_4S$: C, 57·13; H, 5·06; N, 7·40; S, 8·48. Found: C, 57·01; H, 5·22; N, 7·49; S, 8·48%

*4-(4-Chlorobenzenesulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran (**12f**).* White powder (90% yield); mp

190–192°C; IR (KBr) *v*: 3335, 3240 (NH), 1660 (CO), 1250, 1168 cm^{-1} (SO_2); ^1H NMR (d_6-DMSO) δ: 1·33 (6H, 2s, $2CH_3$), 1·88 (2H, m, CH_2), 4·78 (1H, m, CH), 7·33 (7H, m, CH_{arom}). Calculated for $C_{18}H_{18}ClFN_2O_4S$: C, 52·36; H, 4·39; N, 6·78; S, 7·77. Found: C, 52·04; H, 4·53; N, 6·99; S, 7·99%.

*4-(4-Benzenesulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1-benzopyran (**12g**)*. White powder (95% yield); mp 221–223°C; IR (KBr) *v*: 3340, (NH), 1669 (CO), 1275, 1167 cm^{-1} (SO_2); ^1H NMR (d_6-DMSO) δ: 1·3 (6H, 2s, $2CH_3$), 1·97 (2H, m, CH_2), 4·84 (1H, m, CH), 7·03 (1H, m, CH_{arom}), 7·76 (7H, m, CH_{arom}). Calculated for $C_{18}H_{19}N_3O_6S$: C, 53·32; H, 4·72; N, 10·36; S, 7·91. Found: C, 53·38; H, 4·97; N, 10·48; S, 7·98%.

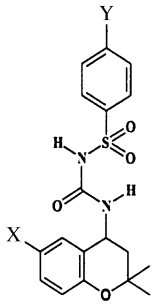
*3,4-Dihydro-2,2-dimethyl-4-(4-methylbenzenesulphonylaminocarbonylamino)-6-nitro-2*H*-1-benzopyran (**12h**)*. White powder (95% yield); mp 229–231°C; IR (KBr) *v*: 3337, (NH), 1666 (CO), 1278, 1166 cm^{-1} (SO_2); ^1H NMR (d_6-DMSO) δ: 1·32 (6H, 2s, $2CH_3$), 1·89 (2H, m, CH_2), 4·87 (1H, m, CH), 7·48 (7H, m, CH_{arom}). Calculated for $C_{19}H_{21}N_3O_6S$: C 54·41; H, 5·05; N, 10·02; S, 7·64. Found: C, 54·69; H, 5·45; N, 10·18; S, 7·70%.

*4-(4-Chlorobenzenesulphonylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1-benzopyran (**12i**)*. White powder (90% yield); mp 213–215°C; IR (KBr) *v*: 3343, (NH), 1664 (CO), 1277, 1166 cm^{-1} (SO_2); ^1H NMR (d_6-DMSO) δ: 1·41 (6H, 2s, $2CH_3$), 1·95 (2H, m, CH_2), 4·91 (1H, m, CH), 7·64 (7H, m, CH_{arom}). Calculated for $C_{18}H_{18}ClN_3O_6S$: C, 49·15; H, 4·12; N, 9·55; S, 7·29. Found: C, 49·44; H, 4·43; N, 9·68; S, 7·70%.

Results and Discussion

The esters **2a–b** were synthesized from *p*-substituted phenols according to a classic esterification reaction catalysed by concentrated sulphuric acid. The acetophenones **4a–b** were synthesized by Fries rearrangement of phenolic acetates **2a–b** according to Fries reaction (Shawcross & Sard 1995). However, acetophenone **4c** was prepared from the methyl ether of 4-(*N*-acetylamino)phenol **3** by Friedel–Crafts reaction and cleavage of the methyl ether in-situ by the excess of aluminium chloride (Chang et al 1961). Compound **3** was prepared from *p*-anisidine by simple acylation with acetyl chloride. Treatment of acetophenones **4a–c** with acetone in the presence of pyrrolidine led to the

Table 1. Effects of the new dihydrobenzopyrans on insulin secretion from rat pancreatic islets and on the contractile activity of K^+ depolarized rat aorta rings.



Compound (50 μM)	X	Y	Residual insulin secretion (%)	n	Myorelaxant activity (ED50 (μM))	n
12a	Br	H	99·9 ± 6·8	16	125·0 ± 18·0	4
12b	Br	CH_3	85·1 ± 5·3	14	65·4 ± 14·7	6
12c	Br	Cl	80·0 ± 5·7	15	34·8 ± 3·7	5
12d	F	H	99·0 ± 4·8	16	>300	4
12e	F	CH_3	91·6 ± 7·4	14	211·0 ± 33·0	4
12f	F	Cl	100·2 ± 5·0	15	111·0 ± 21·0	4
12g	NO_2	H	106·6 ± 5·8	16	163·0 ± 39·0	5
12h	NO_2	CH_3	99·6 ± 4·3	15	66·2 ± 15·6	4
12i	NO_2	Cl	107·2 ± 5·0	16	91·5 ± 15·5	4

Rat pancreatic islets were incubated in the presence of 16·7 mM glucose. ED50 is the drug concentration causing 50% relaxation of the 30 mM KCl-induced contraction of rat aorta rings. Results on pancreatic β-cells and on rat aorta are expressed as means ± s.e.m.; n refers to the number of samples.

chromanones **5a–c** which were reduced to the chromanols **6a–c** with sodium borohydride in methanol (Buckle et al 1990; Shawcross & Sard 1995). The 4-acetylaminobenzopyrans **7a–b** and **9** were prepared by the Ritter reaction from chromanols **6a–b** and **8**, respectively. This is a new synthetic pathway to protected 4-amino chromans. The hydrolysis of **7a–b** and **10** with concentrated hydrochloric acid led to the aminochromans **11a–c**, respectively. The chromanol **8** was prepared from **6c** by hydrolysis with sodium hydroxide. The nitro compound **10** was prepared by oxidation of **9** with peroxyacetic acid in dichloromethane. The last step involved the reaction of each amine **11a–c** with benzenesulphonyl isocyanate, *p*-toluenesulphonyl isocyanate and *p*-chlorobenzenesulphonyl isocyanate to give the target compounds **12a–i** respectively.

Table 1 shows the pharmacological results obtained with the newly synthesized dihydrobenzopyrans on the pancreatic and vascular tissues. Results on pancreatic β-cells were expressed as the percentage residual insulin secretion from rat pancreatic islets incubated in the presence of 16·7 mM glucose (de Tullio et al 1996). All drugs were tested at 50 μM. The myorelaxant activity of the drugs was expressed as ED50, the drug concentration giving 50% relaxation of the 30 mM KCl-induced contraction of rat aorta rings (de Tullio et al 1996).

None of the compounds inhibited insulin secretion. It was concluded that the drugs did not exert significant K_{ATP}-channel opening activity on pancreatic β-cells. The compounds did however exhibit myorelaxant properties. The rank order of preference for the X-substituent appeared to be $Br > NO_2 > F$, while that for the Y-substituent was $Cl > CH_3 > H$. Further pharmacological investigations are required to identify the active compounds as new potassium-channel activators targeting vascular smooth muscle cells.

References

Bernardi, H., Fosset, M., Lazdunski, M. (1988) Characterization, purification and affinity labeling of the brain [^{3}H]glibenclamide-binding protein, a putative neuronal ATP-regulated K^+ channel. Proc. Natl Acad. Sci. USA 85: 9816–9820

Buckle, D. R., Arch J. R., Fenwick, A. E., Houge-Frydrych, C. S., Pinto, I. L., Smith, D. G., Taylor, S. G., Tedder, J. M. (1990) Relaxant activity of 4-amino-3,4-dihydro-2H-1-benzopyran-3-ols and 4-amido-2H-1-benzopyrans on guineapig isolated trachealis. J. Med. Chem. 33: 3028–3034

Chang, C. T., Chen, F. C., Chen, T. S., Hsu, K. K., Ueng, T., Hung, M. (1961) Synthesis of 6-halogenoflavones and related compounds. J. Chem. Soc. 3: 3414–3417

Cho, H., Katoh, S., Sayama, S., Murakami, K., Nakanishi, H., Kajimoto, Y., Ueno, H., Kawasaki, H., Aisaka, K., Ushida, I. (1996) Synthesis and selective coronary vasodilatory activity of 3,4-dihydro-2,2-bis(methoxymethyl)-2H-benzopyran-3-ol derivatives: novel potassium channel openers. J. Med. Chem. 39: 3797–3805

Cook, D. L., Hales, C. N. (1984) Intracellular ATP directly blocks K^+ channels in pancreatic β-cells. Nature 311: 271–273

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. (1996) 3- and 4-substituted 4H-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. 39: 937–947

Noma, A. (1983) ATP-regulated K^+ channels in cardiac muscle. Nature 305: 147–148

Rovnyak, G. C., Ahmed, S. Z., Ding, C. Z., Dzwonczyk, S., Ferrara, F. N., Humphreys, W. G., Grover, G. J., Santafianos, D., Atwal, K. S., Baird, A. J., McLaughlin, L. G., Normandin, D. E., Sleph, P. G., Traeger, S. C. (1997) Cardioselective antiischemic ATP-sensitive potassium channel (K_{ATP}) openers. 5. Identification of 4-(N-aryl)-substituted benzopyran derivatives with high selectivity. J. Med. Chem. 40: 24–34

Shawcross, S. Sard, H. (1995) Cyclization of 3-fluoro and 3,3-dimethylacrylic acid: a structure correction. J. Heterocyclic Chem. 32: 1393–1395

Standen, N. B., Quayle, J. M., Davies, N. W., Brayden, J. E., Huang, Y., Nelson, M. T. (1989) Hyperpolarising vasodilators activate ATP-sensitive K^+ channels in arterial smooth muscle. Science 245: 177–180