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# N-Sulfonamides of Benzopyran-Related Potassium Channel Openers: Conversion of Glyburide Insensitive Smooth Muscle Relaxants to Potent Smooth Muscle Contractors

R. M. Soll,[¶]* P. J. Dollings,[¶] R. J. McCaully,[¶] T. M. Argentieri,[§] N. Lodge,[§] G. Oshiro,[§] T. Colatsky,[§] N. W. Norton,[§] D. Zebick,[§] C. Havens,[§] and N. Halaka[§]

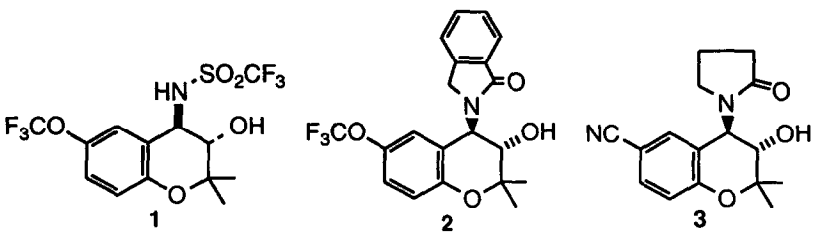
[¶]Department of Medicinal Chemistry and Division of [§]Cardiovascular and Metabolic Diseases, Wyeth-Ayerst Research, CN-8000, Princeton, NJ 08543-8000

**Abstract**: N-sulfonamides of the benzopyran-related class of potassium channel openers were found to inhibit KCl-induced contractions of smooth muscle preparations (rat aorta or bladder preparations) in a glyburide insensitive manner or to augment contractions. These activities were found to be a function of the nature of the sulfonamide substiutents.

The clinical prospects of potassium channel openers has broadened beyond hypertension and now encompasses a range of cardiovascular, respiratory, and central nervous system diseases as well as pathological states involving hyper-reactive smooth muscle such as irritable bladder syndrome and urinary incontinence.[1] However, a limiting factor in the full clinical exploitation of potassium channel openers in these various diseases, particularly that of urinary incontincence, is tissue selectivity.

In the course of our program directed towards bladder selective potassium channel openers, we prepared sulfonamide **1**, an analog of celikalim (**2**).[2,3] Although less active than celikalim as a relaxant of KCl-induced contractions in both bladder and aortic tissue preparations (Table I), the relaxant effects of **1** were not aortic selective, in contrast to either celikalim or levcromakalim (**3**). Furthermore, the relaxant effects of **1** were not glyburide sensitive, suggesting clear differences in the relaxant mechanism of **1** vs. **2** or **3**. These observations are particularly curious in light of recent reports concerning (1) the potent trachael relaxant effects of benzopyran **4** by a mechanism that is inconsistent with potassium channel opening and which differs from the apparent potassium channel opening effects of dehydrated analog **5**,[4] (2) the potent, glyburide insensitive tracheal and portal vein relaxant effects of **6** (UR-8081)[5], of which the eutomeric form (3S, 4R) is identical to levcromakalim (**3**), and (3) the pure calcium channel blocking activity of **7**.[6]

To further explore potential bladder selectivity and potency around **1**, we prepared a series of chiral sulfonamides which were evaluated for pharmacological activity on isolated bladder and aortic tissue. We report (1) conversion from relaxants to potent contractors of bladder tissue is observed upon replacement of the trifluoromethyl group with increasingly large groups or by N-substitution and (2) lack of significant discrimination in potency between the enantiomers of **1** in their ability to inhibit both sets of isolated tissue.




and ----- are used to denote relative stereochemistry
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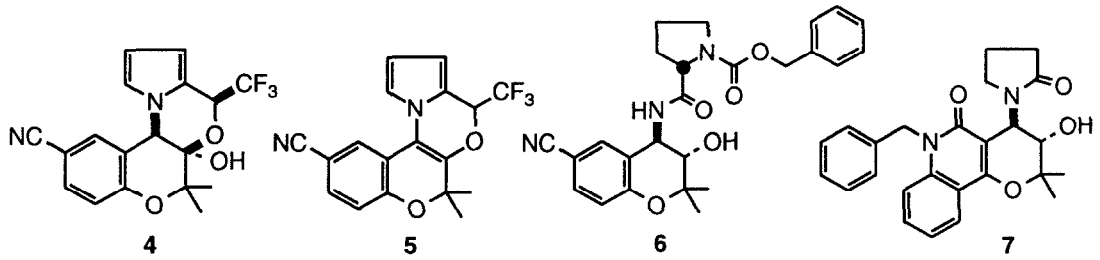
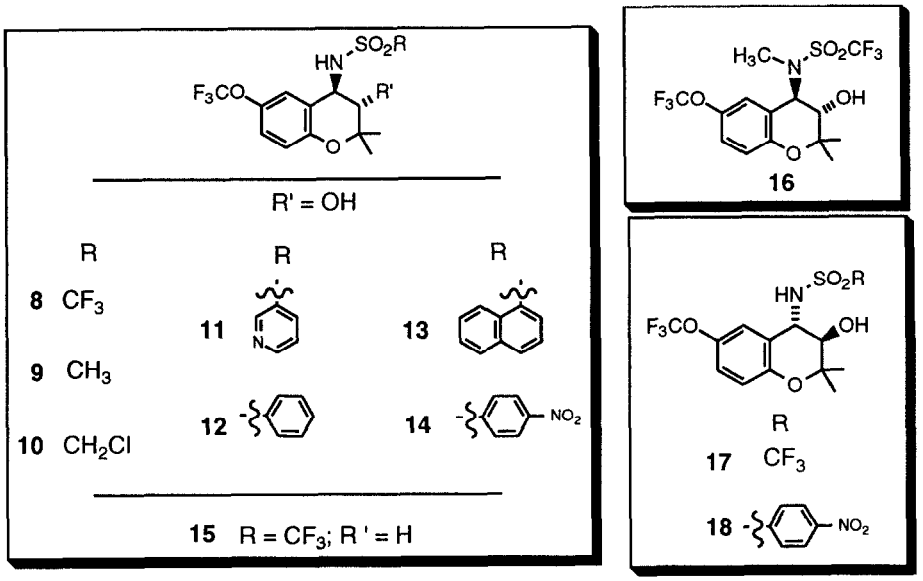


**4** **5** **6** **7**

Chiral sulfonamides **8** - **14** (3S, 4R) were prepared from the corresponding 3S, 4R amine[2] and commercially available sulfonyl chlorides or sulfonic anhydrides (1 equiv) in $CH_2Cl_2$ in the presence of excess pyridine or lutidine.[7] Purification was achieved by flash chromatography. Chiral sulfonamide **15**, $[\alpha]_D^{25}$ -11 (c = 0.95, THF), was prepared via a Barton deoxygenation of **8**.[8] N-Methylsulfonamide **16** $[\alpha]_D^{25}$ -27.8 (c = 0.97, THF) was prepared in 61% yield by anion formation of **8** with n-BuLi (1.0 equiv) at -78 °C in THF followed by MeI quench. Compounds **17** and **18** were prepared from (3R-trans)-4-amino-3,4-dihydro-2,2-dimethyl-6-(trifluoromethoxy)-2H-benzopyran-3-ol, which in turn was obtained through further classical resolution (using di-p-toly-D-tartaric acid) of the mother liquors enriched with this amine from the synthesis of celikalim.[2]




Compounds were examined for their ability to inhibit contractions of bladder[9] and rat aorta strips[10] induced by KCl (15 mM and 25 mM, respectively). Glyburide reversibility of relaxation was also examined as a mechanistic probe for potassium channel ($K_{ATP}$) opening activity. As shown in Table I, the relaxation induced by either celikalim or levcromakalim in either tissue was glyburide sensitive. Levcromakalim did not exhibit bladder selectivity, consistent with other reports.[11] Celikalim was significantly more potent than levcromakalim, but also failed to show bladder selectivity. Trifluorosulfonamide **1** was resolved into its enantiomorphs **8** (3S,4R) and **17** (3R,4S). Interestingly, both enantiomers relaxed bladder tissue nearly

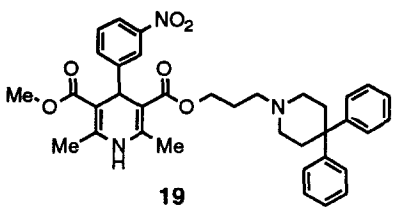
equipotently and in a glyburide insensitive manner. Replacement of the trifluoromethyl group of **8** with a methyl group produced **9** which exhibited little activity at 30 μM. Remarkably, extension of the methyl group to **10**, **11**, **12**, and **13** produced contractors. Particularly noteworthy are the contractions produced by **14** at 30 μM. By comparison, variable results were obtained with the 3R,4S enantiomer (**18**), ranging from relaxation ($IC_{50}$ 4.68 and 8.5 μM) to contraction (+77% at 30 μM) . Hydroxyl group removal of **8** produced **15**, which was found to be slightly less active than **8** but whose relaxant effect was now modestly glyburide sensitive. The importance of the hydrogen to the relaxant effects of **8** was addressed by **16**; methylation converted **8** from a relaxant to that of a potent contractor.

**Table 1.** In Vitro Evaluation of Compounds in KCl-Induced Contractions of Rat Bladder or Rat Aorta.[a]

| Compound | Bladder $IC_{50}$ in μM or (% Activity at 30 μM)[8] | n | %GR[b] | Aorta $IC_{50}$ in μM or (% Activity at 30 μM)[9] | n | %GR[b] |
|---|---|---|---|---|---|---|
| **1** | 4.6 ± 0.7 | 4 | 14 | 8.0 ± 2 | 3 | 2 |
| **2** | 0.03 ± 0.001 | 337 | 80 | 0.013 ± 0.001 | 138 | 55 |
| **3** | 0.15 ± 0.04 | 14 | 68 | 0.06 ± 0.02 | 5 | 75 |
| **8** | 3.6 ± 2.3 | 5 | 0 | 2.0 ± 0 | 2 | ND |
| **9** | (+3, -10, -4) | 3 | 8 | ND[d] | | ND |
| **10** | (+39, +91) | 2 | NA[c] | ND | | ND |
| **11** | (+133, +308) | 2 | NA | ND | | ND |
| **12** | (+44, +180) | 2 | NA | ND | | ND |
| **13** | (+52, +166) | 2 | NA | ND | | ND |
| **14** | (+195, +363) | 2 | NA | ND | | ND |
| **15** | 6.2 ± 2.3 | 2 | 41 | 10.7 ± 1.2 | 2 | ND |
| **16** | (+352, +456) | 2 | NA | ND | | ND |
| **17** | 7.1 ± 2.5 | 2 | 0 | 2.6 ± 0.6 | 2 | ND |
| **18** | 4.68, 8.5, (-16, -12, -10, +27, +77) | 7 | 0 | ND | ND | ND |

a. Data is expressed as mean±SEM of the concentration necessary to inhibit 50% ($IC_{50}$) of the KCl-induced contraction. Where an $IC_{50}$ was not reached, the activity is expressed as the percent increase (+) and/or decrease (-) in the contractile response for each individual experiment.
b. %GR = % glyburide reversibility
c. NA = not applicable
d. ND = not determined

The mechanism(s) by which these compounds effect relaxation are not clear. The relaxant effects of **1**, **8**, and **17** are glyburide insensitive, thereby suggesting activity unrelated to $K_{ATP}$ opening; calcium channel blocking activity might account for the relaxant effects of these compounds by analogy to **7** but definitive results have yet to be determined. In contrast, **15** posseses modest glyburide reversibility, indicating signficant $K_{ATP}$ opening activity in its mechansim of action; by comparison, niguldipine (**19**)[12] and E-4080 (**20**)[13] possess dual potassium channel opening and $Ca^{2+}$-channel blocking activities.



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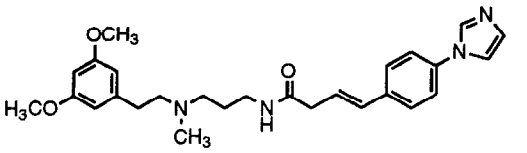

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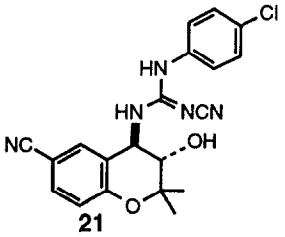
The mechansim by which compounds **10** - **14** as well as **16** produce contractions is not clear but could occur possibly through blocking action on other K-channels. For example, the K-channel blockers apamin and charybdotoxin stimulated myogenic activity of guinea-pig detrusor strips,[14] an effect which was not seen with glyburide. Iberiatoxin also produced a dose dependent stimulation on mechanical activity in an isolated guinea pig detrusor smooth muscle preparation.[13] Addional studies with sulfonamides of this paper may shed insight into this possibility.

The results of the present study are noteworthy for several reasons. Firstly, they demonstrate that subtle changes about the C-4 and C-6 benzopyran substituents produce significant changes in pharmacological characteristics that also may be tissue dependent. For example, BMS-180448 (**21**), an acyclic N-cyanoguanidine derivative of cromakalim that is structurally similar to bladder contractors **12** and **14** , is a cardioselective anti-ischemic $K_{ATP}$ opener.[16] Amides **22** and **23**, structurally close analogs of relaxant **1** and contractor **11**, respectively, exhibit potent antihypertensive effects in SHR and augment Rb efflux in vitro.[17] Secondly, we have shown that the relaxant effects of these benzopyrans are not limited to one enantiomorph, an observation which has been reported recently in homochiral deshydroxy-cromakalim and deshydroxy-Ro-31-6930.[18] Finally, despite clear structural similarities to prototypical benzopyran potassium channel openers, the relaxant effects of this series appear to differ from known benzopyran potassium channel openers by their differential selectivity towards glyburide reversibility. This reversiblity is critical to understanding structure-activity relationships and mechanistic issues of the benzopyran-related potassium channel openers. These results have important implications in the design of potassium channel openers of the benzopyran class.



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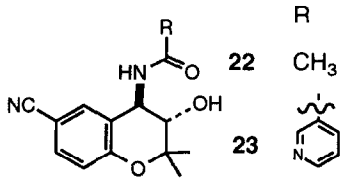

22 $CH_3$

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7. Typical procedure (compound **8**): To a solution of 1.03 g (3.7 mmol) of (3S-trans)-4-amino-3,4-dihydro-2,2-dimethyl-6-(trifluoromethoxy)-2H-benzopyran-3-ol[2] and 1.3 mL (1.1.2 mmol) of 2,6-lutidine was added slowly 690 μL (4.1 mmol) of triflic anhydride. After 10 min, the reaction mixture was quenched with 1 N HCl, extracted into $Et_2O$, dried ($MgSO_4$), and concentrated. Flash chromatography (1 : 1 $Et_2O$ / petroleum ether) gave 1.17 (77% yield) of product, mp 131 - 133 °C; $[\alpha]_D^{25}$ -45.1 (c = 0.833, THF).

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9. Adult male rats weighing between 150 and 200 grams were asphyxiated with $CO_2$ and euthanized by cervical dislocation. Bladders were removed and placed into warmed (37°C), oxygenated physiological salt solution (PSS). After rinsing in PSS, the bladder was cut into strips approximately 2 mm wide and 10 mm long. The strips were suspended in a 10 mL tissue bath with one end fixed to the bottom and the other to a force transducer. Resting tension was set to 1.5 grams and spontaneous, phasic contractions were induced with 15 mM KCl. Contractions were displayed on a Grass polygraph and signals were acquired and analyzed by computer using an MI[2] data acquisition system which determine the area under the contraction curve. After a 90 minute equilibration period, a concentration-response for each compound was performed.

10. Adult male rats weighing between 150 and 200 grams were asphyxiated with $CO_2$ and euthanized by cervical dislocation. The descending aorta was removed and placed into warmed (37°C), oxygenated PSS. The aorta was cleaned of loose fat and adventitia, and cut into rings approximately 2-3 mm in width. Next, the endothelium was removed and the rings were suspended between two stainless steel tissue hooks in a 10 mL tissue bath. One hook was attached to the bottom of the bath and the other to a force transducer. Resting tension was set to 1 gram. Tensions were displayed on a Grass polygraph. After a 60 minute equilibration, the tissues were contracted with 25 mM KCl. Once stabilized (45 minutes), a concentration-response was performed for each compound.

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