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The synthesis and biological evaluation of a range of novel functionalised benzopyrans as potential potassium channel activators

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Abstract—A range of novel benzopyrans have been synthesised and biologically evaluated for K_{ATP} channel activity employing cromakalim **1** as a benchmark K_{ATP} channel opener. Although the compounds that were evaluated demonstrated a reduced ability to relax phenylephrine stimulated rat thoracic tissue, we provide evidence that benzopyrans **7a**–**h** may be operating via an alternative mechanism than ATP-sensitive K^+ channel activity.

Historically the benzopyran cromakalim **1** represents one of the first reported anti-hypertensive agents to act solely via potassium channel modulation.[1] The syntheses of analogues to **1** have increased in intensity over the past few years and several reviews have been published.[2] Therapeutic agents, that function via the opening of potassium channels, have become topical for treating conditions such as hypertension, angina and epilepsy however and more recently urinary incontinence.[3]

Our interest in cromakalim **1** was first highlighted in 1998 when we revealed the results obtained from the screening of a small library of benzopyrans as potential potassium channel activators (Fig. 1).[4]

Our study compared the potential of our compounds, against cromakalim **1**, to inhibit oxytocin induced uterine spasms. The results from these studies showed that cromakalim **1** induced complete inhibition of oxytocin induced uterine spasm at a 5 μM level, whereas analogue **2** produced a 98% reduction at 35 μM and **3** induced a 71% reduction at 8 μM. Despite the relative simplicity of our analogues we concluded that they nevertheless possessed components of the key pharmacophores present in cromakalim **1**. In particular the benzopyran nucleus, a *trans* arrangement at the C-3, C-4 chiral centres and an activated aromatic ring.[5] Benzopyrans, **2** and **3**, were synthesised using a novel variation of an intramolecular Nicholas reaction[6] that was developed in our laboratories. These were obtained in good yield and with extremely high levels of *trans*-diastereoselectivity (Scheme 1).[7]

More recently we have focused our attention upon the development of asymmetric Nicholas cyclisation reactions analogous to those shown above. Our aims were twofold the first was an attempt to synthesise homochiral variants of compound **4** and then to investigate the levels of asymmetric induction during the subsequent cyclisation reaction.[8] Our second aim was to screen these new molecules for potassium channel activity. The asymmetric synthesis of the propargyl alcohols, based upon **4**, was successfully accomplished using an asymmetric alkylation reaction described by Carreira.[9] This procedure involves the addition of a zinc acetylide to aldehyde **5** in the presence of a chiral ligand such as *N*-methylephedrine. This provided access to homochiral propargyl alcohols **6** in high yield and excellent enantioselectivities.[10] Exposure of the dicobalt hexacarbonyl derivatives of the propargyl alcohols **6** to Lewis acid led to a smooth cyclisation reaction. Oxidative decomplexation provided the optically active benzopyrans, **7a**–**h**, in very high yield (Scheme 2).

Keywords: Benzopyrans; Nicholas reaction; Chiral; Potassium channel activators; Cromakalim; Rat thoracic tissue; Smooth muscle relaxation.
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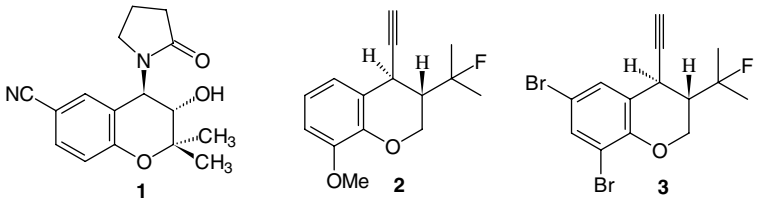
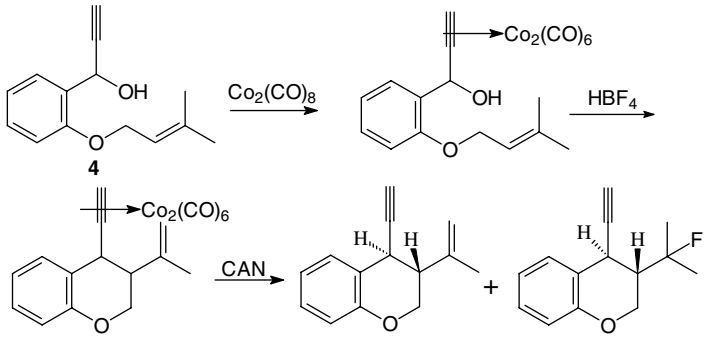
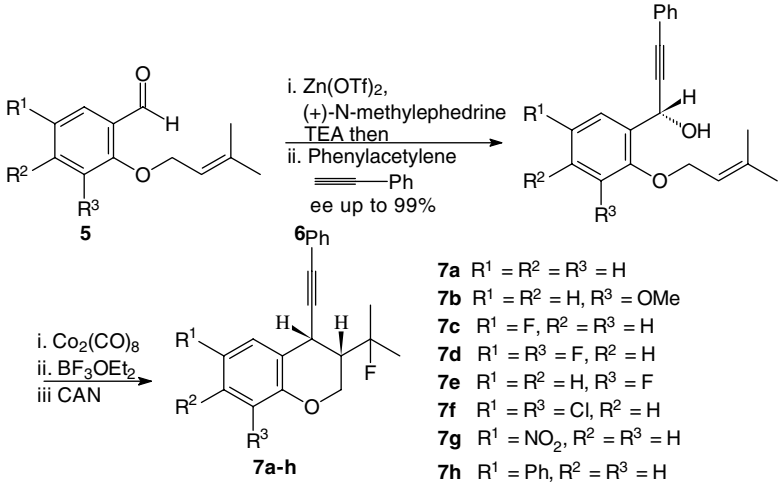


Figure 1. Cromakalim **1** and the most active analogues **2** and **3**.



Scheme 1. Synthesis of benzopyrans.



Scheme 2. Benzopyrans from homochiral propargyl alcohols.

In contrast to our earlier studies[4] the presence of a phenylalkynyl moiety in **6** exerted a significant influence upon the formation of the new stereogenic centres to afford compounds **7a**–**h** with a *cis* relative stereochemistry C-3 and C-4.[11] We were therefore very keen to ascertain any similarity in activity between **7a**–**h** and the corresponding *trans*-isomers **2** and **3**.

Isometric tension recordings on segments of mouse thoracic aorta were undertaken to assay the biological activity of benzopyrans **7a**–**h**. After an initial period of equilibration the tissues were contracted by application of the α-1 adenoceptor stimulant phenylephrine (1 μM). Once the contraction had stabilized cromakalim **1** or one of the compounds under assay **7a**–**h** at 1 and 10 μM was added to the bath for 10 min (Fig. 2).

From Figure 2 it may be seen that cromakalim **1** produced a marked and rapid relaxation which plateaued within 5 min and amounted to a 56% ± 3% at 1 μM and 72% ± 2% at 10 μM ($n = 8$). Although none of the benzopyrans **7a**–**h** proved as effective as cromakalim **1** for inducing vasorelaxation, we were encouraged by the results obtained with compounds **7c**–**e** and **7g** (Fig. 3).

This first series of experiments established that compound **7g** was the most potent benzopyran however it was clear that the vasorelaxant effect was significantly slower than that of cromakalim **1**. Consequently, the maximum relaxant effect of these compounds has been underestimated using the *iso*chronal protocol. An amended protocol was therefore employed in order to determine the full relaxant efficacy of compounds **7a**–**h**. In these experiments the tissue was contracted with phenylephrine and

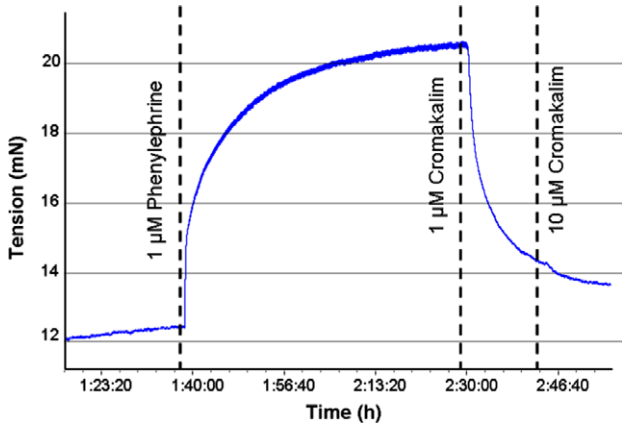


Figure 2. The effect of cromakalim (1 μM) on contracted MTA.

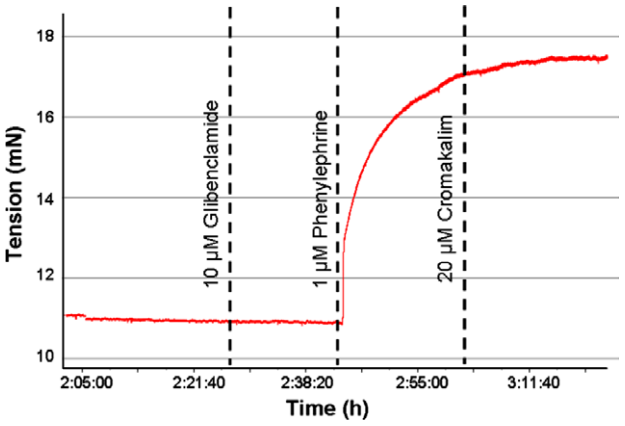


Figure 4. The effect of cromakalim **1** upon contracted MTA tissue in the presence of glibenclamide.

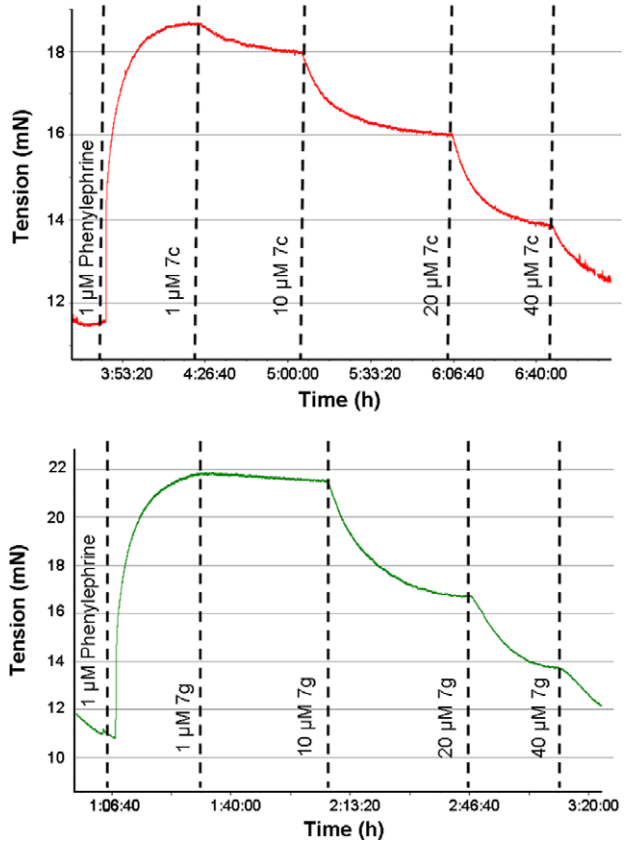


Figure 3. The effects of time and concentration upon the relaxation of MTA using **7c** (above) and **7g** (below).

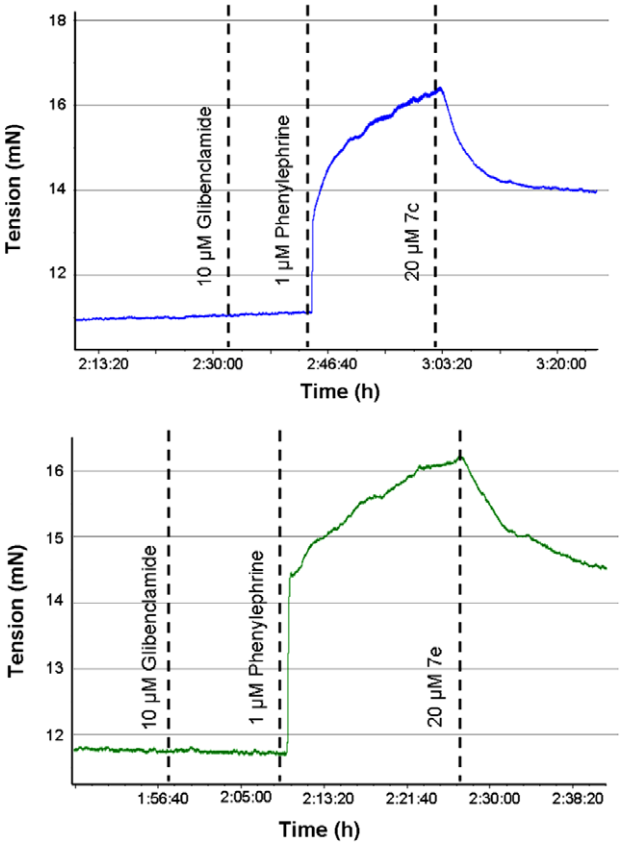


Figure 5. The effect of benzopyrans **7c** (above) and **7e** (below) upon contracted MTA tissue in the presence of glibenclamide.

then concentrations of the relevant benzopyran (1–40 μM) were applied until the relaxation had stabilized. Under these conditions **7c**–**e** and **7g** produced significantly greater relaxations at 10 μM than in the first protocol. The mean relaxations produced by these agents and the time taken are shown (Table 1).

The mode of action of cromakalim **1** has been well documented[12] and involves the activation of ATP-sensitive K^+ channels formed from the combination of *Kir 6.1/6.2* channel proteins and *SUR2* accessory proteins.[12,13] In a series of further experiments we investigated the mode of action of benzopyrans **7a**–**h** in order to ascertain whether they exerted their activity by an analogous mechanism to cromakalim **1**. Tissue segments were initially incubated with 10 μM glibenclamide, a selective blocker of ATP-sensitive K^+ channels, before being contracted by 1 μM of phenylephrine. Not unexpectedly the addition of cromakalim (20 μM) failed to elicit any relaxation of the tissue tension ($n = 6$) (Fig. 4).

In contrast compounds **7c**, **7e** and **7g** (20 μM) produced a mean relaxation of 44 ± 10, 30 ± 12 and 30 ± 18% in the presence of glibenclamide (Fig. 5).

Table 1.

Compound	Relaxation[a] (%)	Time (Min.)	Relaxation[b] (%)	Time (Min.)
7c	36 ± 1	55 ± 3	83 ± 2	33 ± 3
7d	20 ± 8	41 ± 3	65 ± 2	24 ± 2
7e	28 ± 5	43 ± 2	92 ± 2	21 ± 2
7g	43 ± 3	40 ± 2	88 ± 3	30 ± 6

[a] Conc. = 10 μM (n = 3).
[b] Conc. = 40 μM (n = 3).

Whilst the effect of these agents was attenuated in the presence of glibenclamide there was still nevertheless marked relaxation. This suggests that these substituted benzopyrans can relax smooth muscle by another mechanism unrelated to opening of ATP-sensitive K^+ channels. Our investigations into this outcome and the activity of these benzopyrans are on-going and the outcomes will be disseminated in due course.

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