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PYRROLE ANALOGUES OF THE PYRROLIDINONE MOIETY OF THE POTASSIUM CHANNEL ACTIVATOR CROMAKALIM AS RELAXANTS OF GUINEA PIG TRACHEALIS.

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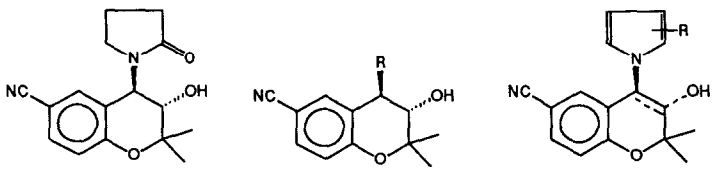
Abstract: A series of C-4 pyrrole substituted benzopyrans and benzopyranols has been prepared, some members of which are potent relaxants of guinea pig trachealis *in vitro*. These compounds appear to act via potassium channel opening. It is envisaged that a pyrrole ring substituted with an electron-withdrawing group can function as a bioisostere of the pyrrolidinone of cromakalim. Two tetracyclic derivatives have also been prepared, one of which (**18**) appears to act as a potassium channel activator in a similar manner to cromakalim while the other (**15**), although a potent relaxant of guinea pig trachealis, has a profile which is inconsistent with this mechanism of action.

Potassium channel activators, typified by cromakalim, are potent smooth muscle relaxants which have been shown to have potential therapeutic utility in hypertension, asthma and urinary incontinence.[1] Whilst structurally distinct potassium channel activators have been reported, most have been modelled on the amidobenzopyranol system and the salient features necessary for relaxation of the airways have been identified.[2] As an extension of these studies it was found that the cyanoenamine **1** (m.p. 236-239 °C, prepared in 22% yield by reaction of the aminoalcohol **2** with cyanoacetone in THF/benzene in the presence of $MgSO_4$) retained the potency of the acetamide **3**[3] as a relaxant of guinea pig isolated trachealis. From this we reasoned that compounds which possessed electron-withdrawing enamine functionality incorporated into an appropriate heterocycle at C-4 would retain activity. That this is indeed the case is shown by our findings with some of the compounds described by the generalised structure **4**.



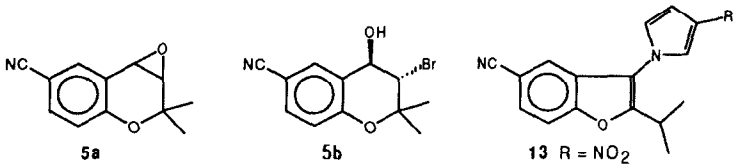
Cromakalim (racemic)

1 R=NHC(Me) CHCN (E)
2 R=NH_2
3 R=NHCOMe

4 benzopyranol or benzopyran

Preparation of the compounds was, in general, carried out by procedures previously described.[4,5] Thus, reaction of the appropriately substituted pyrrole anion with the epoxide **5a** or its precursor bromohydrin **5b** gave the benzopyranols **6** and **7** (see Table for

structures)[6] or the benzopyrans **8** and **11**, the unsubstituted derivatives of which were further elaborated by nitration (to **9** and **10**) or by trifluoroacetylation (to **20** and **21**). The benzopyranol **7** was also dehydrated to its ene analogue **9** using a two step mesylation-elimination sequence. With 3-nitro- and 3-cyanopyrrole, epoxide ring opening to give **10** and **12** was accompanied by the formation of the ring contracted benzofuran products **13** and **14**.[4] Tetracyclic products **15-18** resulted from treatment of the bromohydrin **5b** with the anions derived from 2-acylpyrroles, although the 2-acetylpyrrole benzopyran **19** was also isolated from the reaction with 2-acetylpyrrole.[5]



5a **5b** **13** R = NO_2 **14** R = CN

Of the analogues shown in the table, high airways relaxant potency[7] was displayed by the 3-nitro- and 3-cyanopyrrole benzopyrans **10** and **12**, the corresponding 2-nitro and 2-trifluoroacetyl derivatives **9** and **21** and the 2-nitropyrrole benzopyranol **7**, consistent with our initial hypothesis. In common with known potassium channel activators the relaxation was characterised by a steep-concentration response curve with attenuation of the response by BRL 31660, a known potassium channel blocker.[8]

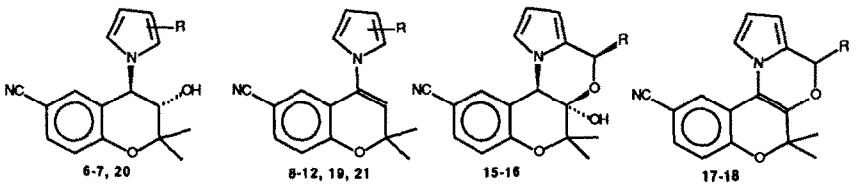
The lack of activity shown by both the unsubstituted pyrrole benzopyranol **6** and the corresponding 2-ethylbenzopyran **8** would suggest the requirement of an electron-withdrawing group, but this statement must be qualified in the light of results obtained with the acyl derivatives **19** and **20**. The relaxation evoked by the unsubstituted pyrrole **11** is also somewhat enigmatic since it does not conform with the above criteria. Its effects are not blocked by BRL 31660 (10 μM), however, suggesting that it does not mediate relaxation through the opening of potassium channels.

Dehydration of cromakalim to the corresponding benzopyran resulted in retention of relaxant potency (IC_{50} 1.57 μM) and whilst for these two compounds the relaxation potencies are similar, it is not unusual for some dihydrobenzopyranol-benzopyran pairs to have disparate potency.[2,9] This is also seen within the pyrrole series of compounds. Thus, the 2-nitropyrrole derivatives **7** and **9** are of similar potency, and activity is restored on conversion of the 2-trifluoroacetyl benzopyranol **20** to its ene analogue **21**.

Single crystal X-ray analysis of cromakalim shows the pyrrolidinone ring disposed orthogonal to the plane of the benzopyran ring with the amide carbonyl directed towards H-4.[10] Furthermore, nmr studies reveal that, despite rapid rotation around the C-4 amide bond, this conformer also predominates in solution.[11] It is envisaged that the pyrrole ring also lies

orthogonal to the plane of the pyran ring and that potency in this series is derived through the substituted enamine moiety functioning as a bioisostere of the pyrrolidinone of cromakalim.

Relaxant activity of 6-cyano-2,2-dimethyl-4-(substituted pyrrolyl)-2*H*-1-benzopyrans and benzopyran-3-ols and their tetracyclic derivatives



Entry	R	m.p. °C	%Yield, Method of Preparation	Inhibition of tone in guinea pig trachealis[a]
cromakalim				1.1 (0.6 -1.9); 0.89 ± 0.02; 7
1				1.23 (0.37-4.05); 0.96 ± 0.13; 4
3				2.90 (0.73-11.53); 0.78 ± 0.08; 4
6	H		A[b]	>20; 0.19; 4
7	2-NO_2	121-2	6, B	0.37 (0.09-1.43); 0.88 ± 0.03; 4
8	2-Et	65-6	13, C	>20; 0.32; 2
9	2-NO_2	117-8	50, D	0.69 (0.15-3.22); 0.88 ± 0.03; 6
10	3-NO_2		E[c]	1.02; 0.79; 2
11	H		E[c]	4.08 (0.68-24.6); 0.78 ± 0.09; 4
12	3-CN		E[c]	2.4 (1.24-4.75); 0.89 ± 0.04; 4
15	CF_3		F[d]	0.08 (0.05-0.14); 0.96 ± 0.14; 4
16	H		F[d]	10.4; 0.85; 2
17	Ph		F[d]	>2; 0.21; 2 (insolubility)
18	Me		F[d]	1.37 (1.16-1.62); 0.80 ± 0.05; 4
19	2-COMe		F[d]	>20; 0.22; 2
20	2-$COCF_3$	146-8	86, G	>20; 0.28; 2
21	2-$COCF_3$	134.5-5	20, G	0.69; (0.37-1.27); 0.91 ± 0.02; 4

[a] IC_{50} in μM with 95% confidence limits (where appropriate); intrinsic activity ± SEM; number of determinations. [b] See ref 12; [c] See ref 4; [d] See ref 5. A (**5a**, pyrrole, NaH, DMSO, 0.5h, RT); B (**5a**, 2-nitropyrrole, $KOBu^t$, DMF, 20h, 100°C, $MgBr_2$, accompanied by 53% *trans* 3,4-diol); C (**5b**, 2-ethylpyrrole, $KOBu^t$, THF, 1h, 67°C); D (**7**, MsCl, CH_2Cl_2, Et_3N, followed by $KOBu^t$, THF; **9** was also prepared (18%) together with **10** (11%) by reaction of **11** with Ac_2O, HNO_3, -10°C to RT, 17h); E (**5b**, substituted pyrrole, $KOBu^t$, DMF, 20h, 100°C); F (**5b**, 2-acylpyrrole, $KOBu^t$, THF, TMEDA, 18h, 67°C); G (**6** or **11**, $(CF_3CO)_2O$, $CHCl_3$, 1.5h, 60°C).

In contrast to the two benzofuran derivatives **13** and **14**, which showed no relaxant effects, two tetracyclic derivatives **15** and **18** were potent airways relaxants, despite the rigidity of the system rendering an orthogonal disposition of the C-4 substituent impossible. Both compounds display steep-concentration-response curves, but whilst the methyl derivative **18** has other properties consistent with potassium channel activation (reversal by BRL 31660 and little or no effect against high KCl-induced tone), the mechanism of action of **15** is less clear. The profile of this compound suggests that its relaxation is not mediated through the opening of potassium channels but is associated with another, as yet undefined, mechanism, since the relaxation is not blocked by BRL 31660 and, unlike typical potassium channel activators, relaxation was also shown against high potassium (60mM) induced tone.

Acknowledgements

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6. All new compounds gave satisfactory elemental analysis and/or spectroscopic data. Compounds with chiral centres are racemic with relative stereochemistry shown.
7. Guinea pig tracheal spiral strips were suspended under isometric conditions in oxygenated Krebs solution. Tension was allowed to develop spontaneously and was maintained at 2g. Compounds were added in a cumulative fashion up to a maximum concentration of 20 μM and the inhibitory effects were calculated as a percentage of the relaxation induced by isoprenaline (10^{-3}M) added at the end of the experiment. The IC_{50} value of each compound was that concentration which produced 50% of the response to isoprenaline as measured from the concentration-response curve, and was generally a geometric mean of 4 to 7 determinations. The intrinsic activity for each compound was calculated as the ratio of its maximum relaxant activity over that produced by isoprenaline and expressed as an arithmetic mean.
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