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BENZOPYRAN POTASSIUM CHANNEL ACTIVATORS RELATED TO CROMAKALIM - AMIDE REPLACEMENTS AT POSITION 4.

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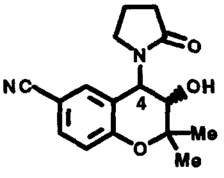
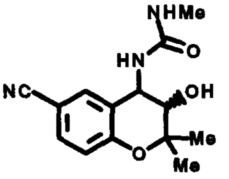
Abstract. The synthesis and antihypertensive activity of a series of benzopyran potassium channel activators related to cromakalim (**1**) in which the pyrrolidinone ring at position 4 has been replaced by a number of potential amide and urea isosteres is reported. The observation that cyanoguanidine **4** is approximately 30-fold more potent than nitroethene **8** is discussed and compared with the pinacidil series.

The discovery[1] of cromakalim (**1**) and its novel mechanism of action[2] has stimulated worldwide interest in potassium channels and their therapeutic application. We have described[3-7] several series of novel benzopyrans with antihypertensive activity. The observation[4] that antihypertensive activity was retained when the pyrrolidinone ring of cromakalim was replaced by an N-methylurea group as in **2** prompted us to introduce a number of urea and thiourea bioisosteres at the 4-position of the benzopyran ring. Following a recent report on benzopyranyl-cyanoguanidine potassium channel openers[8] based on comparison of cromakalim with pinacidil we now report our findings on a range of urea and thiourea replacements at position 4, based on those previously employed in H_2 receptor antagonists.[9]



cromakalim (1)



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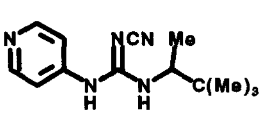
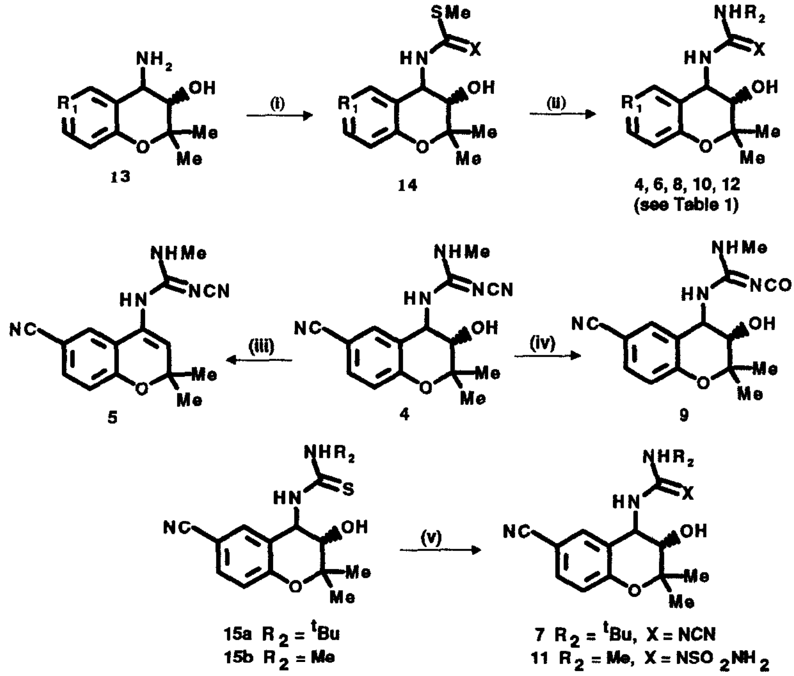


pinacidil (3)

Compounds **4** - **12** were prepared from the known (±)-trans-amino alcohols **13**[3-5] as shown in Scheme 1. Reaction of **13** with the appropriate bis(thiomethyl)imidate in ethanol, followed by treatment of intermediates **14** with an appropriate amine gave compounds **4**, **6**, **8**, **10** and **12**. Dehydration of **4** with NaH in toluene gave chromene **5** and hydrolysis of **4** with dilute HCl in ethanol gave amide **9**. Compounds **7** and **11** were prepared *via* the corresponding thioureas **15** by reaction with phosgene in toluene, followed by treatment with cyanamide and sulfamide in dry tetrahydrofuran, respectively.

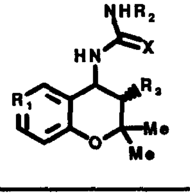
Scheme 1.



Reagents. (i) $(MeS)_2C{=}X$, EtOH; (ii) R_2NH_2, EtOH; (iii) NaH, PhMe, (iv) HCl, EtOH; (v) $COCl_2$, PhMe; XH_2, THF.

Compounds were screened for antihypertensive activity following oral administration in the spontaneously hypertensive rat (SHR)[3] and results are presented in Table 1. Cyanoguanidine **4** retained similar potency to cromakalim and was slightly less potent than urea **2**. Interestingly, in contrast to previous results[4] with urea analogues of cromakalim removal of the N-methyl group of **4** (compound **6**) did not lead to a reduction in potency. Taking into account the comparison of the structures of cromakalim and pinacidil by Atwal et al[8] it is intriguing to note that replacement of the N-methyl group of **4** by t-butyl to give **7** resulted in a marked reduction in potency. Since bulky substituents such as t-butyl gave the highest potency in the pinacidil series,[10] this suggests that either the cyanoguanidine of pinacidil and the amide carbonyl of cromakalim do not fit to the same part of a putative receptor, or that the bulky side chain of pinacidil and its analogues fits to a different region to that occupied by the pyrrolidinone ring of cromakalim. We have noted previously[3,4] that chromanols and chromenes are not always of equivalent potency, and chromene **5** was some 3-10 fold less potent than **4**. We have also shown previously[5] that replacement of the 6-cyanobenzopyran ring of cromakalim by a [3,2-c]-pyranopyridine ring resulted in a slight reduction in potency, and in the cyanoguanidine series, this trend was again observed with pyranopyridine **12** being about half as potent as benzopyran **4**. Replacement of the N-cyano group of **4** by carboxamide, acetyl, or sulfonamide (compounds **9**, **10** and **11**, respectively) produced reductions in potency which mirrored the loss in potency observed in H_2 antagonists[9] for these changes. However, replacement of cyanoguanidine by nitroethene (which gave equivalent potency in the H_2 antagonist series[9]) to give **8** resulted in an unexpected and dramatic reduction in antihypertensive potency in the benzopyran series. These results from oral dosing in SHR for compounds **1**, **2** and **4** - **12** exactly correlated with *in vitro* data from guinea-pig portal vein and trachealis.[11]

Table 1. Antihypertensive Activity of 4 - Substituted - Benzopyrans



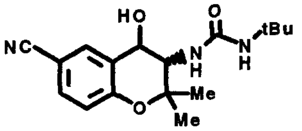
Compound[a]	R_1	R_2	R_3	X	Mpt °C	Dose (p.o.) mg/kg	Max fall in BP ± SEM[b]
cromakalim						1.0	47 ± 1
(1)						0.3	39 ± 4
						0.1	13 ± 5
2	NC-C	Me	OH	O		1.0	61 ± 3
						0.3	31 ± 9
						0.1	14 ± 4
4	NC-C	Me	OH	NCN	225-227	1.0	41 (1)
						0.3	16 ± 1
5	NC-C	Me	$\Delta^{3,4}$	NCN	249-252	3.0	15 ± 4
						1.0	17 ± 2
6	NC-C	H	OH	NCN	248-250	1.0	48(2)
						0.3	24 ± 4
7	NC-C	$C(Me)_3$	OH	NCN	198-201	10.0	10 ± 2
						1.0	8 ± 2
8	NC-C	Me	OH	$CH\text{-}NO_2$	243-244	10.0	12 ± 2
						1.0	7 ± 4
9	NC-C	Me	OH	$NCONH_2$	120-122	3.0	19 ± 2
10	NC-C	Me	OH	NCOMe	166-167	1.0	17 ± 5
11	NC-C	Me	OH	NSO_2NH_2	162-165	3.0	14 ± 3
12	N	Me	OH	NCN	284-286	1.0	25 ± 3

[a] All new compounds gave satisfactory analytical and/or mass spectral data (see ref. 12).

[b] Systolic blood pressure was measured at intervals of 1 h over a period of 1 - 6 h after dosing in groups of 5 SHR. All compounds were administered (via an oral dosing needle placed in the esophagus) as a solution or suspension in 1% w/v methylcellulose solution. On occasion, pulses were determined from only (n) SHR.

The loss of potency observed with **8** contrasts with a recent report[13] which showed that in the pinacidil series the cyanoguanidine group could be effectively replaced by nitroethene and casts doubt on the hypothesis[8] that the cyanoguanidine of **4** and that of pinacidil (and by inference the pyrrolidinone ring of cromakalim **1**) fit to the same part of the putative receptor. Manley and Quast[13] also pointed out that in the pinacidil series replacement of the cyanoguanidine group by a urea leads to a loss in potency. However, we have shown[4] (see compound **2**) that in the benzopyran series, the pyrrolidinone ring of cromakalim can be replaced by an N-methyl urea without loss of potency. Taken together, these data seem to suggest that if cromakalim and pinacidil act at the same receptor, the pyrrolidinone ring of cromakalim and the N-alkyl cyanoguanidine substituent of pinacidil do not occupy the same part of the receptor.

We have recently described[7] a series of 3-substituted benzopyrans such as **16** in which a bulky alkyl substituent on the urea nitrogen was found to be required for optimal potency (as in the pinacidil series).



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In the light of the results presented above, inclusion of these compounds in comparisons with other potassium channel activators such as pinacidil may lead to more meaningful descriptions of the pharmacophore than those reported to date.

References and Footnotes

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Compound **8**: ^{1}H NMR (270 MHz, DMSO-d_6, 60^{o}C) δ 1.35 (s, 3H), 1.54 (s, 3H), 3.00(s, 3H), 3.80 (d, J = 8Hz, 1H), 4.75 (d, J = 8Hz, 1H), 6.05 (br s, O$\underline{\text{H}}$), 6.67 (br s, 1H), 7.05 (d, J = 8 Hz, 1H), 7.65 (d, J = 2Hz, 1H), 7.72 (dd, J = 8, 2Hz, 1H), 10.40 (br s, 2N$\underline{\text{H}}$).
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