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BENZOPYRANYL-CYANOGUANIDINE POTASSIUM CHANNEL OPENERS

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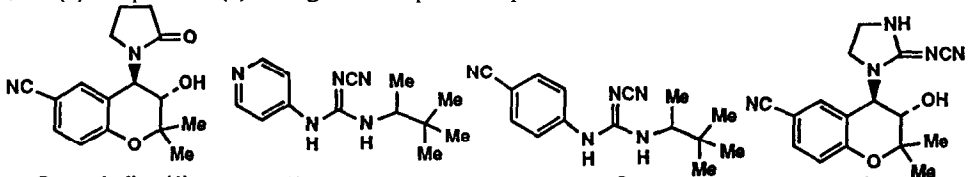
Abstract: To further investigate whether potassium channel openers cromakalim (**1**) and pinacidil (**2**) share common pharmacophoric features, the cyanoguanidine analog **4a** of cromakalim (**1**) was prepared and evaluated for biological activity. The potent vasorelaxing activity displayed by **4a** and some of its analogs support the hypothesis that cromakalim (**1**) and pinacidil (**2**) share common pharmacophoric features.

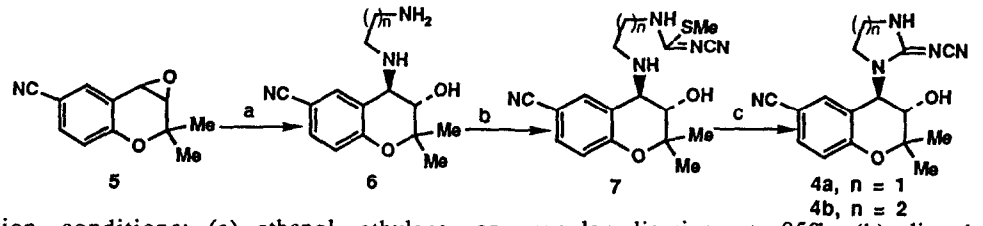
The discovery of potassium channel opening as a primary mechanism for the vasodilatory activities of cromakalim (**1**) and pinacidil (**2**) has attracted the attention of medicinal chemists over the past several years.[1] The design of structurally novel compounds has remained elusive due to the lack of knowledge about the three dimensional structure of receptor proteins to which these compounds bind. Although pharmacological data (e.g., stereoselectivity of pharmacological effects)[2] indicate interaction of these agents with a specific receptor(s), there are as yet no receptor binding data to support those observations. Our objective in this area has been to understand whether the purported potassium channel openers cromakalim (**1**) and pinacidil (**2**) express their biological effects with similar structural requirements. Along those lines, we reported the discovery of the combination compound **3** as a potent vasodilator/antihypertensive agent.[3] To identify additional pharmacophoric features common to cromakalim (**1**) and pinacidil (**2**), we selected as our synthetic target the cyanoguanidine analog **4a**[4] of cromakalim (**1**), the assumption being that the cyanoguanidine of pinacidil (**2**) and the pyrrolidone amide of cromakalim (**1**) are involved in a similar interaction at the presumed receptor site(s). As reported in this publication, the potent vasorelaxing properties of **4a** and some of its analogs support the hypothesis of cromakalim (**1**) and pinacidil (**2**) having common pharmacophoric features.



For the preparation of cyclic cyanoguanidines **4a** and **4b**, the known epoxide **5**[5] was treated with 1,2-diaminoethane or 1,3-diaminopropane to give the amino alcohol **6**. Conversion of **6** to the desired products **4a,b** involved treatment of **6** with dimethyl-N-cyanodithioiminocarbonate followed by cyclization of the resulting intermediate **7** with mercuric acetate (Scheme I, Method A in Table I). As outlined in Scheme II, the alkyl cyanoguanidine analogs **4c-f** and **4h-l** were prepared by treatment of the common intermediate **10**, generated from the amino alcohol **9**[5] by reaction with diphenylcarbonimidate, with the appropriate amine (Method B in Table I). The remaining alkyl cyanoguanidine analog **4g** was prepared by treatment of thiourea **11** with

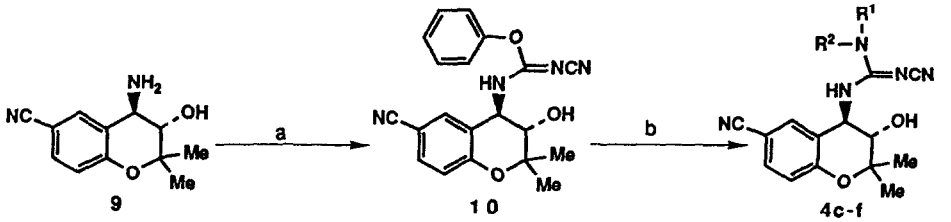
aminoalcohol **9**[5] in the presence of WSC (Scheme III, Method C in Table I).[6] Vasorelaxant potencies were compared by measurement of IC_{50} values for relaxation of the methoxamine-contracted rat aorta.[3] As described in the previous publication,[3] the vasorelaxant response was almost completely reversed by 60 mM potassium chloride, pharmacological behavior that is typical of agents known to act *via* a potassium channel opening mechanism.[7] The ATP-sensitive potassium channel blocker glyburide was able to inhibit the vasorelaxation caused by selected analogs.[8] The IC_{50} values for vasorelaxant activity are given in Table I.

Scheme I



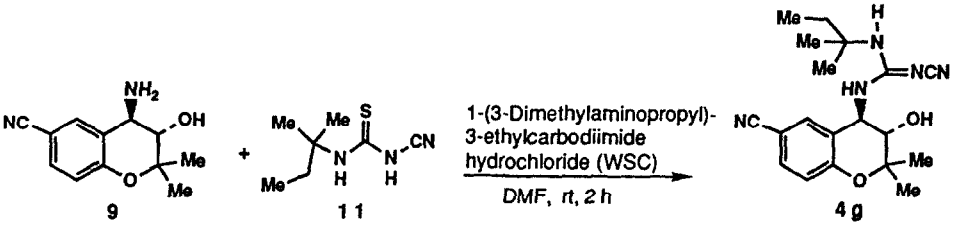
Reaction conditions: (a) ethanol, ethylene- or propylenediamine, rt, 95%; (b) dimethyl-N-cyanodithioiminocarbonate, ethanol,80°, 3 h; (c) mercuric acetate, methanol, rt, 2 h, 50-58% overall from **6**.

Scheme II



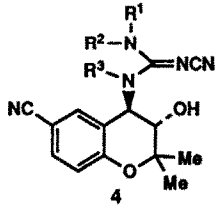
Reaction conditions: (a) diphenylcarbonimidate, 2-propanol, rt, 75%; (b) amine, 2-propanol, rt, 24-85%.

Scheme III



The cyanoguanidine analog **4a** was less potent *in vitro* than either cromakalim (**1**) or pinacidil (**2**). Several analogs of **4a** were prepared to explore structure-activity relationship for vasorelaxant activity. The corresponding six-membered ring analog **4b** was 4-fold more potent than **4a** and it was only 3-fold less active than cromakalim (**1**). The acyclic analog **4c** retained most of the vasorelaxing potency of its cyclic counterpart **4a**. Comparison among alkyl analogs **4c-g** indicates some limitations as to the size of the alkyl group. Substitution of the alkyl group R^1 of **4c** with an amino (**4h**) and a methoxy (**4i**) group was detrimental to potency *in vitro*. While the

Table I: Physical properties and vasorelaxant potencies of benzopyranyl-cyanoguanidine analogs 4a-l.



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Compound	R1	R2	R3	% yield[a]	Method	mp°C[b]	IC_{50}, μM (95% C.I.)[c]
4a	H	-CH_2CH_2-		58	A	254-5 (A)	0.47 (0.34, 0.66)
4b	H	-$CH_2CH_2CH_2$-		50	A	152-3 (B)	0.12 (0.09, 0.16)
4c	CH_2CH_3	H	H	85	B	185-8 (C)	0.38 (0.25, 0.59)
4d	CH_3	H	H	48	B	212-4 (D)	0.20 (0.13, 0.32)
4e	H	H	H	39	B	250-1 (E)	0.32 (0.18, 0.59)
4f	$CHMe_2$	H	H	66	B	150-2 (F)	0.66 (0.41, 1.08)
4g	C(Me)2Et	H	H	38	C	207-8 (G)	29.8 (23.2, 38.3)
4h	$CH_2CH_2NMe_2$	H	H	51	B	172-3 (G)	>100
4i	CH_2CH_2OMe	H	H	63	B	94-6 (H)	1.69 (1.03, 2.79)
4j	Me	Me	H	51	B	196-7 (I)	0.49 (0.23, 1.03)
4k	-$CH_2CH_2CH_2CH_2$-		H	55	B	263-4 (J)	0.034 (0.023, 0.050)
4l			H	24	B	205-7 (K)	13.1 (6.09, 28.2)
1 (Cromakalim)							0.055 (0.041, 0.074)
2 (Pinacidil)							0.070 (0.051, 0.096)

[a]Satisfactory microanalysis was obtained for all crystalline compounds. [b]Solvent for crystallization: A, ethyl acetate; B, ethyl acetate-isopropyl ether; C, acetonitrile-ethyl ether; D, 2-propanol; E, acetone-ethyl acetate; F, 2-propanol-isopropyl ether; G, isopropyl ether; H, ethyl ether; I, acetone-chloroform; J, acetone-methanol; K, 2-propanol-ether. [c]IC_{50} is presented as mean with 95% confidence interval in parentheses, $n \geq 4$ from different animals. [d]see scheme I.

N,N-dimethyl analog **4j** was slightly less active than the corresponding *mono*-methyl derivative **4d**, the cyclic analog **4k** (IC_{50} = 0.034 μM) turned out to be the most potent vasorelaxing agent of this class. As shown by the comparison of **4l** with **4k**, incorporation of a basic nitrogen into the ring led to a large attenuation in potency *in vitro*. Selected analogs of **4** were also tested for antihypertensive activity in the spontaneously hypertensive rats (po) and the data comparing the most potent antihypertensive agent **4d** of this class with cromakalim (**1**) and pinacidil (**2**) is shown in Table II.[3] Although comparable to pinacidil (**2**), the cyanoguanidine analog **4d** was less active than cromakalim (**1**) in lowering blood pressure. For all compounds, the decrease in blood pressure was accompanied by an increase in heart rate, presumably reflexogenic in nature, which normalized after 6 hours (data not shown).

Table II: Antihypertensive activities of 4d, cromakalim (1) and pinacidil (2) in the SHR (po).

	% maximum decrease in blood pressure @45 μmol/kg (n = 6)			
Compound	0-6 hrs	6-12 hrs	12-18 hrs	18-24 hrs
4d	46±2	44±3	23±3	15±5
Cromakalim (**1**)	63±6	35±5	37±8	42±7
Pinacidil (**2**)	40±9	21±6	23±6	14±6

Our results demonstrate cyanoguanidine can effectively mimic the pyrrolidone amide of cromakalim (**1**) suggesting, these functionalities may be playing a similar role in expressing the biological effects of cromakalim (**1**) and pinacidil (**2**). We have previously shown that both molecules require an aryl ring having electron withdrawing substituents or a pyridine ring for optimal activity.[3] Further, both cromakalim (**1**) and pinacidil (**2**) require a lipophilic residue for maximal vasorelaxant/antihypertensive activity.[5,9] These data support the hypothesis that cromakalim (**1**) and pinacidil (**2**) share common pharmacophoric features. Since the data to support receptor binding by cromakalim (**1**) and pinacidil (**2**) do not exist at the present time, it is premature to speculate whether these compounds bind to a single or multiple receptor sites. However, it does appear the two have similar structural requirements for expression of their biological effects.

References And Notes

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