Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 11, pp. 1285-1290, 1994

0960-894X/94 $7.00+0 00

0960-894X(94)00141-3

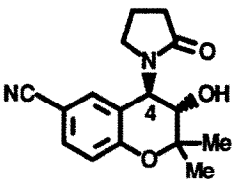
BENZOPYRAN POTASSIUM CHANNEL ACTIVATORS RELATED TO CROMAKALIM - HETEROCYCLIC AMIDE REPLACEMENTS AT POSITION 4.

Gordon Burrell, John M. Evans, Michael S. Hadley, Frances Hicks and Geoffrey Stemp*

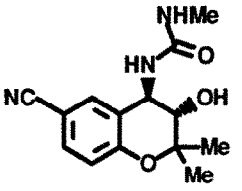
SmithKline Beecham Pharmaceuticals, Coldharbour Road, Harlow, Essex, CM19 5AD, U.K.

Abstract. The synthesis and antihypertensive activity in spontaneously hypertensive rats (SHR) of a series of benzopyran potassium channel activators related to cromakalim (**1**) where the pyrrolidinone at position 4 is replaced by a number of potential heterocyclic amide and ester bioisosteres is reported. Aminotriazole **6** was shown to be the most potent amide replacement in this series.

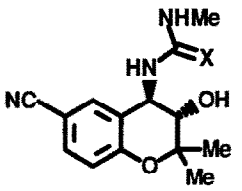
The discovery[1] of cromakalim (**1**) and its novel mechanism of action[2] has stimulated worldwide interest in potassium channel activators and their therapeutic application. The observation[3] that antihypertensive activity was retained when the pyrrolidinone ring of cromakalim was replaced by an N-methylurea **2** prompted us to synthesise a number of potential urea and thiourea isosteres at the 4-position of the benzopyran ring[4], and in this series cyanoguanidine **3** was shown to be at least 30-fold more potent than nitroethene **4.**



cromakalim (**1**)



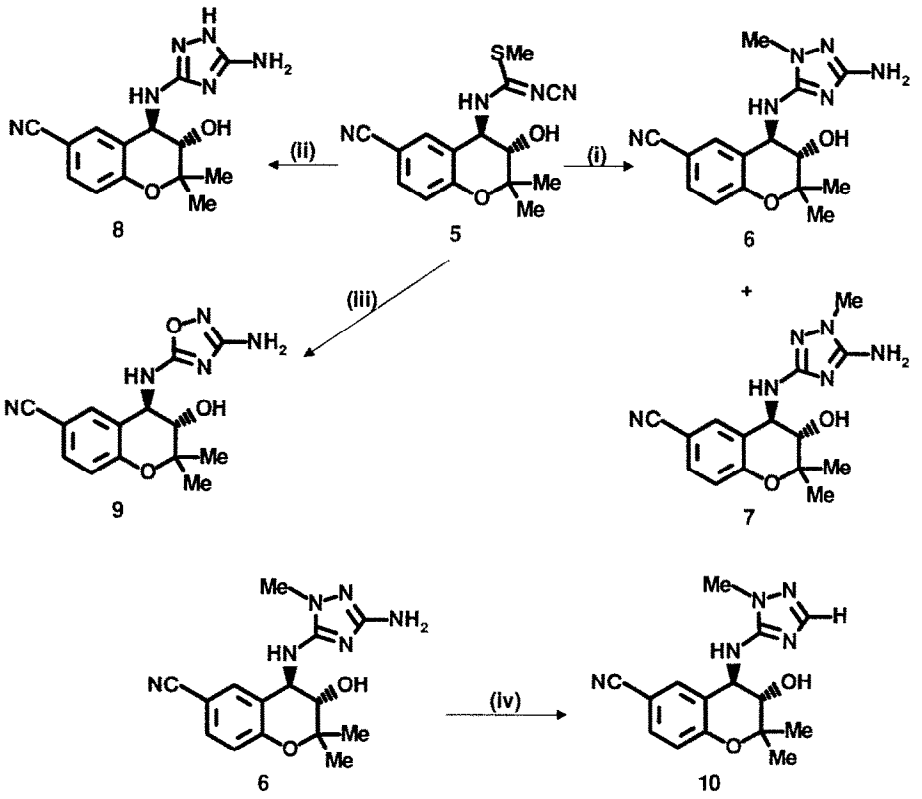
2



3 X = NCN
4 X = $CHNO_2$

One possible explanation for the loss of potency observed with **4** is that the C=N bond of **3** has been replaced by a C=CH bond in **4**, particularly if the lone pair of electrons on the nitrogen of the C=N bond of **3** play a role in the interaction of this compound with the presumed receptor. It was with this potential requirement for a C=N bond in mind that we next turned our attention to the incorporation at position 4 of heterocycles containing a C=N bond. In particular, we were interested in the aminotriazole and aminothiadiazole rings which had previously been shown to be cyanoguanidine replacements in H_2 antagonists[5] and we also considered the 1,2,4-oxadiazole ring a candidate for synthesis since this heterocycle contained an appropriately positioned C=N bond and had been shown to be an effective ester replacement.[6] The syntheses of these analogues are shown in Schemes1 and 2.

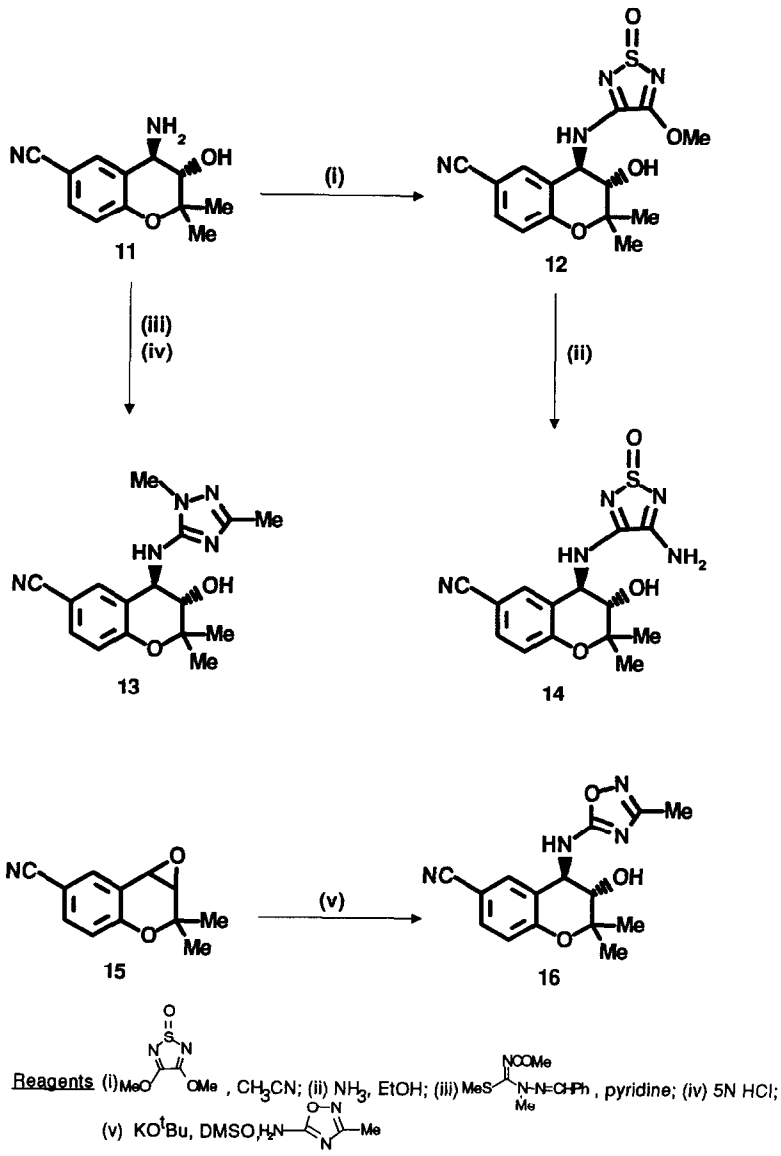
Scheme 1.



Reagents: (i) $MeNHNH_2$; (ii) NH_2NH_2; (iii) NH_2OH; (iv) c. H_2SO_4, $NaNO_2$, H_3PO_2 aq.

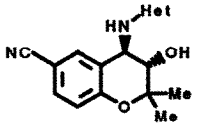
Reaction of (±)-*trans*-methylthioimidate **5**[4] with methylhydrazine in acetonitrile under reflux for 48 hours gave the isomeric aminotriazoles **6** (66%) and **7** (12%), which were conveniently separated by fractional crystallisation. The structures of **6** and **7** were assigned unambiguously from their ^1H coupled ^{13}C Nmr spectra.[7] Treatment of **5** with hydrazine or hydroxylamine under similar conditions gave 1, 2, 4-triazole **8** (64%), and 1, 2, 4-oxadiazole **9** (72%), respectively. The structure of **9** was assigned by analogy with literature precedent.[10] Diazotisation of **6**, followed by work up with hypophosphorous acid gave **10** (20%). Treatment of (±)-*trans*-amino alcohol **11** (Scheme 2) with methyl-N-acetyl-1-methyl-2-(phenyl-methylene)hydrazine-carboximidothioate[8] in pyridine at 50 °C for 72 hours, followed by cyclisation in 5N hydrochloric acid gave **13** (32%). 1, 2, 5-Thiadiazole-1-oxide **14** was prepared in 26% overall yield by treatment of amino alcohol **11** with 3, 4-dimethoxy-1, 2, 5-thiadiazole-1-oxide[9] in methanol under reflux, followed by reaction of the resulting intermediate methoxy-thiadiazole **12** with ammonia in ethanol. 3-Methyl-1, 2, 4-oxadiazole **16** was prepared in 52% yield by reaction of (±)-epoxide **15** with 5-amino-3-methyl-1,2,4-oxadiazole[10].

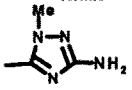
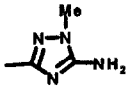
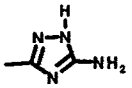
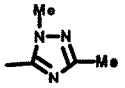
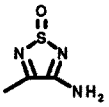
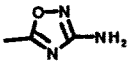
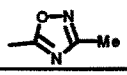
Scheme 2.



Antihypertensive activity of compounds **6** - **10** and **13, 14, 16** was assessed in the spontaneously hypertensive rat[2] and compared with cromakalim (**1**) and N-methylcyanoguanidine **3**, which was identified in our previous work[4] as the most potent 2-oxopyrrolidine replacement (see Table 1).

Table 1. Antihypertensive Activity of Heterocyclic Amide Replacements at Position 4.



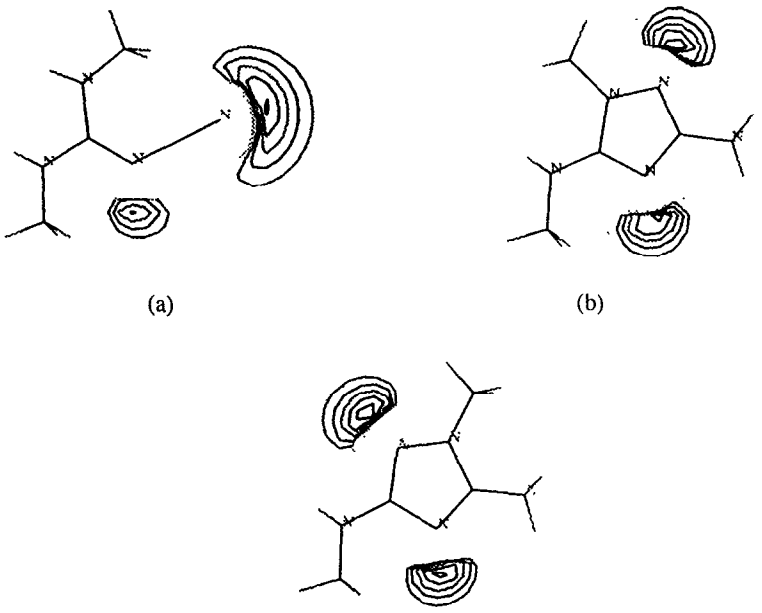
Compound[a]	Het	Mpt °C	Dose mg/kg	Max fall in BP ± SEM[b,c]
cromakalim (1)			1.0	47 ± 1
			0.3	39 ± 4
			0.1	13 ± 5
3			1.0	41 (1)
			0.3	16 ± 1
6		260-261	0.3	56 (1)
			0.1	30 ± 3
7		223-224	10.0	33 ± 5
8		259-261	3.0	19 ± 2
10		247-249	1.0	35 (3)
			0.3	22 ± 4
13		277-280	3.0	37 ± 4
			1.0	22 ± 3
14		275-278	3.0	20 ± 1
9		134-140	3.0	32 ± 1
			1.0	16 ± 2
16		201-203	3.0	31 ± 6

[a]All new compounds gave satisfactory analytical and/or mass spectral data.
[b]Systolic blood pressure was measured at intervals of 1h over a period of 1-6h in groups of 5 SHR. All compounds were administered (via an oral dosing needle placed in the oesophagus) as a solution or suspension in 1% w/v methylcellulose solution. On occasion, pulses were determined from only (n) SHR.
[c]The results from oral dosing in SHR for **1**, **3** and **6** - **10** and **13**, **14**, **16** showed a similar correlation with *in vitro* data involving relaxation of tone in guinea-pig portal vein[11].

Interestingly, N'-methyl-aminotriazole **6** was found to be approximately 3-fold more potent than cromakalim (**1**) and at least 3-fold more potent than cyanoguanidine **3**. However, N"-methyl isomer **7** was some 100-fold less potent than **6**, indicating that the lone pair of electrons on the N"-nitrogen of **6** may play a major

role in the binding of these compounds to the putative receptor. Des-methyl analogue **8** was also found to be at least 30-fold less potent than **6**. Having assigned the structures of **6** and **7** by long-range carbon-proton correlation, we noted that these compounds could be readily distinguished using the chemical shift of the proton at C(4) of the benzopyran ring.[7] In the ^{1}H nmr spectrum of **8** the chemical shift of the C(4) proton (δ 4.55) is very close to that observed for **7**, suggesting that the major tautomeric form of the triazole ring in **8** is that shown in Table 1. This tautomeric form would lack an area of negative potential around the N" nitrogen and this presumably explains the loss of potency with this compound. Figure 1 shows the 2D-electrostatic potential maps of the triazole rings of **6** and **7** and compares them with the cyanoguanidine moiety of **3**.

Figure 1. Electrostatic potential maps of N, N-dimethylcyanoguanidine (a), 3-amino-5-methylamino-1-methyl-1H-1,2,4-triazole (b) and 5-amino-3-methylamino-1-methyl-1H-1,2,4-triazole (c). These represent compounds **3**, **6** and **7**, respectively, where the 4-aminobenzopyran has been replaced by an aminomethyl group. For the purpose of generating a pharmacophore, these moieties can be considered to be approximately orthogonal to the benzopyran ring, in line with the pyrrolidinone of cromakalim.[1] X-Ray coordinates[5] for (a) and standard bond lengths and angles (b), (c) were used prior to energy minimisation. Reference 6 contains details of the methods of calculation and display of these maps, which show the areas of negative potential around each molecule from -75 to -15 kcal/mol.



(a) (b)

(c)

Removal of the 3-amino group of triazole **6** to give **10**, or replacement by methyl **13**, also resulted in a loss in potency, presumably because the electron-donating ability of the 3-amino group has a strong influence on

the electrostatic potentials around the triazole ring. Replacement of triazole by aminothiadiazole S-oxide **14** resulted in a disappointing loss in potency in view of the fact that in H_2 antagonists[9] these ring systems are equi-effective cyanoguanidine mimics. One may speculate that since the major area of negative electrostatic potential around the S=O of **14** is out of the plane of the heterocycle this may explain the loss of potency. Oxadiazoles **9** and **16** were similar in potency to **13**, suggesting that in these ring systems the negative potential areas around the heterocycle are not sufficiently matched to those of **6** to give high potency. Oxadiazoles have been shown[6] to contain an area of negative potential associated with the oxygen of the heterocycle (which is absent in the triazoles) and this presumably has a detrimental influence on the alignment of these rings with the putative receptor.

In conclusion, studies on replacement of the pyrrolidinone ring of cromakalim (**1**) by a variety of non-carbonyl-containing heterocycles have resulted in the identification of the 3-amino-1-methyl-1,2,4-triazole as found in compound **6** as an effective amide replacement at the 4-position of the benzopyran.

References and Footnotes

1. Evans, J. M. and Stemp, G. *Chemistry in Britain.***1991**, 439.
2. Evans, J. M. and Longman, S. D. Potassium Channel Activators. *Annual Reports in Medicinal Chemistry;* Bristol, J. A., Ed.; Academic Press; San Diego, 1991; Vol 26, 73-82.
3. Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G. and Willcocks, K. *J. Med. Chem.* **1986**, *29*, 2194.
4. Burrell, G.; Evans, J. M.; Hicks, F. and Stemp, G. *BioMed. Chem. Letts;* **1993**, 999.
5. Cooper, D. G.; Young, R. C.; Durant, G. J. and Ganellin, C. R. Histamine Receptors. *Comprehensive Medicinal Chemistry: The Rational Design, Mechanistic Study and Therapeutic Application of Chemical Compounds;* Hansch, C.; Sammes, P. G. and Taylor, J. B., Eds.; Pergamon Press, Oxford, 1990, Vol 3, 323-421.
6. Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsworth, H. J.; Wyman, P. A. *J. Med. Chem.* **1991**, *34*, 2726.
7. ^1H and ^{13}C Nmr spectra were recorded at 270 MHz and 67.9 MHz, respectively, in DMSO-d6 as solvent. Compound **5**: ^1H: δ 1.25 (s, 3H), 1.41 (s, 3H), 3.33 (s, 3H), 3.67 (dd, J = 5, 11 Hz, 1H), 4.68 (dd, J = 8, 11 Hz, 1H [H-4]), 4.92 (s, 2H), 5.84 (d, J = 5 Hz, 1H), 6.66 (d, J = 8 Hz, 1H), 6.92 (d, J = 9 Hz), 7.60 (m, 2H); ^{13}C: δ 18.7, 26.7, 32.6, 53.3, 71.5, 80.5, 102.7, 118.0, 119.3, 126.3, 132.7, 132.8, 155.0 (coupled to H-4 and N-Me), 156.3, 159.9. Compound **6**: ^1H: δ 1.24 (s, 3H), 1.48 (s, 3H), 3.42 (s, 3H), 3.72 (dd, J = 5, 11 Hz, 1H), 4.52 (dd, J = 8, 11 Hz, 1H [H-4]), 5.68 (d, J = 5 Hz, 1H), 5.95 (d, J = 8 Hz, 1H), 6.10 (s, 2H), 6.97 (d, J = 9 Hz, 1H), 7.64 (dd, J = 2, 9 Hz, 1H), 7.71 (d, J = 2 Hz, 1H); 18.9, 26.7, 32.7, 52.4, 71.5, 80.3, 102.3, 117.6, 119.4, 127.5, 132.1, 133.1, 154.5 (coupled to N-Me), 156.2, 161.2.
8. Guy, H. G.; Dietz, H. F. US Patent 2,430,332, 30 Mar 1945.
9. Algieri, A. A.; Luke, G. M.; Standridge, M. B.; Partyka, R. A.; Crenshaw, R. R. *J. Med. Chem.* **1982**, *25*, 210.
10. Eloy, F.; Lenaars, R. *Helv. Chim. Acta.* **1966**, *49*, 1430.
11. Taylor, S. G. Personal Communication.

(*Received in Belgium* 11 *January* 1994; *accepted* 14 *April* 1994)