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ATP-SENSITIVE POTASSIUM CHANNEL OPENERS: SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITY OF 4-BICYCLYLOXYBENZOPYRANS

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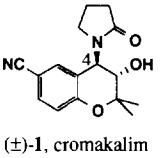
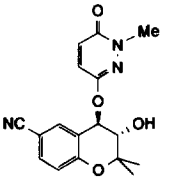
Abstract: Synthesis and hypotensive activity of *trans*-3,4-dihydro-3-hydroxy-4-[(5-oxo-3,4-diazabicyclo[4.1.0]hept-2-en-2-yl)oxy]-2*H*-1-benzopyrans and their congeners are described. Compounds (-)-**9eB** and (-)-**20B** were highly potent ATP-sensitive potassium channel openers.

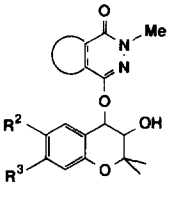
ATP-sensitive potassium channel openers (PCOs) are potent antihypertensive agents acting *via* peripheral vasodilation. Previous studies have produced a lot of compounds with a different framework such as cromakalim ((±)-**1**), pinacidil, aprikalim, diazoxide, nicorandil and minoxidil.[1] Major compounds belong to 4-substituted-3,4-dihydro-2*H*-1-benzopyrans, represented by (±)-**1**. Since the 4-substituents of such compounds are crucial for the activity, most studies have focused on that substituent and consequently produced a variety of the 4-subsituents. However, those substituents are limited to acyclic or monocyclic moieties with few exceptions. Therefore, we are interested in synthesis of dihydrobenzopyrans with a bicyclic moiety at that position: the study would contribute to further understanding of the structural requirement for the 4-substituent, leading to discovery of improved agents. Recently, Bergmann *et al.* have reported a potent PCO coded as EMD 57283 (symakalim, (-)-**2**) which has a unique monocyclic 6-oxo-3-pyridazinyloxy moiety at the 4-position of the benzopyran skeleton.[2] In this paper, we replace this monocyclic pyridazinyloxy moiety with a bicyclic pyridazinyloxy group to produce compound **3** and then assess whether such larger substituents are acceptable or not.



(±)-**1**, cromakalim
(-)-**1**, levcromakalim



(±)-**2**, EMD 56010
(-)-**2**, EMD 57283, symakalim

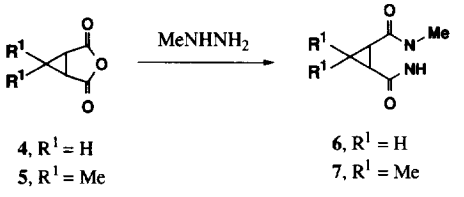


3

Chemistry

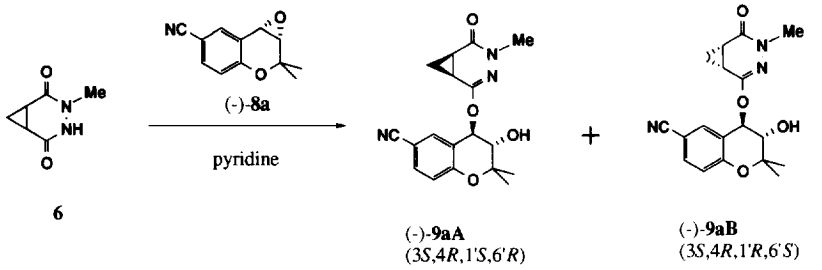
Cyclopropanedicarboxylic anhydride **4**[3] and **5**[4] reacted with methylhydrazine to produce 3,4-diazabicyclo[4.1.0]heptane-2,5-diones (±)-**6** and (±)-**7**, respectively (Scheme 1). Reaction of the compound (±)-**6** or (±)-**7** with racemic 3,4-epoxybenzopyrans (±)-**8a**–(±)-**8e**[5] gave a mixture of two racemates of *trans*-4-[(5-oxo-3,4-diazabicyclo[4.1.0]hept-2-en-2-yl)oxy]-3,4-dihydro-2*H*-1-benzopyran-3-ols **9a**–**9e** and **10**, which were separated by column chromatography to produce racemates A ((±)-**9aA**–(±)-**9eA** and (±)-**10A** with a higher Rf value on TLC) and racemates B ((±)-**9aB**–(±)-**9eB** and (±)-**10B** with a lower Rf value), respectively.

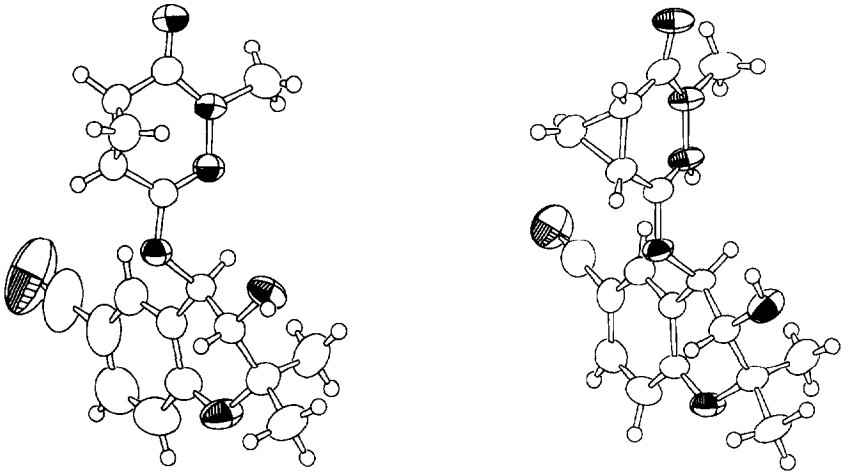
Scheme 1



compound	R^1	R^2	R^3	R^4
(±)-**9aA,B**	H	CN	H	H
(±)-**9bA,B**	H	NO_2	H	H
(±)-**9cA,B**	H	C_2F_5	H	H
(±)-**9dA,B**	H	H	NO_2	H
(±)-**9eA,B**	H	CN	H	Me
(±)-**10A,B**	Me	CN	H	H

Scheme 2





(A) Compound (±)-**9aA**
(displaying (3*S*,4*R*,1'*S*,6'*R*)-isomer only)

(B) Compound (±)-**9aB**
(displaying (3*S*,4*R*,1'*R*,6'*S*)-isomer only)

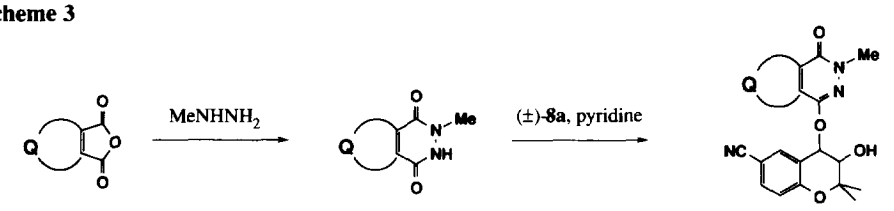
Figure 1. X-ray crystal structure showing configurations of compounds (±)-**9aA** and (±)-**9aB**

Racemates (±)-**9cB** and (±)-**9eB** were further resolved using chiral HPLC (CHIRALPAK™ AD, Daicel Chemical Industries, Co. Ltd.) to give optically pure enantiomers (+)-**9cB** / (-)-**9cB** and (+)-**9eB** / (-)-**9eB**, respectively. With use of optically active epoxide (-)-**8a**,[6] chiral products (-)-**9aA** (3*S*, 4*R*, 1'*S*, 6'*R*) and (-)-**9aB** (3*S*, 4*R*, 1'*R*, 6'*S*) were obtained by a similar reaction (Scheme 2).

The X-ray crystallographic analysis elucidated the configurations of several racemates A and B: configurations of compounds (±)-**9aA** (Figure 1, left) and (±)-**9bA** are (3*S*,4*R*,1'*S*,6'*R*) / (3*R*,4*S*,1'*R*,6'*S*), and conversely those of (±)-**9aB** (Figure 1, right), (±)-**9dB**, (±)-**9eB** and (±)-**10B** are (3*S*,4*R*,1'*R*,6'*S*) / (3*R*,4*S*,1'*S*,6'*R*). Enantiomers (-)-**9aA** and (-)-**9aB**, prepared from (-)-**8a**, were therefore assigned as shown in Scheme 2. In addition, the 4-protons of (±)-**9aA**–(±)-**9dA** and (±)-**10A**, observed at 5.61–5.67 ppm, shifted to higher field than those of racemates B by 0.11–0.14 ppm in NMR spectra. Similarly, (±)-**9eA** with a 3-methyl substituent had a higher chemical shift of 4-H (5.74 ppm) than that of (±)-**9eB** (5.83 ppm). Thus, racemates A are characterized by both their chemical shift of 4-H and Rf value higher than those of racemates B.

Reaction of cyclopentenedicarboxylic anhydride **11** with methylhydrazine offered 3,4-diazabicyclo[4.3.0]nona-1(6)-ene-2,5-dione **13**, which reacted with (±)-**8a** to give *trans*-4-[5-oxo-3,4-diazabicyclo[4.3.0]nona-1(6),2-dien-2-yl)oxy]-2*H*-1-benzopyran (±)-**15** (Scheme 3). Similar reaction of (±)-**8a** with phthalazinedione **14** gave *trans*-4-[4-oxo-3,4-dihydrophthalazin-1-yl)oxy]-2*H*-1-benzopyran (±)-**16**.

Scheme 3

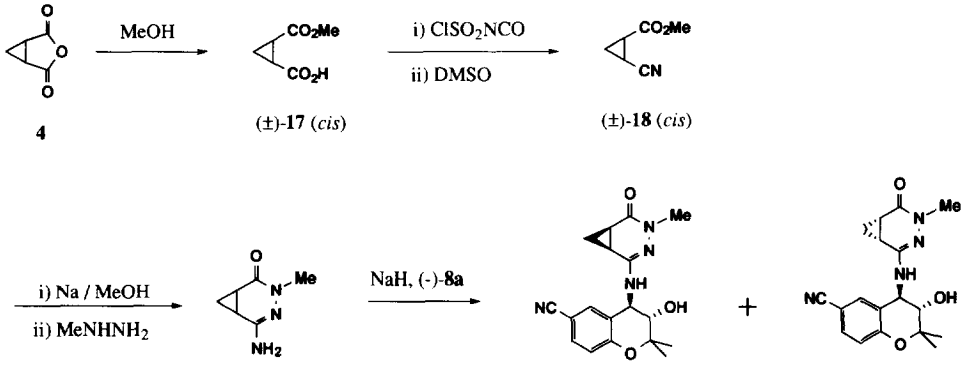


11, Q = -$(CH_2)_3$-
12, Q = -CH=CH-CH=CH-

13, Q = -$(CH_2)_3$-
14, Q = -CH=CH-CH=CH-

(±)-**15**, Q = -$(CH_2)_3$-
(±)-**16**, Q = -CH=CH-CH=CH-

Scheme 4



4

(±)-**17** (*cis*)

(±)-**18** (*cis*)

(±)-**19**

(-)-**20A**
(3*S*,4*R*,1'*S*,6'*R*)

(-)-**20B**
(3*S*,4*R*,1'*R*,6'*S*)

Reaction of racemic methyl *cis*-2-cyanocyclopropanecarboxylate (±)-**18** with methylhydrazine to give 2-amino-3,4-diazabicyclo[4.1.0]hept-2-en-5-one (±)-**19**, which reacted with (-)-**8a** to produce chiral *trans*-4-[(5-oxo-3,4-diazabicyclo[4.1.0]hept-2-en-2-yl)amino]-3,4-dihydro-2*H*-1-benzopyran-3-ols (-)-**20A** (3*S*, 4*R*, 1'*S*, 6'*R*) and (-)-**20B** (3*S*, 4*R*, 1'*R*, 6'*S*) (Scheme 4).

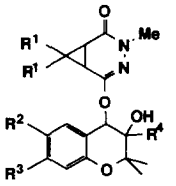
The structures of (-)-**20A** and (-)-**20B** were assumed on the basis of their Rf values and chemical shifts of the 4-H by extrapolating the results of the *O*-bridged compounds into the *NH*-bridged analogues.

Results and discussion

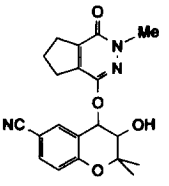
Potassium channel opening activity (^{86}Rb efflux) and antihypertensive activity in spontaneously hypertensive rats (SHRs) after oral administration were determined according to the described methods[7,8] and were shown as $EC_{AUC0.2}$ and ED_{50mmHg}, respectively, (Table 1).

Compound (±)-**9aB** showed potent antihypertensive activity, but not another type racemate (±)-**9aA**, indicating that racemates A of the series of compounds **9a–e** have no or weak activity. In addition, activity of (-)-**9aB** was two-fold potent than that of (±)-**9aB** in both *in vitro* and *in vivo* assays, suggesting that (+)-**9aB** is weakly active or inactive. This result is consistent with the difference in potency between levorotatory **1** (levcromakalim) and the corresponding dextrorotatory enantiomer.[9]

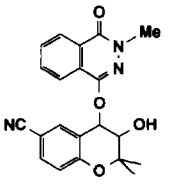
Table 1. Structure and Activity of 4-Heterocyclyloxy-2*H*-1-benzopyrans



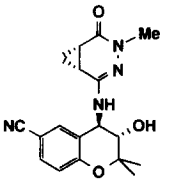
9, **10**



(±)-**15**



(±)-**16**



(-)-**20B**

compound	R^1	R^2	R^3	R^4	configuration[a]	ED_{50mmHg} (mg/kg)	$EC_{AUC0.2}$ (μM)
(±)-**9aA**	H	CN	H	H	racemate A	> 1	NT[b]
(±)-**9aB**	H	CN	H	H	racemate B	0.047	0.39
(-)-**9aB**	H	CN	H	H	(3*S*,4*R*,1'*R*,6'*S*)	0.029	0.18
(±)-**9bB**	H	NO_2	H	H	racemate B	0.049	NT
(-)-**9cB**	H	C_2F_5	H	H	(3*S*,4*R*,1'*R*,6'*S*)	0.047	NT
(±)-**9dB**	H	H	NO_2	H	racemate B	> 0.3	NT
(±)-**9eB**	H	CN	H	Me	racemate B	0.0042	NT
(-)-**9eB**	H	CN	H	Me	(3*S*,4*R*,1'*R*,6'*S*)	0.0023	0.021
(±)-**10B**	Me	CN	H	H	racemate B	> 0.1	NT
(±)-**15**					racemate	0.86	NT
(±)-**16**					racemate	> 10	NT
(-)-**20B**					(3*S*,4*R*,1'*R*,6'*S*)	0.0065	NT
(±)-**1**, cromakalim					racemate	0.31	2.8
(-)-**1**, levcromakalim					(3*S*,4*R*)	0.14	1.6
(±)-**2**, EMD 56010					racemate	0.023	0.25
(-)-**2**, EMD 57283					(3*S*,4*R*)	0.0064	0.16

a) The polar diastereoisomer was shown as racemate B and the less polar diastereoisomer as racemate A on silica gel thin layer chromatography. The relative (or absolute) configurations are not determined except for (±)-**9aA**, (±)-**9aB**, (±)-**9dB**, (±)-**9eB** and (±)-**10B**. b) Not tested.

In a series of 4-[(5-oxo-3,4-diazabicyclo[4.1.0]hept-2-en-2-yl)oxy]-3,4-dihydro-2*H*-1-benzopyran-3-ols, compounds (-)-**9aB**, (±)-**9bB**, (-)-**9cB** and (-)-**9eB** with an electron-withdrawing group at the 6-position of the benzopyran ring exhibited potent activity, but not (±)-**9dB** with such a substituent at the 7-position. These results suggest that the electron-withdrawing group at the 6-position is crucial for the potency. In addition, 6-cyano-3-methylbenzopyran (-)-**9eB** was highly potent, as expected from the report described that introduction of a 3-methyl moiety into **2** increases relaxing activity in arteries.[9] Replacement of the *O*-bridge of (-)-**9aB** with the *NH*-bridge, as (-)-**20B**, increased activity.

Compounds (±)-**15** and (±)-**16** had low potency, suggesting that the size and/or coplanality of the fused ring to the pyridazinyloxy moiety is deleterious for drug-receptor interaction. This speculation also may account for loss of potency in *gem*-dimethylcyclopropane derivative (±)-**10B**.

In conclusion, we obtained highly potent PCOs, (-)-**9eB** and (-)-**20B**, and thus showed that fusion of a cyclopropane moiety to the 4-heterocyclyloxy substituent of benzopyrans was a useful modification method in some PCOs.

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References and notes

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