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4-(2-PYRIDYL)-2,2-DIMETHYLNAPHTHALEN-1-ONES AS NEW POTASSIUM CHANNEL ACTIVATORS WITH INCREASED AIRWAYS SELECTIVITY

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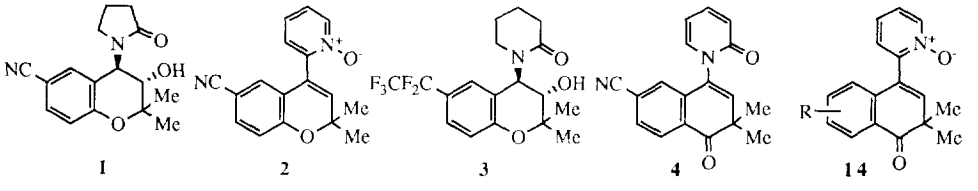
Abstract: A new series of 4-(2-pyridyl)-2,2-dimethylnaphthalen-1-one potassium channel activators has been prepared and their *in vitro*[1] relaxant activities in isolated rat portal vein and guinea-pig tracheal spirals as well as their hypotensive and bronchodilatory effects have been evaluated. Oxidation of the pyridyl nitrogen atom and a double bond between positions 3 and 4 provide compounds with some degree of airways selectivity.

Potassium channel activators are potent smooth muscle relaxants, potentially useful in cardiovascular therapy as antihypertensives and cardioprotectors. Levcromakalim (**1**)[1], which is now undergoing Phase II clinical trials as a long-term antihypertensive, is the most advanced product in this field. Potassium channel activators may also be useful in the treatment of other diseases such as asthma and urinary incontinence[2], provided that tissue-selective compounds with negligible blood pressure lowering effects are obtained. In fact, the disappointing results obtained with levcromakalim in the treatment of human asthma may be due to its lack of selectivity, which precluded the use of higher oral doses due to the appearance of side effects related to its hypotensive effect[3]. Although some compounds such as Ro 31-6930 (**2**)[4] were in clinical trials as antiasthmatic agents for some time, only BRL 55834 (**3**) has been reported[5,6] to be airways-selective after intravenous administration to animals.

We have previously reported on a new family of potassium channel activators, the 1-naphthalenones[7], represented by compound **4**, and as a continuation of our work on this series we now present[8] a new modification of the tetralone framework which has led to the finding of compounds **14** with improved airways selectivity.

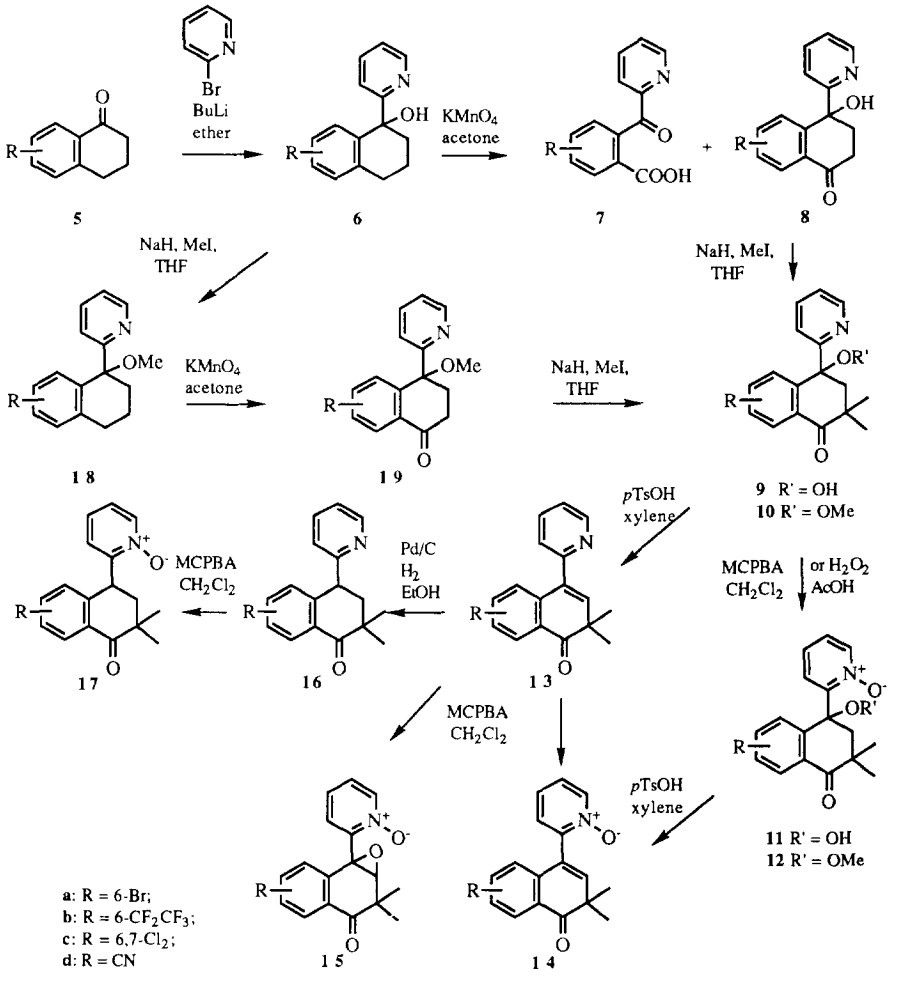


Chemistry

Compounds were prepared according to the procedure described in Scheme I below. Starting 1-tetralones **5a** and **5c** were obtained using published procedures[9], whereas **5b** was prepared treating **5a** with $NaO_2CCF_2CF_3$/CuI/NMP; the 6-cyano substituent was introduced later in the synthesis by conversion of **13a**

to **13d** upon treatment with CuCN/NMP. Reaction of compounds **5** with the 2-anion of pyridine provided good yields (65-75%) of adducts **6**, which were oxidized to tetralones **8** with $KMnO_4$/Acetone/H_2O. In this last step yields were consistently low (15-25%) due to overoxidation to the corresponding carboxylic acids **7** (25-35%), whose formation could not be prevented by changing the reaction conditions or the oxidizing system. Yields of the 6-pentafluoroethyl derivatives were substantially improved (60%) by effecting the oxidation over the methoxyderivative **18b**, thereby reducing the formation of **7b**.

SCHEME I



Treatment of **8** with 3 equivalents of NaH and 2 equivalents of MeI selectively dialkylated the carbon versus the oxygen atom to give alcohol **9**, whereas with excess MeI the trimethylated compounds **10** were obtained. Both **9** and **10** were converted to their N-oxide derivatives **11** and **12** on treatment with *m*-chloroperbenzoic acid in CH_2Cl_2. Dehydration to unsaturated compounds **13** could be effected by heating either the hydroxy (**9**) or methoxy (**10**) compounds in xylene in the presence of *p*-toluenesulfonic acid, with yields between 60-70 %. N-oxides **14** were obtained preferentially by elimination of methoxyderivatives **12**, since oxidation of olefins **13** with *m*-chloroperbenzoic acid provided mixtures of **14** and epoxides **15**. Hydrogenation over Pd/C of **13** provided **16**, which was oxidized to **17**.

Results and discussion

The new compounds were evaluated as smooth muscle relaxants in rat isolated portal vein and guinea-pig tracheal spirals[10] and as oral antihypertensives in spontaneously hypertensive rats (SHR)[10], in comparison with the reference compound levcromakalim **1**[11]. As shown in Table I, the unsaturated (**14**) or unsubstituted (**17**) compounds exhibited high potency in the three tests, while the presence of hydroxy (**11**), methoxy (**12**) or epoxy (**15**) groups at the 4-position of the tetralone nucleus had a detrimental effect on activity. Likewise, the absence of the pyridine N-oxide led to a great loss of potency (**13a** *vs* **14a**).

Preincubation of isolated tracheae with the ATP-dependant potassium channel blocker glibenclamide (1 μM) caused a significant inhibition of the relaxing effect of compounds **14b** and **14d**. These data indicate that a glibenclamide (ATP)-sensitive potassium channel is involved in the activity of compounds **14** as it is in the case of levcromakalim. We have not found any evidence that compounds **14** act on another type of channel, as has been suggested in the case of BRL-55834.[5,6]

Interestingly, the unsaturated compounds **14** showed lower IC_{50} for inhibition of guinea-pig tracheal spirals than for inhibition of NA-induced tone in rat portal vein, a trend contrary to that obtained with levcromakalim and the unsubstituted compound **17** and to what had been previously observed in the tetralone series[7]. These results prompted us to evaluate their *in vivo* selectivity by comparing the maximum inhibition of a methacholine-induced bronchospasm (guinea pig)[12] to the maximum blood pressure decrease (guinea pig and rat)[13], after intravenous administration at four different doses in normotensive anaesthetized animals, in comparison to the reference compound levcromakalim (Table II and Figure 1).

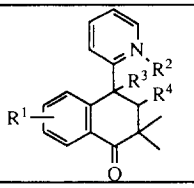
Compounds **14b** and **14d** showed a certain degree of *in vivo* airways selectivity in the anaesthetized guinea-pig. The administration of these compounds at doses up to 0.3 mg/kg, i.v. produced strong protection against methacholine induced bronchospasm (70-90%) with ED_{50} values (dose providing a 50% inhibition of methacholine induced bronchospasm) of 36.0 and 30.3 μg/kg, respectively. They showed much less effect on blood pressure in the same species, with ED_{25} values (dose providing a 25% decrease in blood pressure) of 87.6 and 64.7 μg/kg, respectively. Compound **14c** was less potent in both tests, but still retained some degree of selectivity, while compound **14a** was less effective and not selective. All compounds **14a-d** showed rapid onset of action and effects lasting more than 30 min (data not shown).

The trend observed with compounds **14b-d** was not seen with levcromakalim (0.03-0.3 mg/kg, i.v), which was about four times less potent in inhibiting the methacholine induced bronchospasm (ED_{50} = 160.2

μg/kg) and whose hypotensive potency (ED_{25} = 7.5 μg/kg) was tenfold higher in the guinea-pig. Higher hypotensive potency of levcromakalim compared to **14b**, **14c**, and **14d** was also observed in rats.

Although compounds **14b-d** have no bronchodilatory dose at which no hypotensive effect is observed, the results described here along with the ones reported for BRL 55834, **3** suggest that it is possible to find potassium channel openers that are selective for the smooth muscle of airways. In order to determine whether or not the selectivity observed with compounds **14b** and **14d** will adequately circumvent their hypotensive effects, as well as to assess their usefulness as bronchodilators, more studies need to be performed.

Table I. Compounds **11-17**.



Comp.	R^1	R^2	R^3	R^4	portal vein relaxation IC_{50}^{ab}μM	tracheal relaxation IC_{50}^{cb}μM	tracheal relaxation IC_{50}^{db}μM	max. fall in BP[e]± SEM, mmHg
11d	6-CN	O	OH	H	NC (30)[f]	7.3	-	NT[g]
12a	6-Br	O	OMe	H	NC (20)[f]	>10	-	NT
13a	6-Br	-	$\Delta_{3,4}$		48	>10	-	NT
14a	6-Br	O	$\Delta_{3,4}$		0.81	0.23	-	53.0±8.3
14b	6-CF_2CF_3	O	$\Delta_{3,4}$		0.59	0.11	2.52	97.5±19.5
14c	6,7-Cl_2	O	$\Delta_{3,4}$		0.47	0.21	-	74.0±41.9
14d	6-CN	O	$\Delta_{3,4}$		0.90	0.20	3.60	53.0±15.2
15a	6-Br	O	Epox.$_{3,4}$		NC (12)[f]	1.7	-	NT
17d	6-CN	O	H	H	0.16	2.5	-	99.5±8.8
1					0.10	0.28	1.5	73.0±11.3

[a]Drug concentration required to inhibit NA-induced contractions in rat portal vein by 50%. [b]Each value is the average of two or more preparations. [c]Drug concentration required to inhibit spontaneous tone of guinea pig isolated tracheal spirals. [d]Ibid in the presence of glibenclamide (1 μM) added to the bath 10 min prior to the beginning of accumulative response. [e]Changes in systolic blood pressure (mean ± SEM) measured at intervals of 1h for 4h after oral administration of 0.1 mg/kg of the compound in groups of four SHR. [f]Not calculated. The percentage of inhibition at 10 μM is shown in parentheses. [g]Not tested.

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Table II. In vivo selectivity evaluation of compounds **14a-d.**

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Comp.	Methacholine induced bronchospasm (guinea pig)[a] ED_{50} (μg/kg) (95% C.I.)	Blood pressure decrease (guinea pig)[b] ED_{25} (μg/kg) (95% C.I.)	Blood pressure decrease (rat)[b] ED_{25} (μg/kg) (95% C.I.)
14a	147.9 (123.4-172.4)	89.1 (76.2-101.9)	87.7 (51.3-124.3)
14b	36.0 (13.2-58.9)	87.6 (78.0-97.2)	776.2 (773.0-779.3)
14c	91.2 (22.9-159.5)	93.3 (77.9-108.7)	79.0 (64.2-93.8)
14d	30.3 (24.8-35.7)	64.7 (55.0-74.4)	79.0 (64.2-93.8)
1	160.2 (132.8-188.1)	7.5 (1.5-13.5)	21.5 (13.9-29.5)

[a]See ref 12. [b]See ref 13.

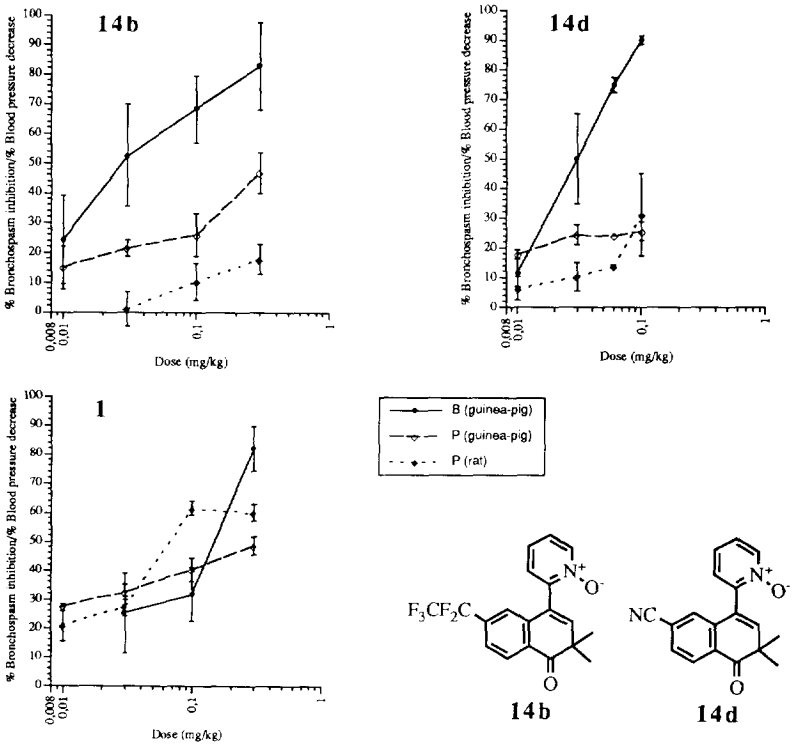

Figure 1. Effects of compounds **14b**, **14d** and levcromakalim, **1** on mean arterial pressure (P) and methacholine-induced bronchospasm (B) in anaesthetized guinea pigs and rats (see refs. 12 and 13). Each data point represents the mean maximum response after *i.v.* acute administration derived from 4-10 experiments. Vertical bars show s.e mean. Airways effects and blood pressure values were measured in different animals.

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10- For a detailed experimental procedure see Ref. 7.

11- Compound **1** was kindly provided by SmithKline Beecham.

12- ***In vivo* inhibition of methacholine induced bronchospasm in anaesthetized guinea pigs.** Male guinea pigs were anaesthetized with urethane (3 g/kg, i.p.). The trachea was cannulated and the animals were paralyzed with gallamine (10 mg/kg, i.v.) and were then artificially ventilated with a pump set at 10 mL/kg stroke volume and a respiratory rate of 70 inflations/min. Lung resistance was measured by the modified air overflow technique of Konzet & Rössler (where the volume of air not entering the lungs was measured by a flow transducer). A varying dose of methacholine (starting from a low dose of 5 μg/kg and increasing every 5 μg/kg until 20 μg/kg, i.v.) was adjusted in each animal to produce maximal bronchospastic response. The selected dose of methacholine was administered every 10 min as a single bolus, until reproducible bronchospasm was established. Bronchodilator effect was expressed as percentage of inhibition of bronchoconstriction response induced by methacholine after drug administration. Test compounds were administered via jugular vein 10 min before the last agonist challenge. Five animals were used for each data point. The dose providing a 50% inhibition of methacholine induced bronchospasm (ED_{50}) was calculated by linear regression of the dose-response curves. The 95% confidence intervals were estimated from the residual deviation of the same curves.

13- **Changes in blood pressure in anaesthetized guinea pigs and rats.** Male guinea pigs and normotensive rats were anaesthetized with urethane (3 g/kg, i.p.) and sodium pentobarbitone (50 mg/kg, i.p.), respectively. A catheter connected to a pressure transducer was placed in the carotid artery to monitor arterial pressure. Test compounds were injected via femoral vein and their hypotensive effect was calculated as the percentage of maximal variation in mean arterial pressure, according to the following formula: (systolic pressure + diastolic pressure x 2)/3. Four animals were used for each data point. The dose providing a 25% decrease in blood pressure (ED_{25}) was calculated by linear regression of the dose-response curves. The 95% confidence intervals were estimated from the residual deviation of the same curves.

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