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SYNTHESIS AND VASORELAXANT ACTIVITY OF *N*-IMINO-2-(BENZOPYRAN-4-YL)PYRIDINE K+ CHANNEL OPENERS

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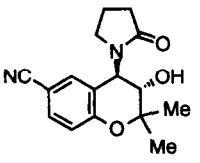
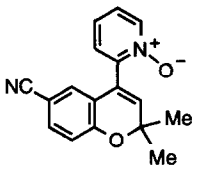
Abstract: The synthesis and vasorelaxant activity of *N*-imino-2-(benzopyran-4-yl)pyridines are described. Some of these compounds displayed potent smooth muscle relaxant activity.

K^+ channel openers such as levcromakalim (**1**) represent a novel class of smooth muscle relaxants.[1] Particular applications include asthma, hypertension, and urinary incontinence.[1] Recently more potent benzopyran-type K^+ channel openers such as Ro 31-6930 (**2**) have appeared. [2]



Levcromakalim (3S, 4R) (**1**)



Ro31-6930 (**2**)

Previously, we constructed a pharmacophore model of K^+ channel openers.[3a] The model suggested that the pyrrolidinone oxygen of levcromakalim may contribute to hydrogen bonding interaction with the receptor. Subsequent analysis with the model revealed that the *N*-oxide of Ro 31-6930 may likewise work as a hydrogen-bond acceptor.[3b] It is known that aromatic amine *N*-imines have chemical and physical similarities, that is, isosterism with aromatic amine *N*-oxides.[4] Thus this work was conducted to know whether the *N*-imines is a bioisoster for the *N*-oxides.[5] In this paper, we report the synthesis and biological activity of *N*-imino-2-(benzopyran-4-yl)pyridines.

Compounds prepared in this study are listed in Table I, and their synthetic routes are outlined in Scheme I and II. Reaction of the benzopyran-4-one **3**[3c] with trifluoromethanesulfonic anhydride and 4-dimethylaminopyridine (DMAP) gave the triflate **4**. The coupling reaction of the triflate **4** with 2-trimethystannylpyridine in the presence of a catalytic amount of $Pd_2(dba)_3(CHCl_3)$, LiCl, and triphenylphosphine in THF gave the pyridine derivative **5**.[6] The pyridine **5** was readily oxidized to the pyridine *N*-oxide **6** by treatment with *m*-chloroperbenzoic acid (*m*-CPBA). The pyridine **5** was allowed to react with *O*-mesitylenesulfonylhydroxylamine (MSH)[7] to give the *N*-aminopyridinium mesitylenesulfonate **7**. In order to obtain stable *N*-imine derivatives,[4] compound **7** was treated with

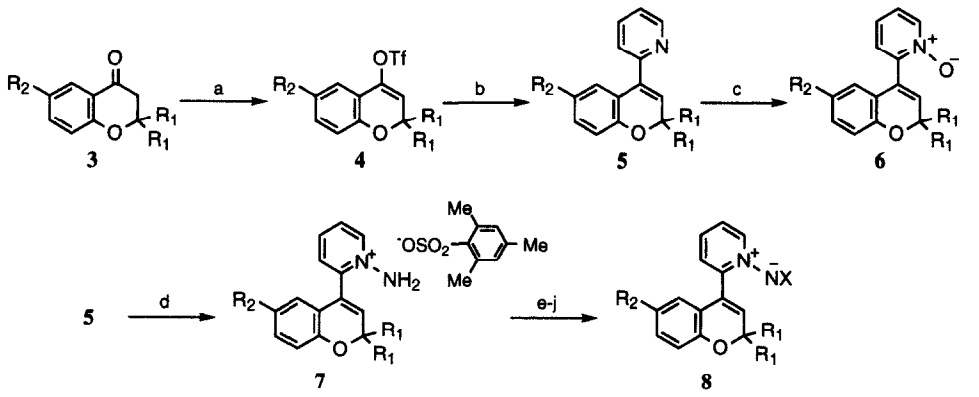
BrCN in the presence of NaH (method A) to afford the expected stable *N*-cyanoimine derivatives **8a-c**. The *N*-imine of **7** (R_1=CH_2F, R_2=NO_2) was also treated with a variety of electrophilic reagents to give the stable *N*-acetyl (**8d**), *N*-benzoyl (**8e**), *N*-methanesulfonyl (**8f**), *N*-nitro (**8g**), and *N*-phenylcarbamoyl (**8h**) derivatives. The 6-perfluoroalkyl *N*-cyanoimino compounds **8i-k** were likewise prepared from the corresponding pyridines **11** (R_2=CF_3, C_2F_5, C_3F_7), which were obtained via several steps from the nitro compound **5a** in the usual ways[8] as shown in Scheme II.

The vasorelaxant activities of compounds were determined by the effects on 30 mM KCl responses in isolated rat aorta and are shown in Table I in comparison with levcromakalim (**1**) and Ro 31-6930 (**2**).

The *N*-cyanoiminopyridines **8a-c** showed vasorelaxant activity almost comparable to or slightly less than the corresponding pyridine *N*-oxides **2** and **6a-b**. On the other hand, replacement of the *N*-cyano group (**8c**) to more bulky electron withdrawing groups remarkably reduced the activity as seen in compounds **8d-h**. These results show that the *N*-cyanoimino group of 2-(benzopyran-4-yl)pyridine K^+ channel opener may be a bioisoster for the *N*-oxide, but size of the imine *N*-substituents seems to be a critical factor with the bulky one being detrimental to the affinity for the receptor. Structure-activity relationships on the 6-substituents revealed that activity seems to vary with the electron withdrawing group with optimum size or hydrophobicity supporting the data of the 6-perfluoroalkyl compounds (**8i-k**) with **8j** showing peak activity.[9] Among compounds prepared, **8j** was found to be approximately 10-fold more potent than the reference compound **2**.

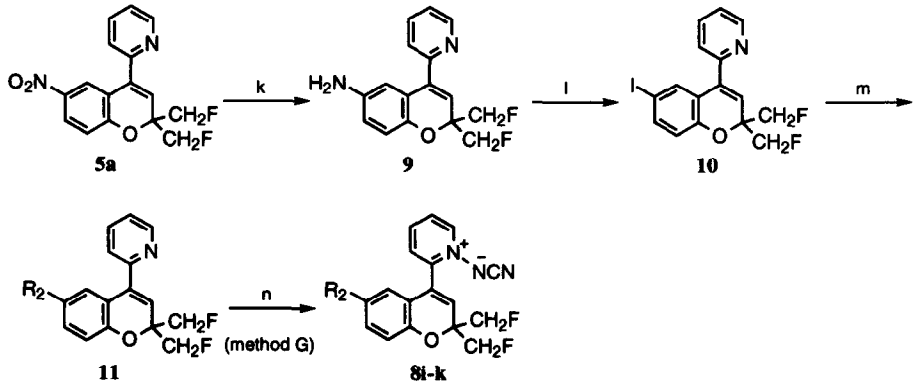
In conclusion, we were able to explain that aromatic amine *N*-imines, an interesting isoelectronic group for aromatic amine *N*-oxides, are a bioisoster for the *N*-oxides in K^+ channel opening action. This also seems to be a first example to show the *N*-imine group playing an apparent role in biological action.

Scheme I



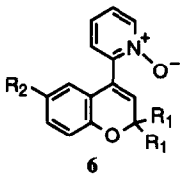
(a) Tf_2O, DMAP, CH_2Cl_2 (b) 2-trimethylstannylpyridine, $Pd_2(dba)_3(CHCl_3)$, PPh_3, LiCl, THF (c) *m*-CPBA, CH_2Cl_2 (d) *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2 (e) BrCN, NaH, DMF (method A) (f) AcCl, Ac_2O (method B) (g) PhCOCl, NaOH (method C) (h) MsCl (mehod D) (i) HNO_3, Ac_2O (method E) (j) PhNCO, CH_2Cl_2 (method F)

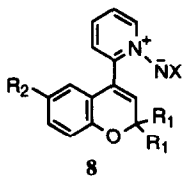
Scheme II



(k) $SnCl_2$, EtOH (l) 1) $NaNO_2$, H_2SO_4 2) KI, H_2O, CH_2Cl_2 (m) R_2COOK, CuI, DMF-toluene
(n) 1) *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2 2) BrCN, NaH, DMF

Table I. Physical properties and vasorelaxant activity of *N*-iminopyridine **8**





Compd.	R_1	R_2	X	method	% yield[a]	mp, °C	Rat aorta pEC50[b]	Rat aorta IA (%)[c]	Rat aorta n[d]
Ro31-6930 (**2**)							7.61±0.03	78.2±8.6	3
6a	CH_2F	CN			36	204-207	7.78±0.10	71.1±5.1	3
6b	CH_2F	NO_2			27	183-184	8.76±0.10	66.3±1.1	3
8a	Me	CN	CN	A	17	229-230	7.01±0.17	63.2±6.7	3
8b	CH_2F	CN	CN	A	26	251-253	7.29±0.11	76.9±6.3	3
8c	CH_2F	NO_2	CN	A	50	212-214	8.34±0.19	72.7±3.1	3
8d	CH_2F	NO_2	COMe	B	68	202-204	<5.0		3
8e	CH_2F	NO_2	COPh	C	26	189-190	<5.0		3
8f	CH_2F	NO_2	SO_2Me	D	14	197-198	5.52±0.09	74.2±0.9	3
8g	CH_2F	NO_2	NO_2	E	10	207-208	6.00±0.14	98.5±2.9	3
8h	CH_2F	NO_2	CONHPh	F	47	103-105	5.04±0.04	89.5±2.0	3
8i	CH_2F	CF_3	CN	G	39	228-230	8.02±0.10	62.3±5.6	3
8j	CH_2F	C_2F_5	CN	G	69	190-191	8.53±0.28	71.9±0.9	3
8k	CH_2F	C_3F_7	CN	G	28	162-163	7.75±0.01	74.6±6.0	3
levcromakalim (**1**)							6.97±0.05	72.5±3.6	8

[a]Satisfactory microanalysis was obtained for all crystalline compounds. [b]Negative logarithm of the molar concentration required to relax rat aorta precontracted with 30 mM KCl by 50% of IA, with ± SEM. See reference 3a for experimental details. [c]Intrinsic activity ± SEM (%). [d]Number of determinations.

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