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Structure-Activity Studies of *N*-Cyano-3-pyridinecarboxamidines and their Amide and Thioamide Congeners

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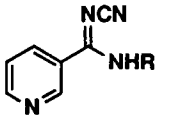
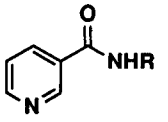
Abstract. The vasorelaxant and cardiac effects of *N*-cyano-3-pyridinecarboxamidine **A** were compared with those of their amide (**B**) or thioamide (**C**) congener. Cyanoamidine was the most potent skeleton in comparison with amide or thioamide, and the activities of these three compounds are more selective for vascular smooth muscle than myocardium.

In the course of our studies to explore a new structural class of potassium channel openers, we designed heteroaromatic cyanoamidine as a common structural feature based on the structures of nicorandil (**4**)[1] and pinacidil[2] and found that *N*-cyano-*N'*-substituted 3-pyridinecarboxamidine **A** had a noticeable character.[3] We first reported that *N*-cyano-*N'*-(2-nitroxyethyl)-3-pyridinecarboxamidine methanesulfonate (**1**; KRN2391) was a novel potassium channel opener.[3a] The *N*-substituent of **1**, *i.e.*, 2-nitroxyethyl, was thought to play an important role not only for a nitrate action but also for a potassium channel opening action. We next investigated to optimize the vasoactivity of cyanoamidine without a nitroxyl group, and found that a phenethyl or a 2-(2-chlorophenyl)ethyl group was effective as a *N*-substituent.[3b] *N*-Cyano-*N'*-phenethyl-3-pyridinecarboxamidine (**2**) and *N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-3-pyridinecarboxamidine (**3**) showed good vasodilating abilities based on a potassium channel opening action. These results revealed that a nitroxyl moiety was not essential to show potassium channel opening property of *N*-cyano-3-pyridinecarboxamidines.



Cyanoamidine (A)



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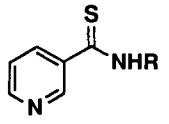
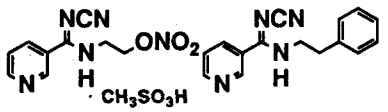
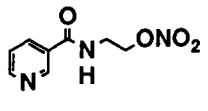


Thioamide (C)



KRN2391 (1) **2** **3**

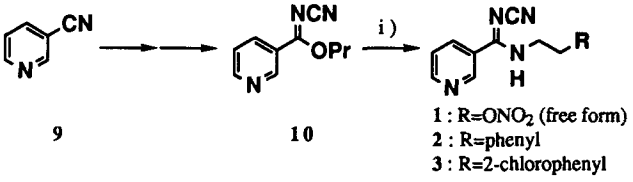


Nicorandil (4)

In this paper, we focused our attention to the structure-activity relationship of *N*-cyano-*N'*-substituted 3-pyridinecarboxamidine **A** *versus* their amide (**B**) and thioamide (**C**) congeners on

the vasodilating, chronotropic, and inotropic effects. *N*-Substituents were fixed to 2-nitroxyethyl, phenethyl, and 2-(2-chlorophenyl)ethyl groups, respectively. We first compared vasodilating activities of these compounds with their antagonism of 25 mM KCl-induced contraction in isolated rat aorta. Next, the chronotropic and inotropic effects were also examined using isolated guinea-pig right and left atria, respectively.

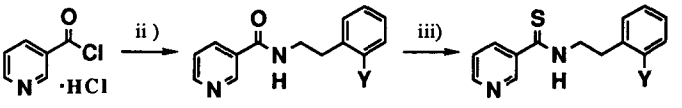
Chart 1



9 10

1 : R=ONO_2 (free form)
2 : R=phenyl
3 : R=2-chlorophenyl

Chart 2

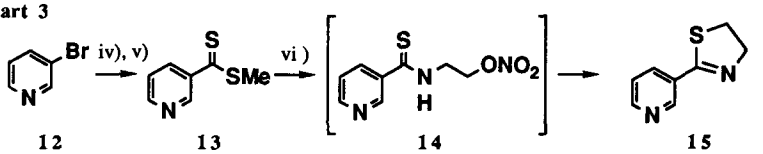


11

5 : Y=H
6 : Y=Cl

7 : Y=H
8 : Y=Cl

Chart 3



12 13 14 15

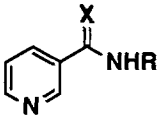
i) $H_2N(CH_2)_2R$, MeOH; ii) 2-(2-Y-phenyl)ethylamine, Et_3N, CH_3CN; iii) Lawesson's reagent, PhMe, reflux; iv) BuLi / ether-hexane, -76 – -70 °C; v) CS_2, -76 °C– r.t. then MeI; vi) $H_2N(CH_2)_2ONO_2$ · HCl, NaOMe / MeOH

Cyanoamidines **1**, **2**, and **3** were prepared from propyl *N*-cyano-3-pyridinecarboximidate (**10**) by treatment with requisite amines according to our reported procedure (Chart 1).[3] Amides **5** and **6** were synthesized by the reaction of nicotinoyl chloride hydrochloride (**11**) and corresponding amines (Compound **5**: mp 77 °C, 60%; compound **6**: syrup, 73%). Treatment of amides **5** and **6** with Lawesson's reagent in refluxing toluene afforded thioamides **7** and **8**, respectively (Compound **7**: mp 106–109 °C, 42%; compound **8**: mp 90 °C, 49%) (Chart 2).[4] Attempts to make **14**, the thioamide analogue of nicorandil (**4**), were failed. We have previously reported that **4** could not be transformed to the corresponding thioamide **14** by treatment with Lawesson's reagent.[3a] In this study, we tried to prepare **14** *via* dithioester **13** (Chart 3). Lithiation of 3-bromopyridine (**12**) with butyl lithium and subsequent addition of carbon disulfide, followed by methyl iodide afforded **13**.[5] Reaction of **13** with 2-nitroxyethylamine could not afford the desired thioamide **14** but 3-(2-thiazolin-2-yl) pyridine (**15**) as a sole product. This result suggested that **13** was first converted to the desired **14**, which spontaneously cyclized to the thiazoline **15** because of its unstability.

The vasodilating effect of compounds **1-8** was studied in isolated rat aorta contracted by 25 mM KCl (see Table).[6] Compounds **1-8** produced a concentration-dependent relaxation. Table shows pD_2 values (-log EC_{50}) calculated by using a concentration-response curve of each compound.[6] Comparing the vasodilating activity of cyanoamidine, amide, and thioamide with the same *N'*-substituents, the order of relaxant potency was cyanoamidine > thioamide > amide. 2-(2-Chlorophenyl)ethyl substituent was more potent than phenethyl counterpart. These results suggested that two parts in the molecule, *i.e.* a group directly attached to pyridine ring and *N*-substituent, play an important role in the vasodilating potency of the 3-pyridine compounds. The importance of *N*-substituent for the vasodilating potency was reported in the previous papers.[3]

The chronotropic and inotropic effects of compounds **1-8** were also examined using isolated guinia-pig right and left atria, respectively (see Table).[7] Cyanoamidines and thioamides produced negative chronotropic and inotropic effects. In contrast, amides had relatively weak action on both atria. In cardiac function, cyanoamidine analogues showed the most potent action as compared with amides or thioamides with the same *N*-substituents. Furthermore, among the three types of 3-pyridine derivatives, *i.e.*, cyanoamidine, amide, and thioamide, the compounds with 2-(2-chlorophenyl)ethyl substituent produced more potent action. These structure-activity relationships in myocardium were similar to those in vascular smooth muscle. However, the concentration of compounds **1-8** to elicit cardiac effects was higher than that to induce their vasorelaxant effects. Therefore, it is considered that compounds **1-8** are more selective for vascular smooth muscle than myocardium.

Table. The pD_2 Values for the Negatrive Chronotropic (Right Atria), Negative Inotropic (Left Atria), and Vasorelaxing (Aorta) Effects



Comp. No.	X	R	pD_2 right atria	pD_2 left atria	pD_2 aorta
1[a)]	NCN	2-nitroxyethyl	$4.42\pm0.20^{***}$	$4.84\pm0.07^{***}$	6.95 ± 0.11
2	NCN	phenethyl	$3.85\pm0.22^{***}$	$4.60\pm0.06^{***}$	6.40 ± 0.12
3	NCN	2-(2-chlorophenyl)ethyl	$5.32\pm0.04^{***}$	$5.51\pm0.41^{***}$	7.57 ± 0.16
4	O	2-nitroxyethyl	<3.5	<3.5	5.62 ± 0.20
5	O	phenethyl	<3.5	<3.5	4.09 ± 0.03
6	O	2-(2-chlorophenyl)ethyl	<3.5	$3.70\pm0.09^{***}$	4.83 ± 0.04
7	S	phenethyl	$4.10\pm0.11^{**}$	$4.39\pm0.19^{*}$	4.95 ± 0.03
8	S	2-(2-chlorophenyl)ethyl	$4.54\pm0.20^{**}$	<4.5	5.64 ± 0.04

* $p<0.05$, ** $P<0.01$, *** $P<0.001$: Significant difference from the values obtained in aorta. See references 4 and 5 for experimental detailes. a) Methanesulfonate.

References and Footnotes

1)(a) Uchida, Y.; Yoshimoto, N.; Murao, S. *Jap. Heart J.* **1978**, *19*, 112. (b) Furukawa, K.; Itoh, T.; Kajiwara, M.; Kitamura, K.; Suzuki, H.; Ito, Y.; Kuriyama, H. *J. Pharmacol. Exp. Ther.* **1981**, *218*, 248.

2)(a) Nielsen, C. K.; Arrigoni-Martelli, E. *J. Med. Chem.* **1978**, *21*, 773. (b) Bray, K. M.; Newgreen, D. T.; Small, R. C.; Southerton, J. S.; Taylor, S. G.; Weir, S. W.; Weston, A. H. *Br. J. Pharmacol.* **1987**, *91*, 421.

3)(a) Nakajima, T.; Izawa, T.; Kashiwabara, T.; Nakajima, S.; Munezuka, Y. *Chem. Pham. Bull.* accepted. (b) Nakajima, T.; Izawa, T.; Kashiwabara, T.; Nakajima, S.; Munezuka, Y. *Chem. Pham. Bull.* accepted.

4) Perregaard, J.; Thomsen, I.; Lawesson, S.O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 321.

5) Yokoyama, M.; Imamoto, T. *Synthesis* **1984**, 797; Malmberg, H.; Nilsson, M. *Tetrahedron* **1986**, *42*, 3981.

6) Kashiwabara, T.; Okada, Y.; Ogawa, N.; Fukushima, H. *Gen. Pharmac.* **1994**, *25*, 487.

7) Jinno, Y.; Kaneta, S.; Ohta, H.; Fukushima, H.; Izawa, T; Ogawa, N. *Asia Pacific J. Pharmacol.* **1993**, *8*, 23.

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