

Design and synthesis of novel 9-substituted-7-aryl-3,4,5,6-tetrahydro-2H-pyrido[4,3-*b*]- and [2,3-*b*]-1,5-oxazocin-6-ones as NK₁ antagonists

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Abstract—Novel 9-substituted-7-aryl-3,4,5,6-tetrahydro-2H-pyrido[4,3-*b*]- and [2,3-*b*]-1,5-oxazocin-6-ones were designed and prepared as part of a search for NK₁ antagonists. Structure–activity relationship studies indicated that the conformational restriction resulting from the incorporation of an oxazocine ring and the presence of a terminal heteroatom on the cyclic amino group at the C-9 position play important roles in NK₁ receptor recognition.

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1. Introduction

Tachykinin, a peptide neurotransmitter that was eventually characterized as the undecapeptide Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂,¹ binds to a series of three neurokinin receptors, NK₁, NK₂, and NK₃, which have selective affinity for substance P (SP), neurokinin A, and neurokinin B, respectively.² Among them, SP³ is known to exhibit a wide variety of biological responses both centrally and peripherally. SP binds to NK₁ receptors and has been implicated in the transmission of pain and stress signals, inflammation, and the contraction of smooth muscle. Therefore, NK₁ antagonists may be useful in the clinic for treatment of a wide range of diseases. Among them, we were interested in the relationship between tachykinin and the activation of micturition-related reflexes,⁴ with a view to possible application in the treatment of pollakiuria and urinary incontinence.

The disclosure by Pfizer of the first two nonpeptide NK₁ antagonists, CP-96345 and CP-99994,⁵ has spurred intensive research in this field. During the last few years, several other structural classes of NK₁ receptor antago-

nists have been reported, such as L-733060,⁶ MK-869,⁷ and TAK-637 (Fig. 1).⁸

A common feature of high-affinity NK₁ antagonists is the presence of an intramolecular face-to-face or edge-to-face π – π interaction between two aromatic rings, which may be important in stabilizing the bioactive conformation.⁹ A conformationally restricted system could increase this interaction, and in TAK-637 this was achieved by introducing an eight-membered ring into the naphthyridine ring. Another important pharmacophore is the bridgehead basic nitrogen, which mediates NK₁ receptor recognition through ion-pair site interaction with the receptor.¹⁰

In our research directed toward novel NK₁ antagonists, we were interested in the 2-[3,5-bis(trifluoromethyl)benzyloxy]-1-phenylethylamine fragment **5** present in the early Merck lead L733060 (**2**), which is the minimum element required for binding to the NK₁ receptor.¹¹ By incorporating this fragment into a pyridine ring, compound **6** (K_B = 25.7 nM) was designed as our starting point. However, in vitro studies in rat microsomes showed that compound **6** was metabolically labile (remaining ratio = 9%). Conversion of the linking group from an oxygen atom to an *N*-methyl carbamoyl group led to compound **7**, which showed a little less NK₁ antagonist activity (K_B = 151 nM) but much better metabolic stability (remaining ratio = 70%) than compound

Keywords: Meisenheimer reaction; Pyrido[4,3-*b*]-1,5-oxazocin-6-one; Pyrido[2,3-*b*]-1,5-oxazocin-6-one.

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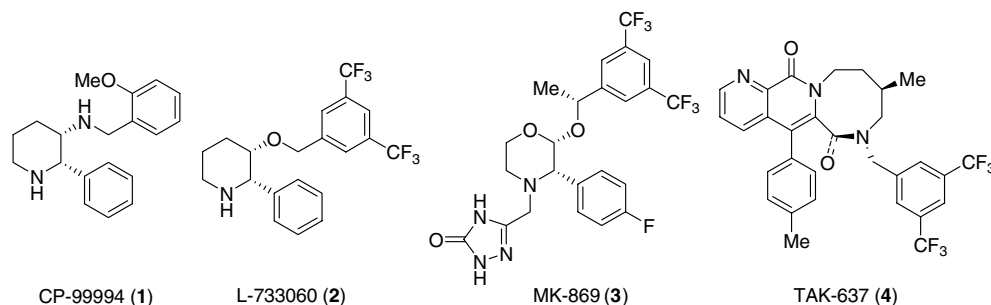
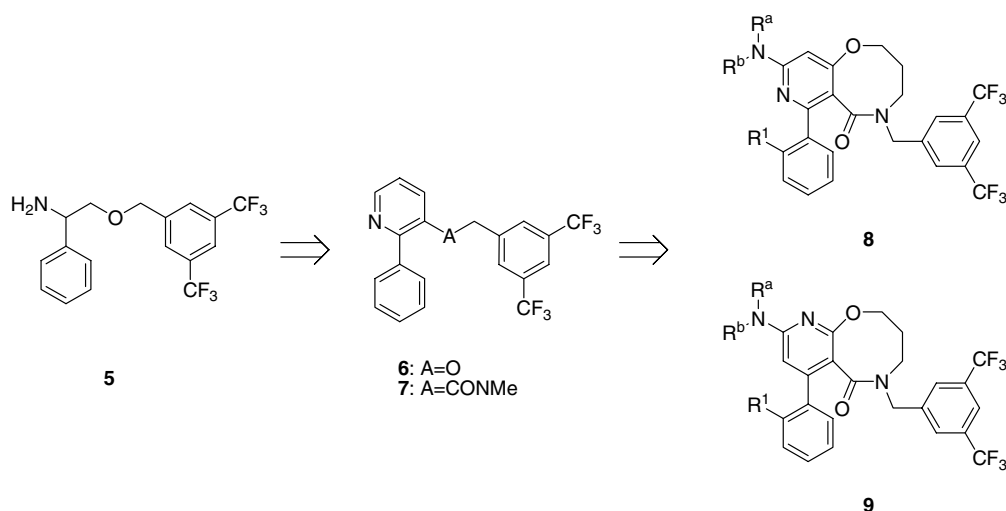


Figure 1.



Scheme 1.

6. Compound **7** is structurally new and simple; therefore, we thought that it would be amenable to the introduction of multiple chemical groupings with the aim of producing novel potent NK₁ antagonists. By incorporating the above mentioned common pharmacophore, an eight-membered ring and a basic amine moiety, into pyridine ring, the general targets **8** and **9** were designed (Scheme 1).

In this paper, we report the molecular design and synthesis of **8** and **9** as new lead compounds for novel NK₁ antagonists.

2. Chemistry

The syntheses of a variety of arylpyridinecarboxamide derivatives are summarized in Schemes 2 and 3.

Scheme 2 illustrates the synthesis of compounds **7a–c**. Treatment of **10** with 3,5-bis(trifluoromethyl)-*N*-methylbenzylamine afforded **11a** and **11b**. Alkoxylation of **11b** with potassium methoxide afforded **12**.¹² The Suzuki coupling reaction of **11a** and **12** with aryl boronic acid took place smoothly to give **7a** and **13**. Formation of chlorides **15a** and **15b** via the Meisenheimer reaction¹³ was accomplished by treatment of **14a** and **14b** with *m*CPBA followed by rearrangement with POCl₃. Cou-

pling of intermediates **15a** and **15b** with morpholine under heat afforded the desired compounds **7b** and **7c**, respectively.

Scheme 3 illustrates the synthesis of compounds **8a,b**, and **9a–i**. Bicyclic intermediates **16a,b**, and **17a–d** were prepared according to the method described previously.¹⁴ Compounds **8a,b**, and **9a–i** were synthesized by treatment of **16a,b**, and **17a–d** via the Meisenheimer reaction, followed by animation with various cyclic amines according to the synthesis of **7b** and **7c**.

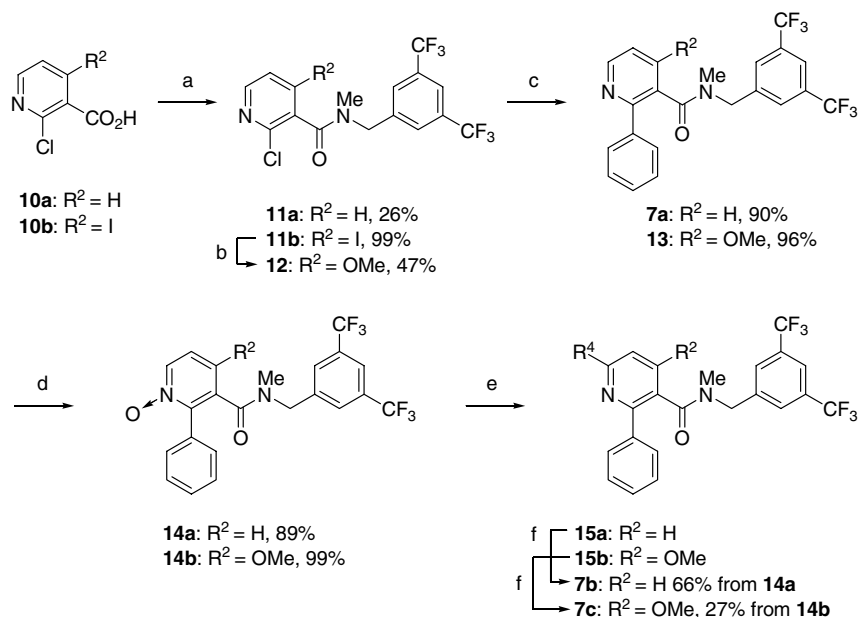
3. Biology

3.1. In vitro studies

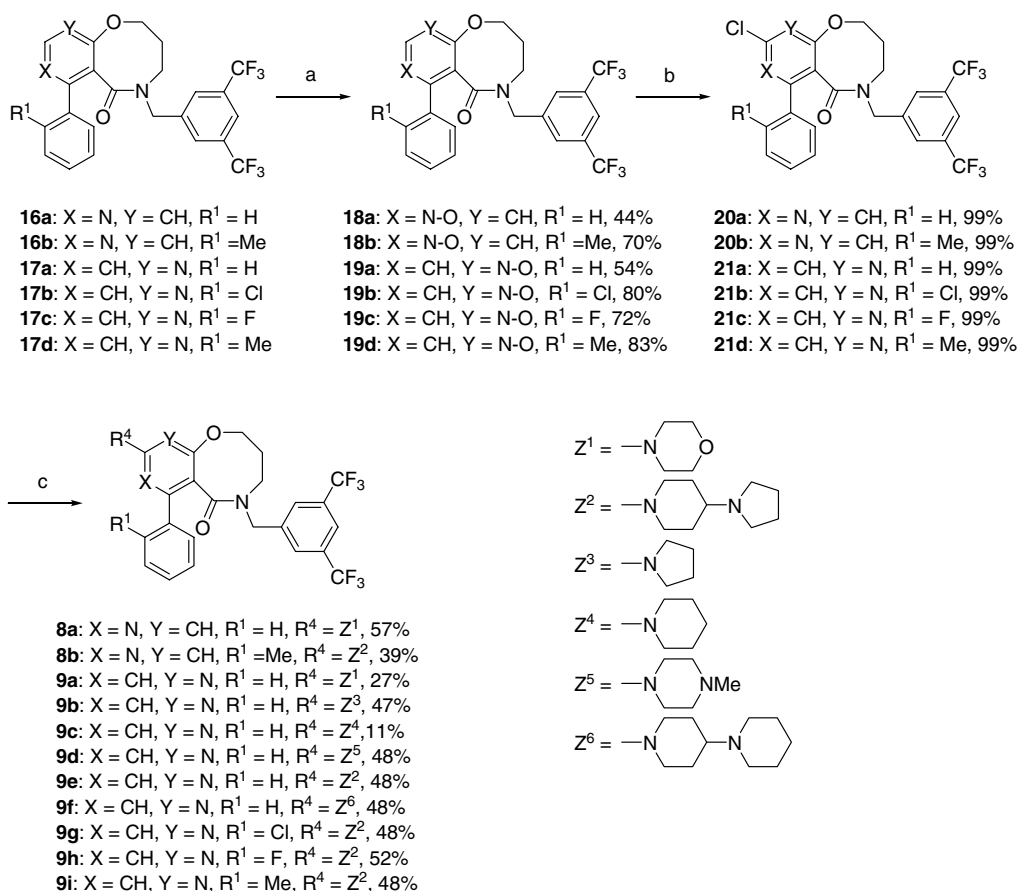
NK₁ receptor antagonist activity toward guinea pig ileum was evaluated by the method previously described¹⁵ with slight modification. The activity was expressed as *K_B* values as determined by the Schild method.¹⁶

3.2. Metabolic stability in rat microsomes

Metabolic stability was expressed as the remaining ratio determined after incubation for 60 min in a shaking water bath at 37 °C.



Scheme 2. Reagents and conditions: (a) (1) $SOCl_2$, DMF, reflux, 2 h; (2) 3,5-bis(trifluoromethyl)-*N*-methylbenzylamine, Et_3N , 0 °C, 1 h then rt, 3 h; (b) MeOK, MeOH, rt, 24 h; (c) phenylboronic acid, 10 mol % $Pd(PPh_3)_4$, 2 M Na_2CO_3 , toluene, dioxane, reflux, 1–5 h; (d) *m*CPBA, CH_2Cl_2 , rt, 24 h; (e) $POCl_3$, reflux, 1–2 h; (f) morpholine, 140–150 °C, 5 h.



Scheme 3. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2 , rt, 24 h; (b) $POCl_3$, reflux, 1 h; (c) R^4H , 150 °C, 5 h.

3.3. In vivo studies

Effective bladder capacity was measured by injection of saline into spinalized guinea pigs according to the method previously described.¹⁷

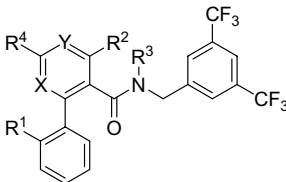
4. Results and discussion

The NK₁ antagonist activity and metabolic stability of the present series of compounds are summarized in Table 1, together with the results for a representative NK₁ antagonist, TAK-637.

The effect of the substituents at the *ortho* and *para* positions on the pyridine ring (R² and R⁴) was examined (7a–c). The NK₁ antagonist activity of 7b, in which R⁴ is a morpholino group, was similar to that of 7a. Compound 7c, carrying an additional methoxy group at R², showed 5 times more potent NK₁ antagonist activity than 7b.

Next, the effect of cyclization between R² and R³ and that of the substituent at the R⁴ position was examined. Compound 16a, which is cyclized between R² and R³, showed NK₁ antagonist activity that was twice as potent as that of 7a. Interestingly, compound 8a, bearing a

Table 1. NK₁ antagonist activity of Arylpyridinecarboxamide derivatives



Compd	X	Y	R ¹	R ²	R ³	R ⁴	NK ₁ antagonist activity ^a K _B (nM)	Metabolic stability ^b remaining ratio (%)
7a	N	CH	H	H	Me	H	151	70
7b	N	CH	H	H	Me		129	100
7c	N	CH	H	OMe	Me		26.3	100
16a	N	CH	H	-O(CH ₂) ₃ -	H	H	69.2	100
8a	N	CH	H	-O(CH ₂) ₃ -		H	2.63	100
9a	CH	N	H	-O(CH ₂) ₃ -		H	2.57	100
9b	CH	N	H	-O(CH ₂) ₃ -		H	13.8	71
9c	CH	N	H	-O(CH ₂) ₃ -		H	13.2	70
9d	CH	N	H	-O(CH ₂) ₃ -		H	1.16	100
9e	CH	N	H	-O(CH ₂) ₃ -		H	0.224	86
9f	CH	N	H	-O(CH ₂) ₃ -		H	2.34	100
9g	CH	N	F	-O(CH ₂) ₃ -		H	0.207	89
9h	CH	N	Cl	-O(CH ₂) ₃ -		H	0.382	100
9i	CH	N	Me	-O(CH ₂) ₃ -		H	0.210	100
8b	N	CH	Me	-O(CH ₂) ₃ -		H	0.339	100
TAK-637							0.270	

^a Compounds were screened for antagonist activity on guinea pig ileum as described in the text.

^b Compounds were screened for metabolic stability on rat microsomes as described in the text.

morpholino group at R⁴, showed NK₁ antagonist activity that was 25 times more potent than that of **16a**. Moreover, the activity of **8a** was 10 times more potent than that of **7c**, which is noncyclized compound. These results indicate that the conformational restriction by the oxazocine ring and introduction of a nitrogen atom is important for NK₁ receptor recognition, as shown in the previous studies of NK₁ antagonists. The NK₁ antagonist activity of **9a**, the regioisomer of the nitrogen atom on the pyridine ring, was similar to that of **8a**.

To explore the effect of the terminal oxygen atom on morpholino moiety, replacement of the cyclic amino group (R⁴) was examined (**9a–f**). A terminal nitrogen atom was favorable (**9d,e,f**). In particular, **9e**, into which a 4-(pyrrolidiny)piperidino group had been introduced, showed excellent NK₁ antagonist activity. These results suggest that the terminal heteroatom on the cyclic amino group at the C-9 position are very important for NK₁ receptor recognition.

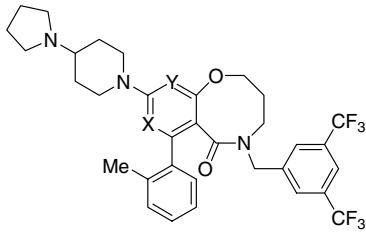
The observed effect of introducing substituents at the *ortho* position on the phenyl ring (R¹) was not significant (**9e,g–i**). On the other hand, the NK₁ antagonist activity of **8b**,¹⁸ the regioisomer of **9i**,^{19,20} was similar to that of **9e**.

As for the metabolic stability, the newly synthesized compounds **7a–c**, **8a,b**, and **9a–i** were considerably improved in comparison with **6**. Above all, **7b,c**, **16a**, **8a,b**, **9a,d,f,h,i** showed good stability. Taking NK₁ antagonist activity and metabolic stability into consideration, **9i** was shown to be the best of all the compounds we synthesized.

We also evaluated the augmentative effect of **9i**, the most effective compound among those tested in the above in vitro assay, and **8b**, the regioisomer of **9i**, on effective bladder capacity of guinea pigs following iv administration (Table 2). Compound **8b** was less potent than TAK-637. In contrast, **9i** showed the greatest in vivo activity (24.2% at a dose of 0.3 mg/kg) of the present series of compounds, although **8b**, **9i**, and TAK-637 showed almost the same in vitro activity. These results suggest that a pyrido[2,3-*b*]-1,5-oxazocine core bearing a 4-(pyrrolidiny)piperidino moiety is favorable for enhanced activity in vivo.

In conclusion, we have succeeded in design and synthesis of novel pyrido-oxazocine derivatives **8** and **9**. The structure–activity relationship study indicated that NK₁ receptor recognition was improved by conformational restriction arising from the incorporation of an oxazocine ring and by the presence of a nitrogen atom at C-9 position. Moreover, it was clarified that a terminal heteroatom on the cyclic amino group at the C-9 position is important for NK₁ receptor recognition. Through these studies, we identified 9-[4-(pyrrolidiny)piperidino]-7-(2-methylphenyl)-3,4,5,6-tetrahydro-2H-pyrido[2,3-*b*]-1,5-oxazocin-6-one (**9i**) as exhibiting highly potent NK₁ antagonist activity in the guinea pig ileum contraction assay and good in vivo activity in increasing the effective bladder capacity of guinea

Table 2. Augmentative effects of **8b** and **9i** on effective bladder capacity in guinea pigs



Compd	X	Y	NK ₁ antagonist activity ^a K _B (nM)	Effective bladder capacity increasing ratio (0.3 mg/kg iv) ^b
8b	N	CH	0.339	3.97%
9i	CH	N	0.210	24.2%
TAK-637			0.270	12.0%

^a Compounds were screened for antagonist activity on guinea pig ileum as described in the text.

^b Effective bladder capacity was measured as the volume of saline injected into spinalized guinea pigs. The capacity-increasing effects of the test compounds were expressed as the ratio of the increase in effective bladder capacity compared with the predrug values.

pigs. Pharmacological studies of **9i** will be reported in due course.

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18. Compound **8b**: ^1H NMR (400 MHz, CDCl_3): δ 1.45–1.85 (6H, m), 1.85–2.08 (5H, m), 2.24 (3H, s), 2.52–2.65 (3H, m), 2.82–2.97 (2H, m), 3.18–3.28 (1H, m), 3.78–3.88 (1H, m), 3.93 (1H, d, $J = 15.3$ Hz), 4.06–4.16 (1H, m), 4.16–4.45 (2H, m), 5.34 (1H, d, $J = 15.3$ Hz), 6.13 (1H, s), 6.92–7.01 (1H, m), 7.01–7.09 (1H, m), 7.16–7.24 (2H, m), 7.58 (2H, s), 7.78 (1H, s). HRMS (EI): calcd for $\text{C}_{34}\text{H}_{36}\text{F}_6\text{N}_4\text{O}_2$ (M^+) 646.2742, found 646.2723.
19. Compound **9i**: This compound exists as a mixture of slowly interconverting conformational isomers (atropisomers). ^1H NMR (400 MHz, CDCl_3): δ 1.50–2.01 (10H, m), 2.04–2.20 (1H, m), 2.20–2.36 (3H, m), 2.54–2.67 (4H, m), 2.88–3.02 (2H, m), 3.11–3.23 (1H, m), 3.63–3.83 (1H, m), 3.94 (0.5H, d, $J = 15.3$ Hz), 3.95 (0.5H, d, $J = 15.3$ Hz), 4.20–4.51 (4H, m), 5.36 (0.5H, d, $J = 15.3$ Hz), 5.39 (0.5H, d, $J = 15.3$ Hz), 6.26 (1H, s), 6.79 (0.5H, d, $J = 7.3$ Hz), 7.02–7.09 (0.5H, br), 7.10–7.16 (0.5H, br), 7.18–7.28 (2H, m), 7.28–7.33 (0.5H, br), 7.53 (2H, s), 7.76 (1H, s). HRMS (EI): calcd for $\text{C}_{34}\text{H}_{36}\text{F}_6\text{N}_4\text{O}_2$ (M^+) 646.2742, found 646.2704.
20. There is a possibility that **9i** is an equilibrating mixture of conformational isomers. In NMR spectroscopy, the signal of the benzylic methylene protons of **9i**¹⁹ was separated as two pairs of doublets (δ 3.94, 3.95, 5.36, 5.39; each 0.5H, $J = 15.3$ Hz) and that of the aryl protons was broadened and separated. These results might indicate that **9i** suffers from restricted rotation about the biaryl bond, which might reflect the stacking conformation desirable for NK_1 receptor recognition.^{8,21} This feature of the NMR spectrum of **9i**, however, was not observed with compounds **8b**.¹⁷
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