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Design and synthesis of novel 9-substituted-7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[4,3-*b*]- and [2,3-*b*]-1,5-oxazocin-6-ones as NK_1 antagonists

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Abstract—Novel 9-substituted-7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[4,3-*b*]- and [2,3-*b*]-1,5-oxazocin-6-ones were designed and prepared as part of a search for NK_1 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 NK_1, receptor recognition.

1. Introduction

Tachykinin, a peptide neurotransmitter that was eventually characterized as the undecapeptide Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2,[1] binds to a series of three neurokinin receptors, NK_1, NK_2, and NK_3, which have selective affinity for substance P (SP), neurokinin A, and neurokinin B, respectively.[2] Among them, SP[3] is known to exhibit a wide variety of biological responses both centrally and peripherally. SP binds to NK_1 receptors and has been implicated in the transmission of pain and stress signals, inflammation, and the contraction of smooth muscle. Therefore, NK_1 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 NK_1 antagonists, CP-96345 and CP-99994,[5] has spurred intensive research in this field. During the last few years, several other structural classes of NK_1 receptor antagonists have been reported, such as L-733060, [6] MK-869,[7] and TAK-637 (Fig. 1).[8]

A common feature of high-affinity NK_1 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 NK_1 receptor recognition through ion-pair site interaction with the receptor.[10]

In our research directed toward novel NK_1 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 NK_1 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 NK_1 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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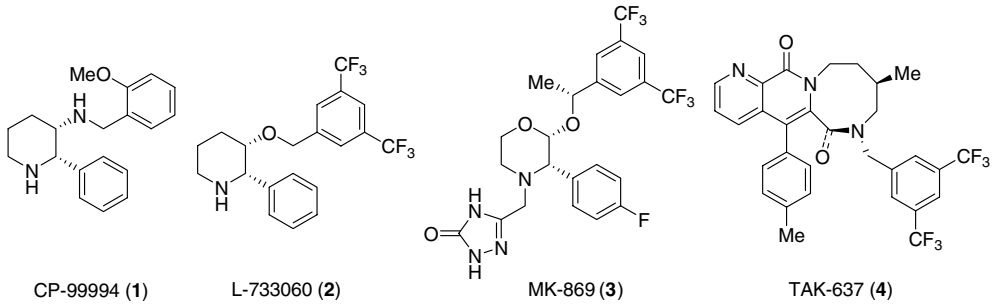
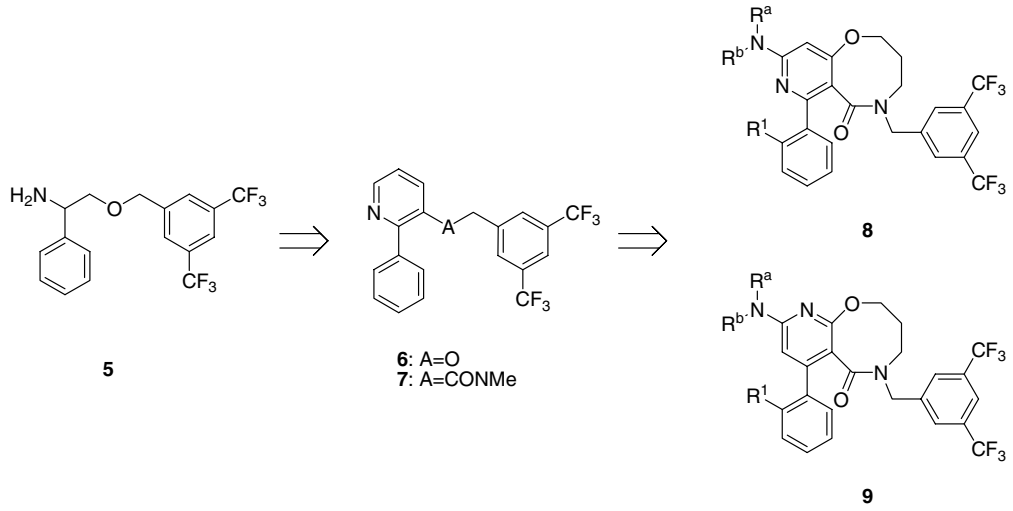


Figure 1.



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 NK_1 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 NK_1 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 reaction[13] was accomplished by treatment of **14a** and **14b** with *m*CPBA followed by rearrangement with $POCl_3$. Coupling 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 animes according to the synthesis of **7b** and **7c**.

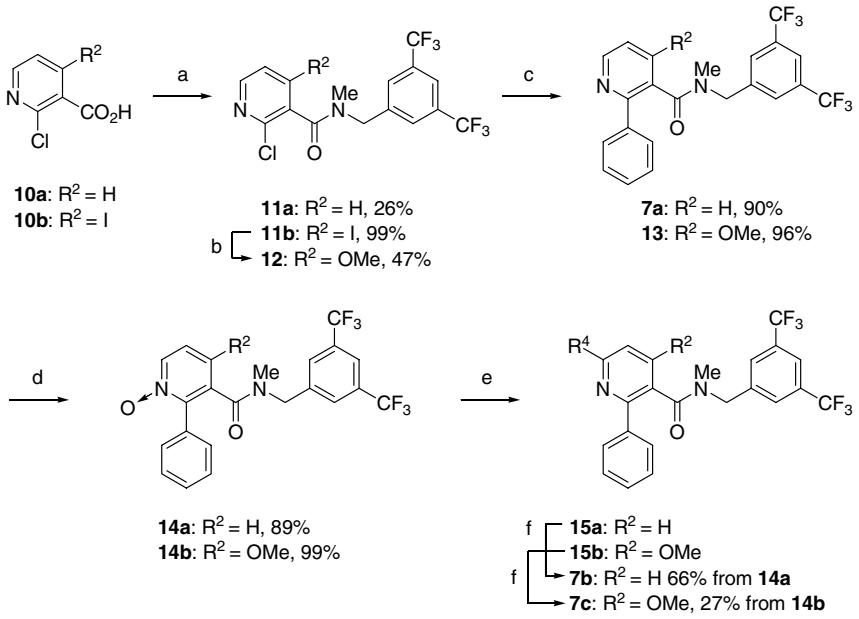
3. Biology

3.1. In vitro studies

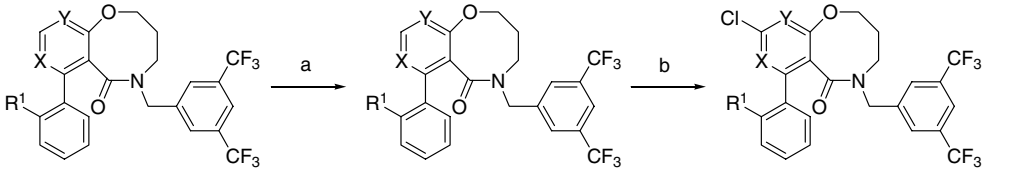
NK_1 receptor antagonist activity toward guinea pig ileum was evaluated by the method previously described[15] with slight modification. The activity was expressed as K_B values as determined by the Schild method.[16]

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.



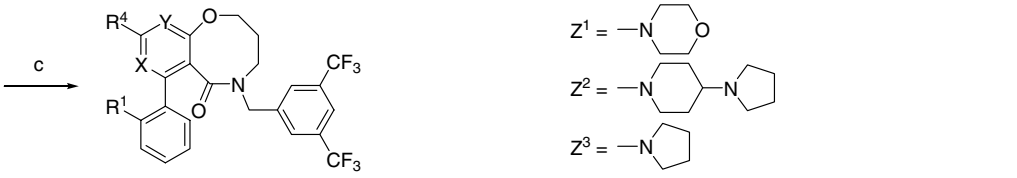
Scheme 2. Reagents and conditions: (a) (1) $SOCl_2$, DMF, reflux, 2 h; (2) 3,5-bis(trifluoromethyl)-*N*-methylbenzylamine, Et_3N, 0 °C, 1 h then rt, 3 h; (b) MeOK, MeOH, rt, 24 h; (c) phenylboronic acid, 10 mol % $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, dioxane, reflux, 1–5 h; (d) *m*CPBA, CH_2Cl_2, rt,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



16a: X = N, Y = CH, R^1 = H
16b: X = N, Y = CH, R^1 =Me
17a: X = CH, Y = N, R^1 = H
17b: X = CH, Y = N, R^1 = Cl
17c: X = CH, Y = N, R^1 = F
17d: X = CH, Y = N, R^1 = Me

18a: X = N-O, Y = CH, R^1 = H, 44%
18b: X = N-O, Y = CH, R^1 =Me, 70%
19a: X = CH, Y = N-O, R^1 = H, 54%
19b: X = CH, Y = N-O, R^1 = Cl, 80%
19c: X = CH, Y = N-O, R^1 = F, 72%
19d: X = CH, Y = N-O, R^1 = Me, 83%

20a: X = N, Y = CH, R^1 = H, 99%
20b: X = N, Y = CH, R^1 = Me, 99%
21a: X = CH, Y = N, R^1 = H, 99%
21b: X = CH, Y = N, R^1 = Cl, 99%
21c: X = CH, Y = N, R^1 = F, 99%
21d: X = CH, Y = N, R^1 = Me, 99%



8a: X = N, Y = CH, R^1 = H, R^4 = Z^1, 57%
8b: X = N, Y = CH, R^1 =Me, R^4 = Z^2, 39%
9a: X = CH, Y = N, R^1 = H, R^4 = Z^1, 27%
9b: X = CH, Y = N, R^1 = H, R^4 = Z^3, 47%
9c: X = CH, Y = N, R^1 = H, R^4 = Z^4,11%
9d: X = CH, Y = N, R^1 = H, R^4 = Z^5, 48%
9e: X = CH, Y = N, R^1 = H, R^4 = Z^2, 48%
9f: X = CH, Y = N, R^1 = H, R^4 = Z^6, 48%
9g: X = CH, Y = N, R^1 = Cl, R^4 = Z^2, 48%
9h: X = CH, Y = N, R^1 = F, R^4 = Z^2, 52%
9i: X = CH, Y = N, R^1 = Me, R^4 = Z^2, 48%

Scheme 3. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, rt, 24 h; (b) $POCl_3$, reflux, 1 h; (c) R^2H, 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]

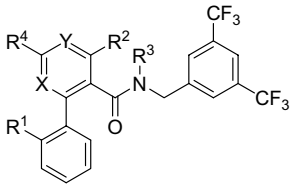
4. Results and discussion

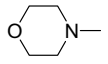
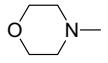
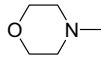
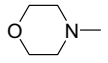
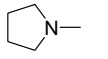
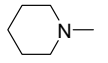
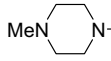
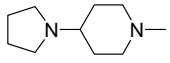
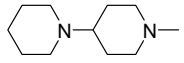
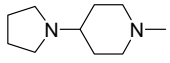
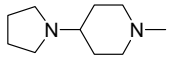
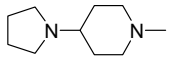
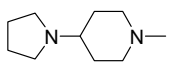
The NK_1 antagonist activity and metabolic stability of the present series of compounds are summarized in Table 1, together with the results for a representative NK_1 antagonist, TAK-637.

The effect of the substituents at the *ortho* and *para* positions on the pyridine ring (R^2 and R^4) was examined (**7a**–**c**). The NK_1 antagonist activity of **7b**, in which R^4 is a morpholino group, was similar to that of **7a**. Compound **7c**, carrying an additional methoxy group at R^2, showed 5 times more potent NK_1 antagonist activity than **7b**.

Next, the effect of cyclization between R^2 and R^3 and that of the substituent at the R^4 position was examined. Compound **16a**, which is cyclized between R^2 and R^3, showed NK_1 antagonist activity that was twice as potent as that of **7a**. Interestingly, compound **8a**, bearing a

Table 1. NK_1 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	69.2	100
8a	N	CH	H	–O(CH_2)$_3$–			2.63	100
9a	CH	N	H	–O(CH_2)$_3$–			2.57	100
9b	CH	N	H	–O(CH_2)$_3$–			13.8	71
9c	CH	N	H	–O(CH_2)$_3$–			13.2	70
9d	CH	N	H	–O(CH_2)$_3$–			1.16	100
9e	CH	N	H	–O(CH_2)$_3$–			0.224	86
9f	CH	N	H	–O(CH_2)$_3$–			2.34	100
9g	CH	N	F	–O(CH_2)$_3$–			0.207	89
9h	CH	N	Cl	–O(CH_2)$_3$–			0.382	100
9i	CH	N	Me	–O(CH_2)$_3$–			0.210	100
8b	N	CH	Me	–O(CH_2)$_3$–			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 R^4, showed NK_1 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 NK_1 receptor recognition, as shown in the previous studies of NK_1 antagonists. The NK_1 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 (R^4) 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 NK_1 antagonist activity. These results suggest that the terminal heteroatom on the cyclic amino group at the C-9 position are very important for NK_1 receptor recognition.

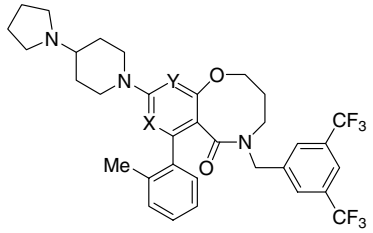
The observed effect of introducing substituents at the *ortho* position on the phenyl ring (R^1) was not significant (**9e**,**g–i**). On the other hand, the NK_1, antagonist activity of **8b**,[18] the regioisomer of **9i**,[19,20] was similar to that of **9e**.

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 NK_1 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*]-l,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 NK_1 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 NK_1 receptor recognition. Through these studies, we identified 9-[4-(pyrrolidiny)piperidino]-7-(2-methylphenyl)-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (**9i**) as exhibiting highly potent NK_1 antagonist activity in the guinea pig ileum contraction assay and good in vivo activity in increasing the effective bladder capacity of guinea pigs. Pharmacological studies of **9i** will be reported in due course.

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.

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18. Compound **8b**: ^{1}H 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 (El): calcd for $C_{34}H_{36}F_6N_4O_2$ (M^+) 646.2742, found 646.2723.
19. Compound **9i**: This compound exists as a mixture of slowly interconverting conformational isomers (atropisomers). ^{1}H 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 $C_{34}H_{36}F_6N_4O_2$ (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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