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Analysis of crucial structural requirements of 2-substituted pyrimido[4,5-*b*][1,5]oxazocines as NK_1 receptor antagonist by axially chiral derivatives

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Abstract—This study aimed to identify the crucial structural features of 2-substituted 8-methylpyrimido[4,5-*b*][1,5]oxazocine derivatives. Axially chiral 8-methylpyrimido[4,5-*b*][1,5]oxazocines bearing a substituent at the C-2 position were synthesized and evaluated as NK_1 antagonists. The results revealed that (*aR*, 8*S*)-stereochemistry and the substituent at the C-2 position are important for NK_1 receptor recognition.

1. Introduction

Neurokinin receptors exist as three subtypes, NK_1, NK_2, and NK_3, which have selective affinities for Substance P (SP), neurokinin A, and neurokinin B, respectively.[1] Among them, SP exhibits a wide variety of biological responses, both centrally and peripherally.[2] SP has been implicated in the transmission of pain and stress signals, inflammation, and the contraction of smooth muscle because it binds to the NK_1 receptor. Therefore, NK_1 antagonists may be efficacious in the treatment of a wide range of diseases. Since Pfizer discovered CP-96345 and CP-99994, the first non-peptide NK_1 antagonists, extensive research among several other structural classes of NK_1 receptor antagonists has been on-going.[3–6]

Most NK_1 antagonists have a common pharmacophore that contains two phenyl rings and a linkage that incorporates either an ester- or amide-moiety.[7] The interactions of these parts with the receptor can be examined using mutagenesis studies.[8] Some potent NK_1 antagonists[9–11] have an eight-membered lactam moiety as an amide-based linkage between the two phenyl rings (Fig. 1). The eight-membered ring system is known to be an effective core region[9] and it fits well with the NK_1 receptor; however, occasionally slow ring flipping occurs causing analytical and pharmaceutical complications.[9]

Takeda et al.[9] reported that introducing an asymmetric methyl group to the eight-membered ring of TAK-637 could resolve the ring flipping problem. As a result, its preparation as a single diastereomer (C-9 and axial) was successful because the axial chirality of the eight-membered lactam carbonyl moiety is triggered by introducing a C-9 asymmetric methyl group. In addition, (*aR*, 9*R*) stereochemistry is important for the compound's activity as an NK_1 antagonist.[9,10]

We have previously reported on pyrimido[4,5-*b*][1,5]oxazocine derivatives[11] such as KRP-103 (**3**), a new structural class of potent and selective NK_1 antagonists. On the basis of the report by Takeda et al.,[9] we synthesized compounds represented by the general structure A , shown in Figure 2. This work led to an analysis of the structural requirements of the pyrimido[4,5-*b*][1,5]oxazocine skeleton in two key regions; (1) the axial chirality of eight-membered lactam carbonyl moiety and (2) the C-2 substituent on the pyrimido[4,5-*b*][1,5]oxazocine ring. Here, we report on the synthesis and structure–activity relationships (SAR) of this new class of compounds focusing on the axially chiral 2-substituted pyrimido[4,5-*b*][1,5]oxazocines.

Keywords: 2-substituted 8-methylpyrimido[4,5-b][1,5]oxazocine; Axial chirality; NK1 antagonist.
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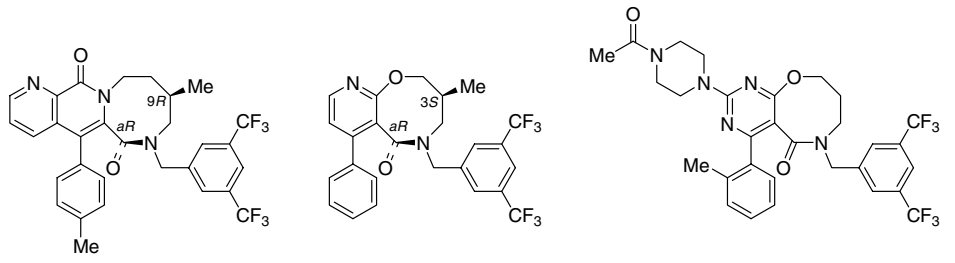


Figure 1. Examples of NK_1 antagonist including eight-membered lactam moiety.

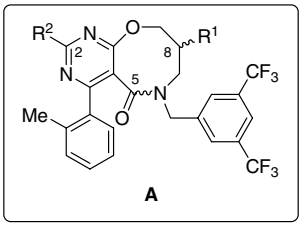


Figure 2. General structure of target compounds.

2. Chemistry

The synthesis of the pyrimido[4,5-*b*][1,5]oxazocine derivatives bearing a functionalized amine moiety at the C-2 position is shown in Scheme 1. Treatment of **4** with thionyl chloride, followed by amide formation with 3-aminopropanol derivatives and subsequent cyclization using potassium carbonate, led to the bicyclic compounds **5**–**7**. Palladium coupling reactions of **5**–**7** with *o*-tolylboronic acid produced biaryl compounds, C-2 methylthio groups of which were oxidized to give methanesulfonyl derivatives **11**–**13**. Sodium borohydride reduction[12] of **11**–**13** gave rise to the C-2 non-substituted derivatives (**14a**–**16a**). Substitution reactions of the C-2 methanesulfonyl group of **11**–**13** with various amine derivatives produced the desired compounds (**14b**–**d**, **15b**–**d**, and **16b**–**d**).

The stereochemistry of axial chirality was revealed by NMR analysis using **15a**. The NOE correlation of **15a** was observed between the C-8 proton and one of the benzylic protons and was similar to that of TAK-637 (Fig. 3).[9b] These results indicate that **15a** has (*aR*, 8*S*) stereochemistry. Therefore, the stereochemistry of **14a**–**d** and **15a**–**d** is (*aS*, 8*R*) and (*aR*, 8*S*), respectively. In addition, the diastereomer of **14a**–**d** or **15a**–**d** could not be determined by the ^{1}H NMR spectrum.

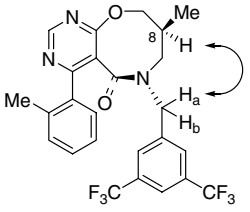
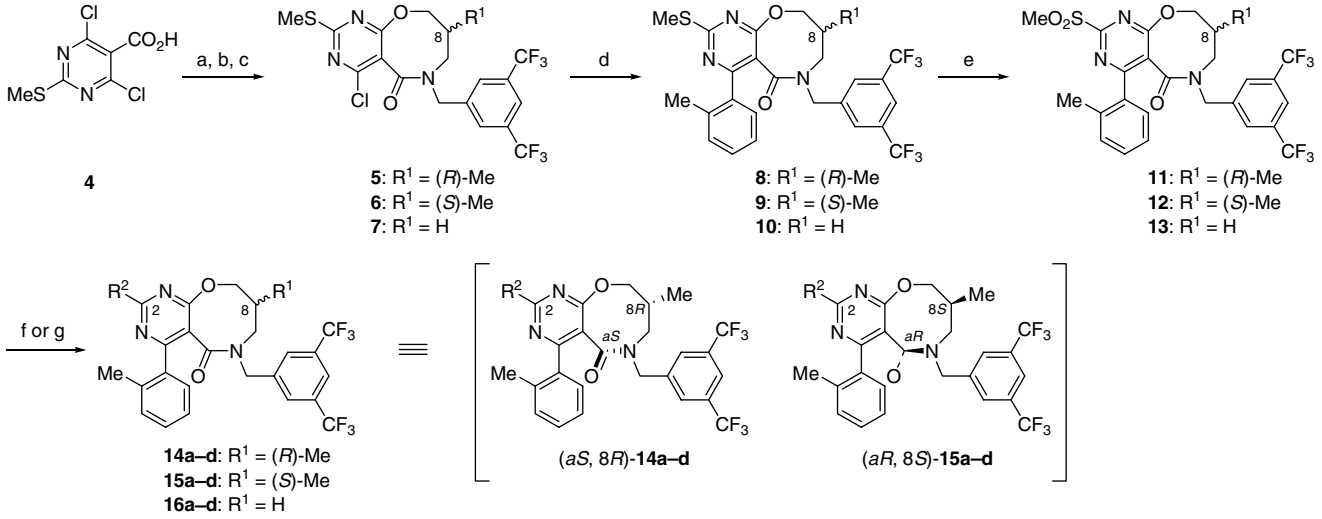


Figure 3. NOE correlation between C-8 proton and benzylic methylene proton of **15a**.



Scheme 1. Reagents: (a) $SOCl_2$; (b) (2*R*)- or (2*S*)-3-[3,5-bis(trifluoromethyl)benzylamino]-2-methyl-1-propanol or 3-[3,5-bis(trifluoromethyl)benzylamino]-1-propanol, Et_3N, THF; (c) K_2CO_3, DMF (53–66%, 3 steps); (d) *o*-tolylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3 (73–95%); (e) *m*CPBA, THF (89–100%); (f) R^3R^4NH, diisopropylethylamine, dioxane (60–89%); (g) $NaBH_4$, $CHCl_3$-MeOH (37–65%).

3. Results and discussion

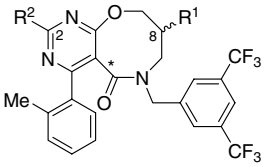
The results of the NK_1 antagonist activity for the newly synthesized compounds **14a–d**, **15a–d**, and **16a**,**b**,**d**, and the representative compound **16c** are shown in Table 1. In addition, the stereochemistry at C-8 and the axial chirality for **14a–d**, **15a–d** are shown.

The compounds bearing the 8*S*-methyl group showed more potent NK_1 antagonist activity than the corresponding compounds bearing the 8*R*-methyl group (**14a–d** vs **15a–d**, respectively). These results indicate that (*aR*, 8*S*)-stereochemistry is important for NK_1 receptor recognition which is similar to that reported by Takeda on pyrido[4,5-*b*]-1,5-oxazocine derivatives.[10]

Interestingly, the NK_1 antagonist activities of **15a–d** are comparable to those of **16a–d** (e.g., **15c**, K_B = 0.139 nM; **16c**, K_B = 0.105 nM). These data indicate that the binding conformation of **16a–d** to the NK_1 receptor is similar to that of **15a–d**, that is, the equilibrium between (*aR*)-**16** and (*aS*)-**16** is completely biased toward (*aR*)-**16** (Fig. 4) which has the same conformation as the (*aR*, 8*S*)-isomers, **15a–d**. In this case, the axially chiral compound is not advantageous from a pharmaceutical perspective. These results are in accord with the NMR studies,[13,14] which indicate that equilibrium between (*aR*)-**16** and (*aS*)-**16** is freely interchangeable at room temperature.

Some other interesting trends are notable in the data. The difference in activities between the (*aR*, 8*S*)- and (*aS*, 8*R*)-isomers depends on the type of substituent at the C-2 position. Those compounds bearing a small substituent at C-2 position, e.g., a hydrogen or dimethylamino group, showed clear differences in their activities (12–120 times) between the (*aR*, 8*S*)- and the (*aS*, 8*R*)-isomers (**14a** vs **15a**, K_B = 162, 12.6 nM, respectively; **14d** vs **15d**, K_B = 52.9, 0.427 nM, respectively). In contrast, in the case of compounds bearing a terminal acetyl group as the 2-substituent, there were only slight differences in the activities between the two (**14c** vs **15c**, K_B = 0.345, 0.139 nM, respectively; **14d** vs **15d**, K_B = 0.545, 0.217 nM, respectively). From these results, the substituent at the C-2 position, such as an acetylpiperazinyl group, was effective in the key region for NK_1 receptor recognition, regardless of the axial chirality of the carbonyl moiety on the eight-membered lactam.

Table 1. NK1 antagonist activity of pyrimido[4,5-*b*][1,5]oxazocine derivatives



Compound	R^1	R^2	Stereo		K_B[a] (nM)
			C-8	Axial (*)	
14a	Me		*R*	*S*	162
15a	Me	H	*S*	*R*	12.6
16a	H		—	—	11.6
14b	Me		*R*	*S*	52.9
15b	Me	$-NMe_2$	*S*	*R*	0.427
16b	H		—	—	0.679
14c	Me		*R*	*S*	0.345
15c	Me	—N NAc	*S*	*R*	0.139
16c	H		—	—	0.105
14d	Me	Me	*R*	*S*	52.9
15d	**Me**	—N NAc	*S*	*R*	0.217
16d	H	Me	—	—	0.679

[a] Data present means of K_B value of guinea pig ileum contraction assay (n = 3–5). Compounds were screened for antagonist activity on guinea pig ileum as described in the text.

4. Conclusion

On the basis of the SAR study, we have clarified the structural requirements for NK_1 antagonists in two key regions: (1) the stereochemistry of the axially chiral eight-membered lactam carbonyl group and (2) the C-2 substituent. The (*aR*, 8*S*)-stereochemistry is important for NK_1 antagonist activity. However, in the case of the pyrimido[4,5-*b*][1,5]oxazocine skeleton, an axially chiral compound is not always pharmaceutically advantageous compared with a non-chiral compound, which can interchange between possible atropisomers. In addition, the substituent at the C-2 position is effective in the key region for NK_1 receptor recognition, regardless of axial chirality. These SAR studies can be used to explore new types of NK_1 receptor antagonists.

5. Experimental

5.1. Chemistry

Melting points were determined with a Yamato MP-500 melting point apparatus and are uncorrected. ^1H NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with

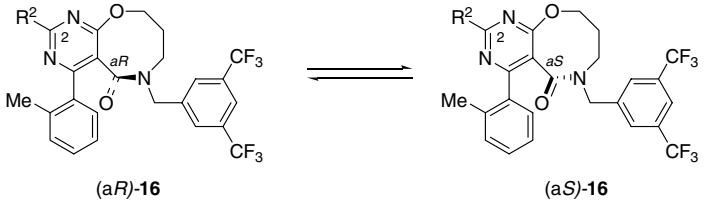


Figure 4. Proposed equilibrium of **16**.

TMS and the solvent peak as internal standards, on a JEOL ECA-400 (400 MHz) spectrometer. Mass spectra (MS) were obtained on a Hitachi M-2000 mass spectrometer. Column chromatography was carried out on Merck silica gel 60. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60F254 plates, and the compounds were visualized by UV illumination (254 nm) or by heating after spraying with phosphomolybdic acid in ethanol. The data for elemental analysis are within ±0.4% of theoretical values and were determined by a Yanaco CHN corder MT-5.

5.1.1. (8*R*)-6-[3,5-Bis(trifluoromethyl)benzyl]-4-chloro-8-methyl-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (5). A mixture of 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid (**4**)[11] (645 mg, 2.70 mmol) and thionyl chloride (5.0 mL) was refluxed for 0.5 h and concentrated. A solution of the residue in THF (5 mL) was added dropwise to a solution of (2*R*)-3-[[3,5-bis(trifluoromethyl)benzyl]amino]-2-methyl-1-propanol[10] (850 mg, 2.70 mmol) and triethylamine (2.0 mL) in THF (20 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 2 h at room temperature. After concentration in vacuo, to a solution of the residue in DMF (10 mL) was added potassium carbonate (750 mg, 5.43 mmol) and the mixture was stirred for 1 h at 80 °C. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 2:1) of the residue gave **5** as a pale yellow foam (717 mg, 53%). $[\alpha]_D^{23} = -33.9°$ (*c* 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, d, J = 6.7 Hz), 2.17–2.29 (1H, m), 2.56 (3H, s), 3.15 (1H, dd, J = 15.3 and 5.5 Hz), 3.35 (1H, dd, J = 15.3 and 13.5 Hz), 4.05 (1H, d, J = 15.3 Hz), 4.21 (1H, dd, J = 13.4 and 2.4 Hz), 4.59 (1H, dd, J = 13.4 and 1.8 Hz), 5.61 (1H, d, J = 15.3 Hz), 7.83 (3H, s). HRMS (EI) for $C_{19}H_{16}ClF_6N_3O_2S$ (M^+): calcd, 499.0556; found, 499.0592. Anal. Calcd for $C_{19}H_{16}ClF_6N_3O_2S$: C, 45.65; H, 3.23; N, 8.41. Found: C, 45.27; H, 3.04; N, 8.36.

5.1.2. (8*S*)-6-[3,5-Bis(trifluoromethyl)benzyl]-4-chloro-8-methyl-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1, 5]oxazocin-5-one (6). The compound **6** (1.16 g, 66%) was prepared from **4** (835 mg, 3.49 mmol) and (2*S*)-3-[[3,5-bis(trifluoromethyl)benzyl]amino]-2-methyl-1-propanol[10] (1.10 g, 3.49 mmol) in a manner similar to that described for the preparation of **5**. Pale yellow foam. $[\alpha]_D^{24} = +36.8°$ (*c* 1.02, $CHCl_3$). ^1H NMR spectrum was identical with that of **5**. HRMS (EI) for $C_{19}H_{16}ClF_6N_3O_2S$ (M^+): calcd, 499.0556; found, 499.0579. Anal. Calcd for $C_{19}H_{16}ClF_6N_3O_2S$: C, 45.65; H, 3.23; N, 8.41. Found: C, 45.47; H, 3.00; N, 8.38.

5.1.3. (8*R*)-6-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-2-methylthio-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (8). To a mixture of **5** (690 mg, 1.38 mmol) and *o*-tolylboronic acid (225 mg, 1.65 mmol) in toluene (4 mL) and 1,4-dioxane (4 mL) were added 2 M Na_2CO_3 (4 mL) and $Pd(PPh_3)_4$ (160 mg, 0.138 mmol), and the mixture was stirred under reflux for 6 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate, then washed with 2 M Na_2CO_3 and brine, and dried over Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (AcOEt/Hexane = 1:1) of the residue gave **8** as a pale yellow foam (581 mg, 76%). $[\alpha]_D^{25} = -9.96°$ (*c* 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, d, J = 6.7 Hz), 2.16–2.29 (1H, m), 2.28 (3H, s), 2.56 (3 H, s), 3.18 (1H, dd, J = 15.3 and 4.9 Hz), 3.45 (1H, dd, J = 14.7 and 12.7 Hz), 3.90 (1H, d, J = 14.7 Hz), 4.19 (1H, dd, J = 13.4 and 3.1 Hz), 4.52 (1H, dd, J = 13.4 and 1.8 Hz), 5.31 (1H, d, J = 14.7 Hz), 6.87–6.93 (1H, m), 6.99–7.05 (1H, m), 7.17–7.25 (2H, m), 7.58 (2H, s), 7.81 (1H, s). HRMS (EI) for $C_{26}H_{23}F_6N_3O_2S$ (M^+): calcd, 555.1415; found, 555.1396. Anal. Calcd for $C_{26}H_{23}F_6N_3O_2S$: C, 56.21; H, 4.17; N, 7.56. Found: C, 56.36; H, 4.14; N, 7.19.

5.1.4. (8*S*)-6-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-2-methylthio-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (9). The compound **9** (950 mg, 73%) was prepared from **6** (1.12 g, 2.24 mmol) and *o*-tolylboronic acid (366 mg, 2.69 mmol) in a manner similar to that described for the preparation of **8**. Pale yellow foam. $[\alpha]_D^{25} = +11.7°$ (*c* 1.08, $CHCl_3$). ^1H NMR spectrum was identical with that of **8**. HRMS (EI) for $C_{26}H_{23}F_6N_3O_2S$ (M^+): calcd, 555.1415; found, 555.1437. Anal. Calcd for $C_{26}H_{23}F_6N_3O_2S$: C, 56.21; H, 4.17; N, 7.56. Found: C, 56.22; H, 4.13; N, 7.41.

5.1.5. (8*R*)-6-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-2-methylsulfonyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (11). To a solution of **8** (560 mg, 1.01 mmol) in THF (3 mL) was added *m*CPBA (435 mg, 2.52 mmol) portionwise under ice cooling. The mixture was stirred for 30 min at 0 °C and then for 2 h at room temperature. The resulting mixture was diluted with ethyl acetate, then washed with saturated sodium hydrogen carbonate. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt 1:1) of the residue gave **11** as a white solid (528 mg, 89%). Mp: 204–205 °C. $[\alpha]_D^{25} = -13.6°$ (*c* 0.680, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, d, J = 7.3 Hz), 2.23 (3H, s), 2.25–2.36 (1H, m), 3.25–3.45 (2H, m), 3.34 (3H, s), 3.94 (1H, d, J = 14.7 Hz), 4.31 (1H, dd, J = 13.5 and 2.4 Hz), 4.63 (1H, dd, J = 13.5 and 1.8 Hz), 5.29 (1H, d, J = 14.7 Hz), 6.86 (1H, d, J = 7.9 Hz), 6.99 (1H, dd, J = 7.9 and 7.9 Hz), 7.21–7.30 (2H, m), 7.57 (2H, s), 7.84 (1H, s). HRMS (ESI^+) for $C_{26}H_{24}F_6N_3O_4S$ (M^++1): calcd, 588.13917; found, 588.14095.

Anal. Calcd for $C_{26}H_{23}F_6N_3O_4S$: C, 53.15; H, 3.95; N, 7.15. Found: C, 52.96; H, 3.76; N, 7.06.

5.1.6. (8*S*)-6-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-2-methylsulfonyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (12). The compound **12** (862 mg, 93%) was prepared from **9** (875 mg, 1.58 mmol) and *m*CPBA (682 mg, 3.95 mmol) in a manner similar to that described for the preparation of **11**. White solid. Mp: 202–205 °C.

$[\alpha]_D^{25} = +16.2°$ (*c* 0.830, $CHCl_3$). ^1H NMR spectrum was identical with that of **11**. HRMS (ESI^+) for

$C_{26}H_{24}F_6N_3O_4S$ (M^++1): calcd, 588.13917; found, 588.13874.

Anal. Calcd for $C_{26}H_{23}F_6N_3O_4S$: C, 53.15; H, 3.95; N, 7.15. Found: C, 53.02; H, 3.78; N, 7.08.

5.1.7. (8*R*)-6-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (14a). To a solution of **11** (70.0 mg, 0.119 mmol) in $CHCl_3$-EtOH (1 mL; 1:1 v/v) was added $NaBH_4$ (23.0 mg, 0.608 mmol) at room temperature and the mixture was stirred at same temperature for 1 h. To the resulting mixture was added water and the mixture was stirred at room temperature for 0.5 h, diluted with ethyl acetate, and then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt/hexane = 2:1) of the residue gave **14a** as a white foam (22.6 mg, 37%). $[\alpha]_D^{26}$ = +13.9° (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d, *J* = 7.3 Hz), 2.17–2.30 (1H, m), 2.21 (3H, s), 3.20 (1H, dd, *J* = 15.3 and 4.9 Hz), 3.42 (1H, dd, *J* = 15.3 and 12.2 Hz), 3.92 (1H, d, *J* = 15.3 Hz), 4.22 (1H, dd, *J* = 13.4 and 3.1 Hz), 4.56 (1H, dd, *J* = 13.5 and 1.8 Hz), 5.33 (1H, d, *J* = 15.3 Hz), 6.92 (1H, d, *J* = 7.9 Hz), 7.00–7.08 (1H, m), 7.20–7.28 (2H, m), 7.56 (2H, s), 7.82 (1H, s), 8.87 (1H, s). HRMS (EI) for $C_{25}H_{21}F_6N_3O_2$ (M^+): calcd, 509.1538; found, 509.1492. Anal. Calcd for $C_{25}H_{21}F_6N_3O_2$: C, 58.94; H, 4.15; N, 8.25. Found: C, 58.64; H, 4.03; N, 8.21.

5.1.8. (8*R*)-6-[3,5-Bis(trifluoromethyl)benzyl]-2-(dimethylamino)-8-methyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (14b). To a solution of **11** (88.2 mg, 0.150 mmol) in THF (0.5 mL) was added dimethylamine (1.0 mL, 2.0 mmol, 2 M solution in methanol) at room temperature and the mixture was stirred at 80 °C for 3 h. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt/hexane = 2:1) of the residue gave **14b** as a white foam (68.0 mg, 82%). $[\alpha]_D^{25}$ = +20.4° (*c* 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, *J* = 6.7 Hz), 2.12–2.24 (1H, m), 2.26 (3H, s), 3.10 (1H, dd, *J* = 15.3 and 4.9 Hz), 3.19 (6H, s), 3.47–3.56 (1H, m), 3.88 (1H, d, *J* = 14.7 Hz), 4.11 (1H, dd, *J* = 13.5 and 3.1 Hz), 4.44 (1H, dd, *J* = 13.5 and 2.4 Hz), 5.32 (1H, d, *J* = 14.7 Hz), 6.90–6.96 (1H, m), 6.98–7.06 (1H, m), 7.16–7.24 (2H, m), 7.56 (2H, s), 7.79 (1H, s). HRMS (FAB^+) for $C_{27}H_{27}F_6N_4O_2$ (M^++1): calcd, 533.2038; found, 533.2004. Anal. Calcd for $C_{27}H_{26}F_6N_4O_2$: C, 58.69; H, 4.74; N, 10.14. Found: C, 58.49; H, 4.67; N, 10.00.

5.1.9. (8*R*)-2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-8-methyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (14c). The compound **14c** (79.7 mg, 84%) was prepared from **11** (88.2 mg, 0.150 mmol) and 1-acetylpiperazine (23.0 mg, 0.179 mmol) in a manner similar to that described for the preparation of **14b**. White foam. $[\alpha]_D^{25}$ = +9.94° (*c* 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, d, *J* = 6.7 Hz), 2.10–2.28 (1H, m), 2,13 (3H, s), 2.25 (3H, s), 3.13 (1H, dd, *J* = 15.3 and 5.5 Hz), 3.45–3.56 (3H, m), 3.61–3.72 (2H, m), 3.80–3.95 (5H, m), 4.13 (1H, dd, *J* = 13.4 and 3.1 Hz), 4.46 (1H, dd, *J* = 13.5 and 2.4 Hz), 5.32 (1H, d, *J* = 15.3 Hz), 6.90–6.96 (1H, m), 6.99–7.07 (1H, m), 7.17–7.28 (2H, m), 7.56 (2H, s), 7.80 (1H, s). HRMS (FAB^+) for $C_{31}H_{32}F_6N_5O_3$ (M^++1): calcd, 636.2409; found, 636.2378. Anal. Calcd for $C_{31}H_{31}F_6N_5O_3 0.3H_2O$: C, 58.09; H, 4.87; N, 10.93. Found: C, 57.93; H, 4.75; N, 10.84.

5.1.10. (8*R*)-2-(4-Acetyl-3,5-dimethyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-8-methyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (14d). The compound **14d** (56.6 mg, 63%) was prepared from **11** (80.0 mg, 0.136 mmol) and 1-acetyl-2,6-dimethylpiperazine (25.5 mg, 0.163 mmol) in a manner similar to that described for the preparation of **14b**. White foam. $[\alpha]_D^{26}$ = +3.99° (*c* 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, d, *J* = 6.7 Hz), 1.20–1.35 (6H, m), 2.10–2.23 (1H, m), 2.14 (3H, s), 2.26 (3H, s), 3.01–3.09 (3H, m), 3.47–3.57 (1H, m), 3.90 (1H, d, *J* = 15.3 Hz), 4.09–4.16 (1H, m), 4.46 (1H, dd, *J* = 13.4 and 1.8 Hz), 4.62–4.79 (3H, m), 5.30 (1H, d, *J* = 15.3 Hz), 6.87–6.96 (1H, m), 6.98–7.08 (1H, m), 7.18–7.26 (2H, m), 7.57 (2H, s), 7.80 (1H, s). HRMS (EI) for $C_{33}H_{35}F_6N_5O_3$ (M^+): calcd, 663.2644; found, 663.2626. Anal. Calcd for $C_{33}H_{35}F_6N_5O_3$ $0.5H_2O$: C, 58.92; H, 5.24; N, 10.41. Found: C, 58.86; H, 5.33; N, 10.06.

5.1.11. (8*S*)-6-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (15a). The compound **15a** (45.7 mg, 60%) was prepared from **12** (88.2 mg, 0.150 mmol) and $NaBH_4$ (29.0 mg, 0.767 mmol) in a manner similar to that described for the preparation of **14a**. White foam. $[\alpha]_D^{26}$ = −11.5° (*c* 1.06, $CHCl_3$). ^{1}H NMR spectrum was identical with that of **14a**. HRMS (EI) for $C_{25}H_{21}F_6N_3O_2$ (M^+): calcd, 509.1538; found, 509.1510. Anal. Calcd for $C_{25}H_{21}F_6N_3O_2$: C, 58.94; H, 4.15; N, 8.25. Found: C, 58.65; H, 4.05; N, 8.14.

5.1.12. (8*S*)-6-[3,5-Bis(trifluoromethyl)benzyl]-2-(dimethylamino)-8-methyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (15b). The compound **15b** (69.2 mg, 83%) was prepared from **12** (88.2 mg, 0.150 mmol) and dimethylamine (1.0 mL, 2.0 mmol, 2 M solution in methanol) in a manner similar to that described for the preparation of **14b**. White solid. Mp: 83–86 °C. $[\alpha]_D^{26}$ = −18.3° (*c* 1.04, $CHCl_3$). ^{1}H NMR spectrum was identical with that of **14b**. HRMS (FAB^+) for $C_{27}H_{27}F_6N_4O_2$ (M^++1): calcd, 533.2038; found, 533.2078. Anal. Calcd for $C_{27}H_{26}F_6N_4O_2$: C, 58.69; H, 4.74; N, 10.14. Found: C, 58.59; H, 4.67; N, 9.95.

5.1.13. (8*S*)-2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-8-methyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (15c). The compound **15c** (85.2 mg, 89%) was prepared from **12** (88.2 mg, 0.150 mmol) and 1-acetylpiperazine (23.0 mg, 0.179 mmol) in a manner similar to that described for the preparation of **14b**. White foam. $[\alpha]_D^{26}$ = −8.51°

(*c* 1.03, $CHCl_3$). ^1H NMR spectrum was identical with that of **14c**. HRMS (FAB^+) for $C_{31}H_{32}F_6N_5O_3$ (M^++1): calcd, 636.2409; found, 636.2412. Anal. Calcd for $C_{31}H_{31}F_6N_5O_3 0.3H_2O$: C, 58.09; H, 4.87; N, 10.93. Found: C, 57.88; H, 4.74; N, 10.81.

5.1.14. (8*S*)-2-(4-Acetyl-3,5-dimethyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-8-methyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (15d). The compound **15d** (60.2 mg, 60%) was prepared from **12** (88.2 mg, 0.150 mmol) and 1-acetyl-2,6-dimethylpiperazine (28.0 mg, 0.179 mmol) in a manner similar to that described for the preparation of **14b**. White foam. $[\alpha]_D^{26} = -2.84°$ (*c* 1.01, $CHCl_3$). ^1H NMR spectrum was identical with that of **14d**. HRMS (EI) for $C_{33}H_{35}F_6N_5O_3$ (M^+): calcd, 663.2644; found, 663.2626. Anal. Calcd for $C_{33}H_{35}F_6N_5O_3$ $0.5H_2O$: C, 58.92; H, 5.24; N, 10.41. Found: C, 58.96; H, 5.38; N, 10.08.

5.1.15. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (16a). The compound **16a** (48.6 mg, 65%) was prepared from **13**[11] (86.0 mg, 0.150 mmol) and $NaBH_4$ (28.5 mg, 0.753 mmol) in a manner similar to that described for the preparation of **14a**. White solid. Mp: 171–172 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.97–2.10 (1H, m), 2.15–2.27 (1H, m), 2.21 (3H, s), 3.35 (1H, ddd, J = 15.3, 5.5 and 1.2 Hz), 3.67–3.78 (1H, m), 3.89 (1H, d, J = 15.3 Hz), 4.43–4.50 (2H, m), 5.32 (1H, d, J = 15.3 Hz), 6.93 (1H, d, J = 7.3 Hz), 7.06 (1H, t, J = 7.3 Hz), 7.20–7.31 (2H, m), 7.56 (2H, s), 7.82 (1H, s), 8.87 (1H, s). HRMS (EI) for $C_{24}H_{19}F_6N_3O_2$ (M^+): calcd, 495.1381; found, 495.1350. Anal. Calcd for $C_{24}H_{19}F_6N_3O_2$: C, 58.18; H, 3.87; N, 8.48. Found: C, 58.06; H, 3.74; N, 8.45.

5.1.16. 6-[3,5-Bis(trifluoromethyl)benzyl]-2-(dimethylamino)-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (16b). The compound **16b** (38.7 mg, 72%) was prepared from **13** (57.4 mg, 0.100 mmol) and dimethylamine (1 mL; 2 M solution in methanol) in a manner similar to that described for the preparation of **14b**. White foam. ^1H NMR (400 MHz, $CDCl_3$) δ 1.90–2.02 (1H, m), 2.07–2.18 (1H, m), 2.27 (3H, s), 3.19 (6H, s), 3.26 (1H, dd, J = 15.3 and 4.3 Hz), 3.75–3.88 (1H, m), 3.84 (1H, d, J = 14.7 Hz), 4.29–4.41 (2H, m), 5.33 (1H, d, J = 14.7 Hz), 6.95 (1H, d, J = 7.3 Hz), 7.02–7.08 (1H, m), 7.19–7.25 (2H, m), 7.57 (2H, s), 7.80 (1H, s). HRMS (ESI^+) for $C_{26}H_{25}F_6N_4O_2$ ($M+H^+$): calcd, 539.18817; found, 539.18740. Anal. Calcd for $C_{26}H_{24}F_6N_4O_2$: C, 57.99; H, 4.49; N, 10.40. Found: C, 57.74; H, 4.57; N, 10.21.

5.1.17. 2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (16c). The compound **16c** (60.7 mg, 65%) was prepared from **13** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **14b**. White solid. Mp: 162–164 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.92–2.04 (1H, m), 2.10–2.20 (1H, m), 2.13 (3H, s), 2.25 (3H, s), 3.30 (1H, dd, J = 15.1 and 4.4 Hz), 3.50 (2H, dd, J = 4.4 and 4.4 Hz), 3.63–3.70 (2H, m), 3.76–3.95 (6H, m), 4.30–4.43 (2H, m), 5.32 (1H, d, J = 15.1 Hz), 6.95 (1H, br d, J = 7.3 Hz), 7.05 (1H, br dd, J = 7.3 and 7.3 Hz), 7.20–7.25 (2H, m), 7.57 (2H, s), 7.81 (1H, s). HRMS (EI) for $C_{30}H_{29}F_6N_5O_3$ (M^+): calcd, 621.217500; found, 621.2192. Anal. Calcd for $C_{30}H_{29}F_6N_5O_3$: C, 57.97; H, 4.70; N, 11.27. Found: C, 57.90; H, 4.70; N, 11.33.

5.1.18. 2-(4-Acetyl-3,5-dimethyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (16d). The compound **16d** (203 mg, 62%) was prepared from **13** (281 mg, 0.500 mmol) and 1-acetyl-2,6-dimethylpiperazine (86.0 mg, 0.550 mmol) in a manner similar to that described for the preparation of **14b**. White solid. Mp: 130–133 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (6H, s), 1.90–2.03 (1H, m), 2.09–2.20 (1H, m), 2.14 (3H, s), 2.27 (3H, s), 3.04–3.16 (2H, m), 3.30 (1H, dd, J = 15.8 and 5.5 Hz), 3.75–3.90 (1H, m), 3.87 (1H, d, J = 14.6 Hz), 4.30–4.42 (2H, m), 4.63–4.80 (2H, m), 5.30 (1H, d, J = 14.6 Hz), 6.90–6.98 (1H, m), 7.02–7.08 (1H, m), 7.20–7.30 (2H, m), 7.58 (2H, s), 7.81 (1H, s). HRMS (FAB^+) for $C_{32}H_{34}F_6N_5O_3$ ($M+H^+$): calcd, 650.2566; found, 650.2588. Anal. Calcd for $C_{32}H_{33}F_6N_5O_3$ $1H_2O$: C, 57.57; H, 4.98; N, 10.49. Found: C, 57.42; H, 5.11; N, 10.10.

5.2. Biology

5.2.1. NK_1 receptor antagonist test[15]. Guinea pigs were stunned by a blow on the head and then exsanguinated from the carotid artery and the ileum was isolated. The ileum was mounted in an organ bath containing Tyrode's solution, which was maintained at 32 °C and gased with 95% O_2 and 5% CO_2. The ileum was subjected to a resting tension of 1 g and allowed to equilibrate for 20 min before the experiment was started. As a control, a concentration-response curve for substance P obtained in the absence of test compounds was used. The NK_1 receptor antagonist activity of each test compound was determined from a concentration-response curve obtained by pretreatment with at least three concentrations of a test compound in DMSO solution for 10 min and subsequently applying substance P in a cumulative manner. The activity was expressed as a K_B value determined by the Schild method.[16]

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