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Amide-based atropisomers in tachykinin NK_1-receptor antagonists: synthesis and antagonistic activity of axially chiral *N*-benzylcarboxamide derivatives of 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one

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Abstract—A series of novel *N*-benzylcarboxamide derivatives of bicyclic compounds, 3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one and 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one, were synthesized by cyclization of *N*-benzyl-2-chloro-*N*-(2-hydroxyethyl)-[and -(3-hydroxypropyl)-] nicotinamides, respectively. Atropisomerism was observed in 5-[3,5-bis(trifluoromethyl)benzyl]-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-ones due to steric hindrance of the carboxamide moiety and restriction of its rotation. Cyclization of *N*-[3,5-bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*S*)-3-hydroxy-2-methylpropyl]-5-methyl-4-phenylnicotinamide gave (3*S*)-5-[3,5-bis(trifluoromethyl)benzyl]-3,8-dimethyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3*b*][1,5]oxazocin-6-one, which exists predominantly in the thermodynamically stable *aR*-conformer in $CDCl_3$. This compound showed excellent NK_1-antagonistic activity with IC_{50} value (in vitro inhibition of [^{125}I]-Bolton–Hunter-substance P binding in human IM-9 cells) of 0.47 nM, which is ca. 200-fold more potent than that of its enantiomer, indicating that the atropisomer chirality affects NK_1-receptor recognition.
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1. Introduction

In our previous papers,[1–4] we described the synthesis of the axially chiral 1,7-naphthyridine-6-carboxamide derivatives, represented by **1** (Scheme 1)[1,2] and TAK-637 (Scheme 2),[3,4] as orally active tachykinin NK_1-receptor antagonists. Because the carboxamide moiety of these compounds exists at the sterically hindered position, rotation around the $-C_{(6)[\text{or }(5a)]}-C(=O)-$ bond is restricted, yielding separable and stable atropisomers.

Compound **1**, which has a *trans*-amide form,[5] was separated into *aR*- and *aS*-atropisomers by preparative high-performance liquid chromatography (HPLC) using a chiral column. They have significant stability in solution, e.g., they were not interconverted in dimethyl sulfoxide (DMSO) at 37 °C for 16 h and underwent racemization only after storage at 50 °C for 6 days. The enantiomeric atropisomers differed in activity at the tachykinin NK_1-receptor, with *aR* isomer being more active (i.e., eutomer) [IC_{50}, nM: *aR*, 0.24; *aS*, 1.4] (Scheme 1).[2]

TAK-637 [(*aR*,9*R*)-**3**], which is an 8-membered cyclic analogue of **1** with *aR* stereochemistry, was formed atropodiastereoselectively by cyclization of the chiral (*R*) methyl intermediate *R*-**2** in preference to the *aS*-isomer [(*aS*,9*R*)-**3**] in a ratio of ca. 98:2. The diastereomerically pure *aR*-form (TAK-637) was obtained by a single recrystallization of the crude product, and the minor *aS*-isomer was isolated from the mother liquor by repeated preparative HPLC (Scheme 2).

The *aR* stereochemistry of TAK-637 was determined by single-crystal X-ray structural analysis,[3,4] which also revealed the *trans*-conformation of the amide bond and a stacking conformation between the $C_{(5)}$-phenyl and the $N_{(7)}$-benzylic phenyl groups. The relative spatial orientation of the $C_{(9)}$-methyl group and the *N*-benzyl group in TAK-637 (*aR*,9*R*) is important for high atropodiastereoselectivity; these two groups are disposed in opposite directions, both in the crystalline form (as observed in the X-ray analysis) and in solution (i.e., the NOE was observed between the $C_{(9)}$-proton and a benzylic methylene proton by NMR spectroscopic studies), whereas the same groups in the minor

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Keywords: Atropisomer; Stereoselective synthesis; Tachykinin NK_1 antagonist; Pyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one; Pyrido[2,3-*b*][1,5]oxazocin-6-one.

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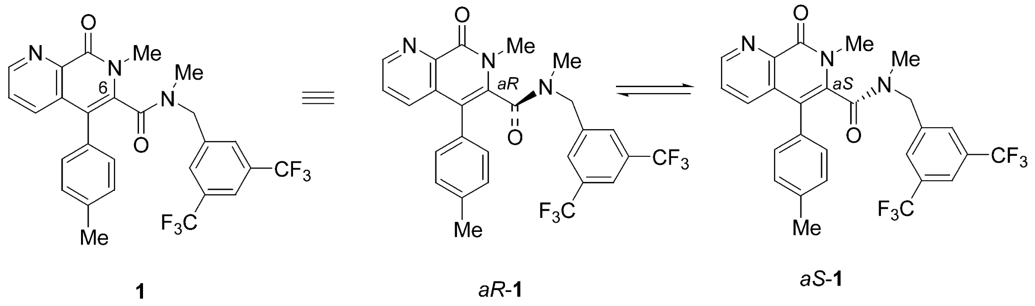
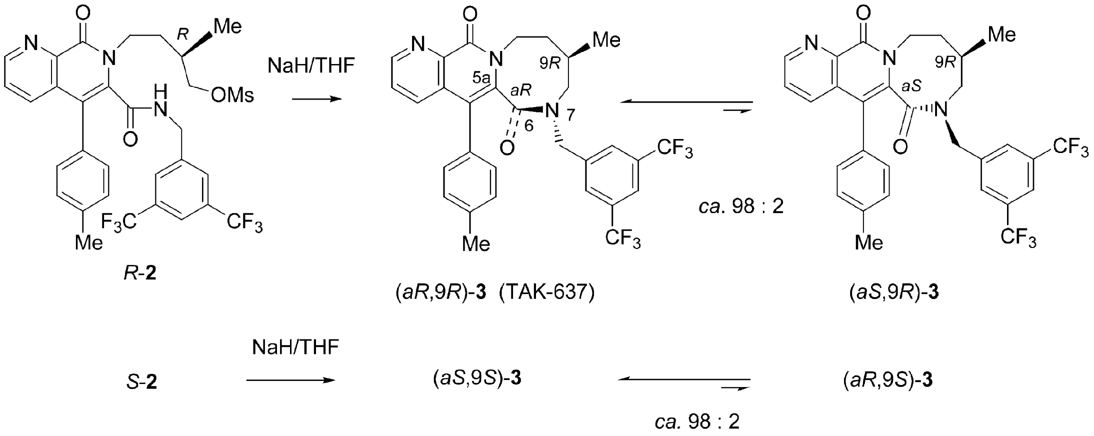


Scheme 1. Atropisomers of **1**.

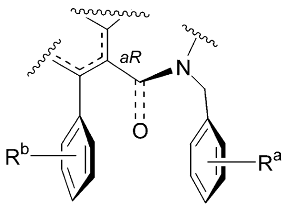


Scheme 2. Atropodiastereoselective formation of **3** from the chiral intermediates (*R*-**2** and *S*-**2**).

isomer [(*aS*,9*R*)-**3**] are shown to be disposed in the same orientation in solution as observed by the NOE between the $C_{(9)}$-methyl protons and a benzylic methylene proton.[4] The repulsion of these groups in (*aS*,9*R*)-**3** may cause steric instability, leading to the preferential formation of the thermodynamically stable atropisomer (*aR*,9*R*)-**3** in the cyclization of the chiral intermediate *R*-**2**. The enantiomers [(*aS*,9*S*)-**3** and (*aR*,9*S*)-**3**] were similarly obtained starting from the enantiomeric *S*-methyl intermediate (*S*-**2**).

The NK_1-antagonistic activity of these stereoisomers [IC_{50}, nM: (*aR*,9*R*)-**3**, 0.45; (*aS*,9*R*)-**3**, 20; (*aS*,9*S*)-**3**, 340; (*aR*,9*S*)-**3**, 8.6] and X-ray analysis of (*aR*,9*R*)-**3** indicate that the pharmacophore of this class antagonists is **A** (Fig. 1), in which the *aR* stereochemistry and the stacking conformation between the two phenyl groups are important for NK_1-receptor binding.[4]

In this paper, we describe the amide-based atropisomerism in the *N*-benzylcarboxamide derivatives of bicyclic 3,4-dihydropyrido[3,2-*f*][1,4] oxazepin-5(2*H*)-one (**4**), 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (**5**) and its chiral derivatives (**6**) using the chemistry developed in our previous studies. Those NK_1-antagonistic activities are also examined to obtain more simplified, bicyclic analogues of TAK-637.

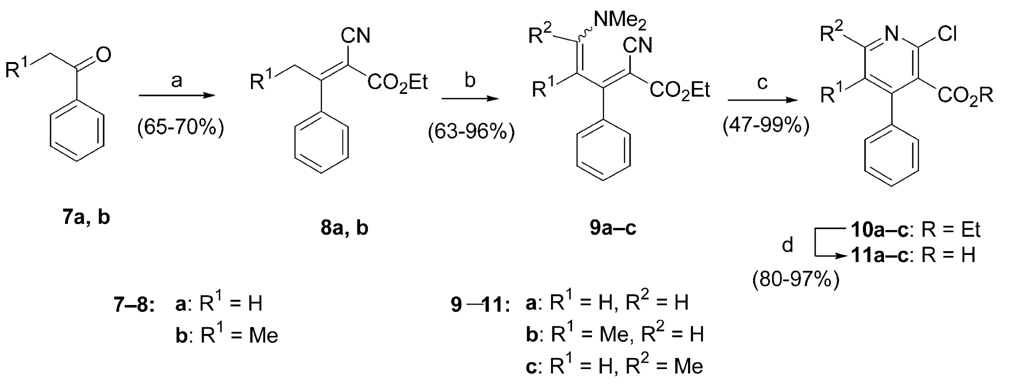


A

Figure 1. Pharmacophore structure (**A**) required for NK_1-receptor recognition.

2. Synthetic chemistry

The synthesis of bicyclic compounds (**4–6**) is outlined in Schemes 3 and 4. Key components are 2-chloro-4-phenyl-3-pyridine carboxylic acids (**11a–c**), which were prepared according to a procedure similar to that previously reported.[6] Thus, commercially available acetophenones (**7a** and **7b**) were condensed with ethyl cyanoacetate, followed by reaction with dimethylformamide dimethyl acetals to afford the enamines (**9a–c**). Formation of the pyridine ring was achieved by reacting the enamines with anhydrous hydrogen chloride to afford ethyl 2-chloro-4-phenylpyridine-3-carboxylates (**10a–c**), which were hydrolyzed to give acids (**11a–c**). Other components (Schemes 3), *N*-3,5-bis(trifluoromethyl) benzylamino-alkanols (**15i–iv**), were prepared from 3,5-bis(trifluoromethyl) benzyl alcohol (**12**) by mesylation, followed by displacement with amino-alkanols (**14i–iv**).[7]Amidation of pyridine carboxylic acids (**11a–c**) (via the acid chloride) with *N*-benzylamino-alkanols (**15i–iv**) followed by intramolecular cyclization using sodium hydride in tetrahydrofuran (THF) under reflux afforded the desired 7- and 8-membered cyclic compounds (**4–6**). The stereochemical features of the bicyclic compounds are described in Section 4.


a
(65-70%)
b
(63-96%)
c
(47-99%)
d
(80-97%)
7a, b
8a, b
9a–c
10a–c: R = Et
11a–c: R = H
7–8: a: R1 = H
b: R1 = Me
9–11: a: R1 = H, R2 = H
b: R1 = Me, R2 = H
c: R1 = H, R2 = Me

Scheme 3. Preparation of 2-chloro-3-phenyl-2-carboxylic acids **11a–c**. Reagents: (a) $NCCH_2CO_2Et$, AcONa/AcOH/PhH (azeotropic); (b) for **9a** and **9b**: $Me_2NCH(OMe)_2$, rt, for **9c**: $Me_2NCMe(OMe)_2$, rt; (c) 4 N-HCL in AcOEt; (d) 4 N-NaOH(aq)/EtOH.

3. Biology

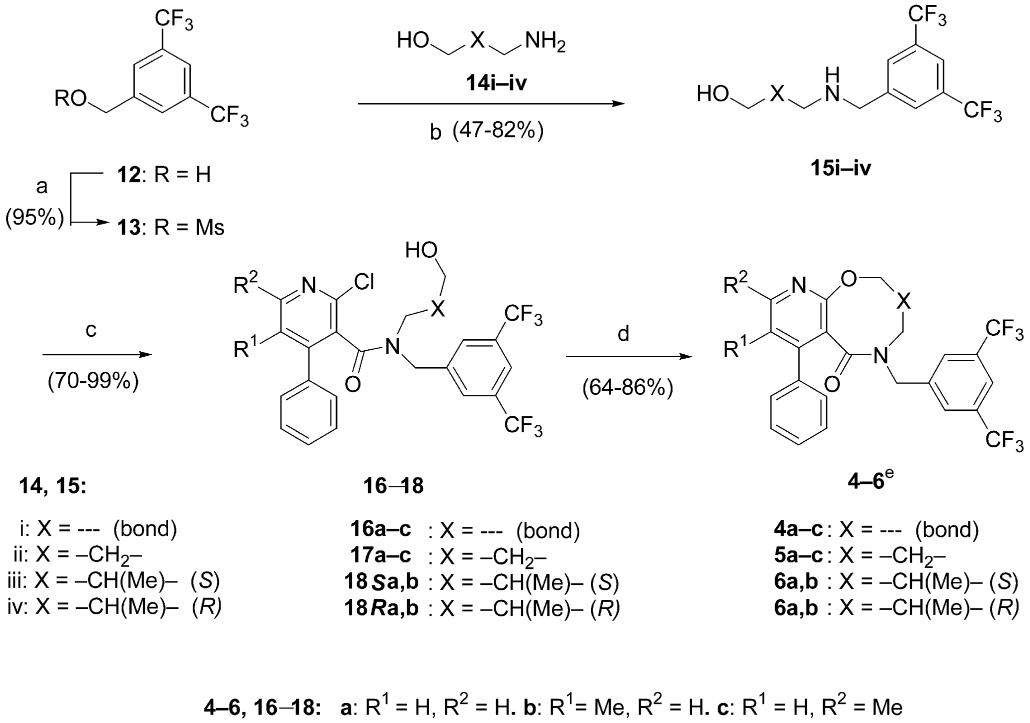
The compounds prepared were evaluated in vitro for inhibition of [^{125}I]-Bolton–Hunter (BH)-substance P binding in human IM-9 cells.[1,8]

4. Results and discussion

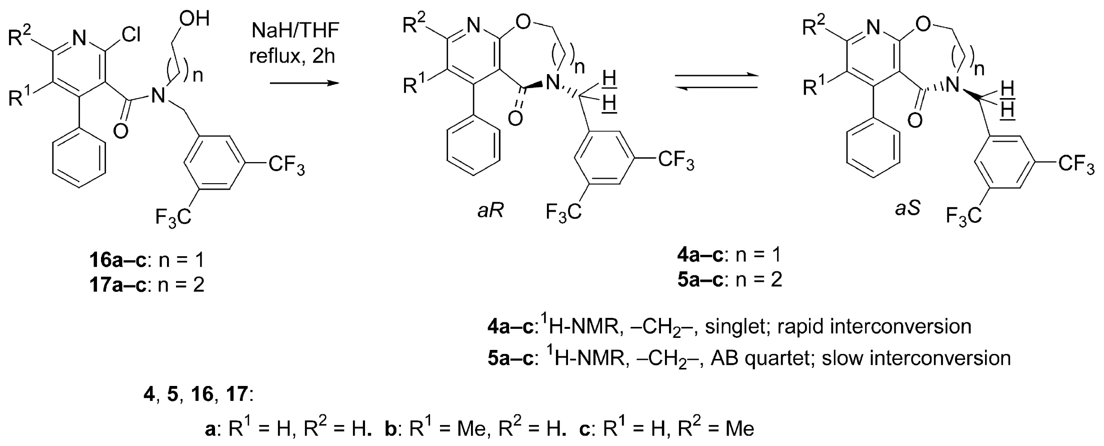
4.1. Atropisomerism

Since the carboxamide moiety of the compounds **4–6** exists at a sterically hindered position, the presence of stable atropisomers (*aR*- and *aS*-forms) was anticipated, as was observed in **1** and TAK-637. First, the *N*-benzylcarboxamide derivatives of bicyclic 3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one (**4**) and 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (**5**), which do not have a methyl substituent on the 7- and 8-membered ring, were synthesized (Scheme 5), and those structures were analyzed by ^{1}H NMR spectroscopy since the pattern of *N*-benzylic methylene protons in the NMR spectrum is diagnostic for the detection of the atropisomers. In compounds with a 7-membered ring (**4a–c**), the methylene protons appeared as a singlet,[9] whereas those of the compounds with an 8-membered ring (**5a–c**) appeared as an AB pattern (J=15.2–15.6 Hz) (Table 1). These data indicate that the conformers (atropisomers) of **4** are rapidly interconverted[9] even on the NMR timescale at room temperature, whereas those of **5** are slowly interconverted, with the methylene protons being diastereotopic.[2,4] Thus, although the separation of the atropisomers of **5** has not been attempted, we presume that compounds **5** exist as racemates.

Based on these data, we next synthesized the *N*-benzylcarboxamide derivatives of 7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (**6**), which bear a chiral methyl group on the 8-membered ring, expecting the


14i–iv
b (47-82%)
12: R = H
13: R = Ms
a
(95%)
15i–iv
c
(70-99%)
d
(64-86%)
14, 15:
i: X = --- (bond)
ii: X = –CH2–
iii: X = –CH(Me)– (S)
iv: X = –CH(Me)– (R)
16–18
16a–c : X = --- (bond)
17a–c : X = –CH2–
18Sa,b : X = –CH(Me)– (S)
18Ra,b : X = –CH(Me)– (R)
4–6e
4a–c : X = --- (bond)
5a–c : X = –CH2–
6a,b : X = –CH(Me)– (S)
6a,b : X = –CH(Me)– (R)
4–6, 16–18: a: R1 = H, R2 = H. b: R1= Me, R2 = H. c: R1 = H, R2 = Me

Scheme 4. Preparation of bicyclic compounds. Reagents: (a) MsCl, Et_3N/THF; (b) **14i–iv**, THF; (c) acid chlorides of **11a** or **11b**, Et_3N/THF; (d) NaH, THF, reflux, 2 h; (e) for specification of the reside X in **4–6** including stereochemistry originating from atropisomerism, see Schemes 5 and 6.


NaH/THF
reflux, 2h
aR
aS
16a–c: n = 1
17a–c: n = 2
4a–c: n = 1
5a–c: n = 2
4a–c: ^{1}H-NMR, –CH$_2$–, singlet; rapid interconversion
5a–c: ^{1}H-NMR, –CH$_2$–, AB quartet; slow interconversion
4, 5, 16, 17:
a: R^1 = H, R^2 = H. b: R^1 = Me, R^2 = H. c: R^1 = H, R^2 = Me

Scheme 5. Cyclization of the intermediates (**16** and **17**) and interconversion between a*R*- and a*S*-isomers in the products (**4** and **5**).

enantioselective formation of the axial chirality induced by the chirality at $C_{(3)}$, as was observed in the synthesis of TAK-637 (Scheme 6).

Heating a THF solution of the chiral intermediates with the *S*-methyl group (**18*S*a** and **18*S*b**) under reflux for 2 h in the presence of sodium hydride gave the cyclized compounds (3*S*)-**6a**[10] and (3*S*)-**6b**[10] as colorless crystalline substances, respectively. Similarly, the enantiomeric intermediates with the *R*-methyl group, **18*R*a** and **18*R*b**, afforded (3*R*)-**6a** and (3*R*)-**6b**, respectively, in satisfactory yields (Table 2, Scheme 6).

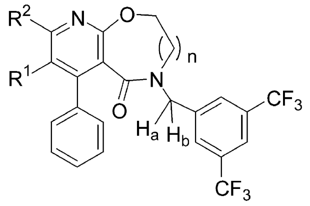
The ^{1}H NMR spectra (in $CDCl_3$) revealed that all of these compounds showed signals due to two diastereomers in a ratio of ca. 98:2[11] as determined by the peak area of the methyl group(s) at $C_{(3)}$ [for (3*S*)-**6b**; δ, major 0.83 (d, J=6.6 Hz) and minor 1.31 (d, J=7.3 Hz)] and/or $C_{(8)}$ [for (3*S*)-**6b**; δ, major 2.07 (s) and minor 1.98 (s)]. The ratio (ca. 98:2) was not altered by repeated crystallization of (3*S*)-**6b** or by heating (3*S*)-**6b** in toluene under reflux for 2 h. From these data, we assumed that (3*S*)-**6b** is a single isomer in the solid state and exists as two conformers in solution.[12]

The stereochemistry was deduced by detailed NMR spectroscopic analysis in $CDCl_3$ using (3*S*)-**6b**: the signals of the major isomer were in good agreement with those of TAK-637,[4] revealing (*aR*,3*S*)[10] stereochemistry [i.e., the NOE observed between the $C_{(3)}$-proton (H-3) and a benzylic methylene proton (H-1′a) (Fig. 2) indicates that the axial chirality is *aR*, and the chemical shifts and coupling constants of the 8-membered ring protons ($-C_{(3)}HMe-C_{(4)}H_2-$) together with long range coupling between a $C_{(4)}$-proton (H-4b) and a benzylic methylene proton (H-1′b) (J=1.4 Hz) also support the (*aR*,3*S*) structure]. On the other hand, the signals of the minor isomer (see Section 6) correspond well to those of the minor *aS*-isomer of TAK-637, indicating that the minor peaks observed in the NMR spectrum are those of the (*aS*,3*S*)-isomer.

In the NOESY spectrum of (3*S*)-**6b**, intersite exchange peaks were observed between the two isomers at the positions of CH_3-3, CH_3-8, H-4b, H-2a and H-2b, demonstrating that these isomers are interconverted in solution.[13]

Taking all this evidence into consideration, the structure of (3*S*)-**6b** could reasonably be explained as (*aR*,3*S*) in the

Table 1. Physicochemical properties and NK_1-antagonistic activity of 3,4-dihydrophyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-ones (**4a–c**) and 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-ones (**5a–c**)

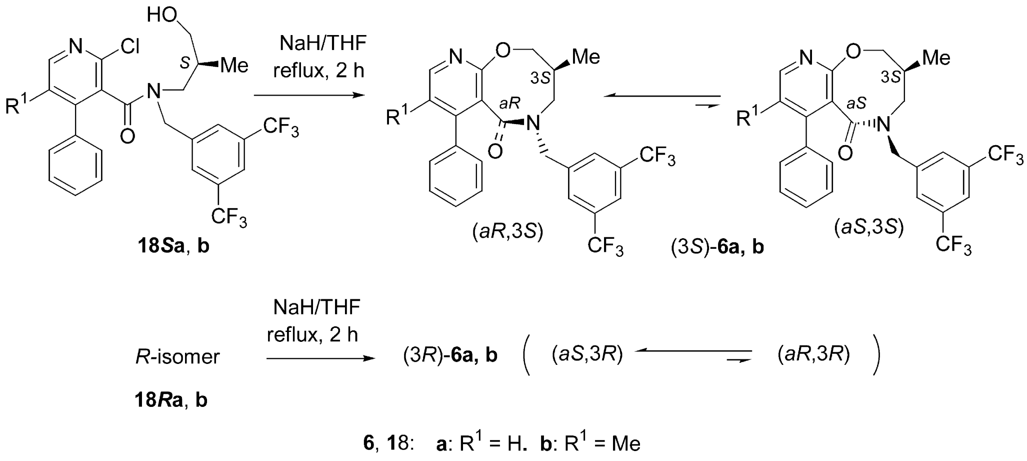


Compound no.	R^1	R^2	*n*	Yield (%)	Mp (°C)	^{1}H NMR[a] ppm, δ (Hz) ($-CH_aH_b-$)	NK_1-antagonistic activity[b] IC_{50} (nM)
4a	H	H	1	86	200–201	4.88 (2H, s)	4.3
4b	Me	H	1	80	179–181	4.80 (2H, s)	1.1
4c	H	Me	1	83	151–153	4.87 (2H, s)	3.3
5a	H	H	2	82	188–189	4.17, 5.50 (each 1H, d, J=15.2 Hz)	7.1
5b	Me	H	2	64	180–182	4.05, 5.45 (each 1H, d, J=15.6 Hz)	1.6
5c	H	Me	2	77	164–165	4.14, 5.49 (each 1H, d, J=15.2 Hz)	2.5

TAK-637 showed IC_{50} value of 0.45 nM in this assay.

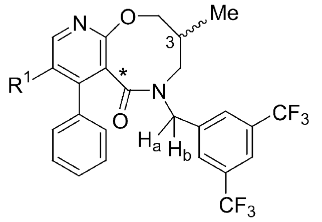
[a] In $CDCl_3$: s=singlet, d=doublet.

[b] Inhibition of [^{125}I]-BH-SP binding in human 1M-9 cells (lymphoblast cells).



Scheme 6. Cyclization of the intermediates with *S*-Me and *R*-Me (**18*S*** and **18*R***).

Table 2. Physicochemical properties and NK$_1$-antagonistic activity of chiral 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-ones (**6**)



Compound no.	R^1	Chirality		Yield (%)	Mp (°C)	$[\alpha]_D$ (in CHCl$_3$)	^{1}H NMR^a ppm,δ (Hz) (–CH$_a$H$_b$–)^b	NK$_1$-antagonistic activity^a IC$_{50}$ (nM)
		At C$_{(3)}$	At axial (*)^c					
(3*S*)-**6a**	H	*S*	*R*	82	142–143	−75.1	4.19, 5.49 (each 1H, d, *J*=15.6 Hz)	1.4
(3*S*)-**6b**	Me	*S*	*R*	65	147–148	−106.8	4.06, 5.44 (each 1H, d, *J*=15.3 Hz)	0.47
(3*R*)-**6c**	H	*R*	*S*	74	142–143	+75.2	4.19, 5.49 (each 1H, d, *J*=15.6 Hz)	69
(3*R*)-**6b**	Me	*R*	*S*	68	147–149	+102.5	4.06, 5.44	96

[a] See corresponding footnotes of Table 1.

[b] The peaks for the major atropisomer are described.

[c] In solution (CDCl$_3$), ca. 2% of the atropisomer exists as determined by ^{1}H NMR.

solid state, and to be in an equilibrium state between the (*aR*,3*S*)- and (*aS*,3*S*)-isomers in a ratio of ca. 98:2 in solution,[11] which may result from the low free energy of activation.

The predominantly formed (*aR*,3*S*) structure determined for (3*S*)-**6b** is also established for (3*S*)-**6a**. Consequently, the enantiomers (3*R*)-**6a** and (3*R*)-**6b** should have an (*aS*,3*R*) stereochemistry. The conformational preference at the axial chirality is well explained by the thermodynamically stable conformation in these isomers, i.e., the C$_{(3)}$-methyl group and the *N*-[3,5-bis(trifluoromethyl)-benzyl] group are disposed in opposite direction as observed in TAK-637 (see Fig. 2).

4.2. NK$_1$-Antagonistic activity

The NK$_1$-antagonistic activity of the bicyclic compounds without a methyl substituent on the 7- and 8-membered ring (**4a**–**c** and **5a**–**c**) are shown in Table 1. The in vitro potency is similar for both series of compounds. It is noteworthy that the compounds with a methyl group on the benzene ring at 7- or 8-position (**4b** and **5b**) showed improved affinity compared with compounds without a methyl group (**4a**, **4c**, **5a** and **5c**), which presumably reflects the stacking conformation desirable for receptor recognition, i.e., the methyl group in **4b** and **5b** constricts the two phenyl rings so as to take that conformation, as shown in Figure 3.[14]

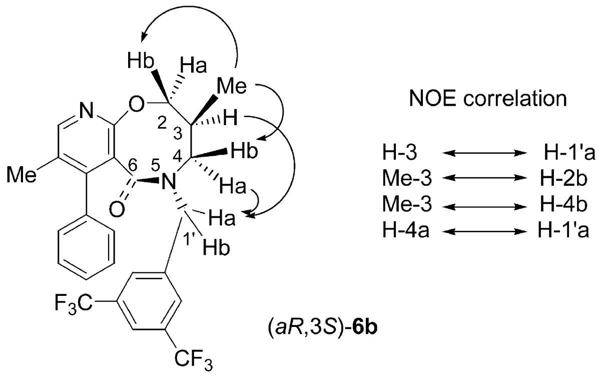
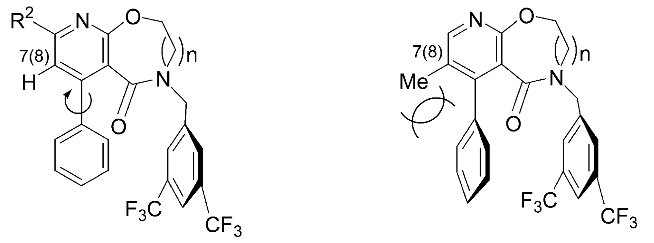


Figure 2. NOE correlation in (a*R*,3*S*)-**6b**.



4a: R^2 = H, n = 1
4c: R^2 = Me, n = 1
5a: R^2 = H, n = 2
5c: R^2 = Me, n = 2

4b: n = 1
5b: n = 2

Figure 3. Stacking conformation in **4b** and **5b** (right) caused by the 7- or 8-methyl group.

Table 2 shows the NK_1-antagonistic activity of the optically active compounds with an 8-membered ring (**6**). It was clearly shown that the enantiomers differ in activity, i.e., the (3*S*)-isomers which have a predominantly *aR* stereochemistry showed ca. 50–200-fold higher potency than the (3*R*)-enantiomers, indicating that the axial chirality is recognized by the NK_1 receptor. The methyl substituent on the benzene ring again improved the affinity by ca. 3-fold [(3*S*)-**6a** versus (3*S*)-**6b**].[13]

5. Conclusion

This study demonstrated that cyclization of the chiral intermediates (**18*S*** and**18*R***) gave thermodynamically stable conformers at the amide-based axial bond, the chirality of which was induced by the $C_{(3)}$ chirality. As observed in 1,7-naphthyridine-6-carboxamide derivatives (TAK-637 and **1**), in these compounds the *aR* axial chirality and the stacking conformation of the two phenyl rings are also important for NK_1-receptor recognition. Synthesis of NK_1 antagonists having other heterocycles based on the chemistry described in this study will be the subject of the forthcoming paper.

6. Experimental

6.1. Chemistry

Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. ^1H NMR spectra were taken on Varian Gemini 200 (200 MHz) spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts were given in ppm with tetramethylsilane as the internal standard and coupling constants (*J*) are given in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra were obtained on a JEOL JMS-AX505W spectrometer. Optical rotations were determined with a JASCO DIP-370 digital polarimeter. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd. Extracted solutions were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4. The yields reported are not optimized.

6.1.1. Ethyl 2-cyano-3-phenylbut-2-enoate (8a). This compound was prepared according to the published method.[6]

6.1.2. Ethyl 2-cyano-3-phenylpent-2-enoate (8b). A mixture of **7b** (33.6 g, 250 mmol), ethyl cyanoacetate (28.3 g, 250 mmol), ammonium acetate (3.85 g, 50 mmol), acetic acid (12 g), and benzene (50 mL) was refluxed for 10 h, while water was removed azeotropically using Dean–Stark apparatus. After evaporation of the solvent, Et_2O (100 mL) was added to the residue. The mixture was washed with H_2O, 0.5 N HCl, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine successively. The organic layer was dried and concentrated. The residue was distilled under reduced pressure (3 mm Hg, 160 °C) to afford **8b** as a pale yellow oil (37.0 g, 65%): ^1H NMR 1.00–1.15 (3H+3H×1/2, m), 1.38 (3H×1/2, t, *J*=7.2 Hz), 2.87 (2H×1/2, q, *J*=7.6 Hz), 3.11 (2H×1/2, q, *J*=7.4 Hz), 4.08 (2H×1/2, q, *J*=7.4 Hz), 4.35 (2H×1/2, q, *J*=7.2 Hz), 7.05–7.20 (1H, m), 7.30–7.55 (4H, m).

6.1.3. Ethyl 2-cyano-5-(dimethylamino)-3-phenylpenta-2,4-dienoate (9a). This compound was prepared according to the published method.[6]

6.1.4. Ethyl 2-cyano-5-(dimethylamino)-4-methyl-3-phenylpenta-2,4-dienoate (9b). *N*,*N*-Dimethylformamide dimethyl acetal (9.40 mL, 70.2 mmol) was added dropwise to **8a** (13.4 g, 58.4 mmol) at 0 °C. After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure to afford **9b** as a red oil (16.0 g, 96%). The oil was used for next reaction without preparation and further purification.

6.1.5. Ethyl 2-cyano-5-(dimethylamino)-3-phenylhexa-2,4-dienoate (9c). *N*,*N*-Dimetylacetamide dimethyl acetal (containing 5–10% MeOH) (26.7 g, 180 mmol) was added dropwise to **8a** (30.0 g, 131 mmol) at 0 °C. After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure. The resulting solid was washed with Et_2O–AcOEt (1:1) to afford **9c** as yellow crystals (23.3 g, 63%); ^1H NMR 1.12 (3H×1/5, t, *J*=7.0 Hz), 1.33 (3H×4/5, t, *J*=7.0 Hz), 1.39 (3H×4/5, s), 1.51 (3H×1/5, s), 3.12 (6H×1/5, s), 3.15 (6H×4/5, s), 4.00 (2H×1/5, q, *J*=7.0 Hz), 4.25 (2H×4/5, q, *J*=7.0 Hz), 5.78 (1H×1/5, s), 7.12 (1H×4/5, s), 7.15–7.48 (5H, m).

6.1.6. Ethyl 2-chloro-4-phenylnicotinate (10a). This compound was prepared according to the published method.[6]

6.1.7. Ethyl 2-chloro-5-methyl-4-phenylnicotinate (10b). A solution of 4 N HCl in AcOEt (150 mL) was added to **9b** (17.9 g, 62.9 mmol), and the mixture was stirred at room temperature for 30 h. After evaporation of the solvent, AcOEt was added to the residue. The mixture was washed successively with H_2O, 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried and concentrated. The residue was subjected to chromatography on silica gel using hexane–AcOEt (4:1) as eluant to afford **10b** as colorless oil (8.23 g, 47%). Recrystallization from AcOEt–hexane gave colorless crystals: mp 89–90°C; ^1H NMR 0.98 (3H, t, *J*=7.2 Hz), 2.11 (3H, s), 4.06 (2H, q,

J=7.2 Hz), 7.15–7.30 (2H, m), 7.37–7.50 (3H, m), 8.33 (1H, s).

6.1.8. Ethyl 2-chloro-6-methyl-4-phenylnicotinate (10c). Compound **9c** (6.61 g, 81.9 mmol) was treated according to a procedure similar to that described for the preparation of **10b** to afford **10c** as a pale yellow oil (15.4 g, 68%); ^{1}H NMR 1.08 (3H, t, J=7.0 Hz), 2.60 (3H, s), 4.18 (2H, q, J=7.0 Hz), 7.13 (1H, s), 7.30–7.50 (5H, m).

6.1.9. 2-Chloro-4-phenylnicotinic acid (11a). This compound was prepared according to the published method.[6]

6.1.10. 2-Chloro-5-methyl-4-phenylnicotinic acid (11b). A mixture of **10b** (8.20 g, 29.7 mmol), EtOH (10 mL) and 4 N aqueous NaOH solution (10 mL) was refluxed for 4 h, and then concentrated under reduced pressure. The residue was acidified with concentrated HCl, and the mixture was extracted with AcOEt. The extract was washed with brine, dried and evaporated to afford **11b** as colorless crystals (5.97 g, 81%). Recrystallization from AcOEt–isopropyl ether (IPE) gave colorless crystals: mp 204–206 °C; ^{1}H NMR 2.18 (3H, s), 7.15–7.30 (2H, m), 7.37–7.60 (3H, m), 8.33 (1H, s). Anal. Calcd $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.02; H, 4.09; N, 5.69.

6.1.11. 2-Chloro-6-methyl-4-phenylnicotinic acid (11c). Compound **10c** (6.60 g, 25.2 mmol) was treated according to a procedure similar to that described for the preparation of **11b** to afford **11c** as colorless crystals (4.70 g, 80%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 191–194 °C; ^{1}H NMR 2.59 (3H, s), 7.16 (1H, s), 7.45 (5H, s), 9.53 (1H, br.s). Anal. Calcd $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.06; H, 4.06; N, 5.65.

6.1.12. 3,5-Bis(trifluoromethyl)benzyl methanesulfonate (13). Methanesulfonyl chloride (1.74 mL, 22.5 mmol) was added dropwise to a solution of 3,5-bis(trifluoromethyl)-benzyl alcohol **12** (5.00 g, 20.5 mmol) and triethylamine (3.14 mL, 22.5 mmol) in THF (50 mL) at 0°C. After stirring at room temperature for 30 min, the mixture was concentrated. The residue was diluted with AcOEt (50 mL) and washed with brine. The organic layer was dried and concentrated to afford **13** as colorless crystals (6.28 g, 95%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 61–62°C; ^{1}H NMR 3.09 (3H, s), 5.33 (2H, s), 7.87 (2H, s), 7.91 (1H, s). Anal. Calcd $C_{10}H_8F_6O_3S$: C, 37.27; H, 2.50. Found: C, 37.25; H, 2.72.

6.1.13. 2-{[3,5-Bis(trifluoromethyl)benzyl]amino}alkanols (15i–iv). A typical procedure is described for 2-{[3,5-bis(trifluoromethyl)benzyl]amino}ethanol **15i**: A solution of **13** (1.89 g, 5.86 mmol) in THF (10 mL) was added dropwise to a solution of 2-aminoethanol **14i** (3.6 mL, 59.6 mmol) in THF (30 mL) at 0 °C. After stirring at room temperature for 1 h, the mixture was concentrated. The residue was diluted with AcOEt (50 mL), and washed with H_2O and brine. The organic layer was dried and concentrated to give **15i** as colorless crystals (1.38 g, 82%). Recrystallization from EtOH–Et_2O gave colorless crystals: mp 107–108°C; ^{1}H NMR 1.38 (2H, s), 2.83 (2H, t, J=5.4 Hz), 3.72 (2H, t, J=5.4 Hz), 3.96 (2H, s), 7.78 (1H, s), 7.82 (2H, s). Anal. Calcd $C_{11}H_{11}F_6NO$: C, 46.00; H, 3.86; N, 4.88. Found: C, 46.01; H, 3.86; N, 4.89.

Similarly, compounds **15ii–iv** were prepared from **13** and the corresponding amino-alkanols **14ii–iv**.

6.1.14. 3-{[3,5-Bis(trifluoromethyl)benzyl]amino}propan-1-ol (15ii). From **13** (6.65 g, 20.6 mmol) and 3-aminopropanol **14ii** (15.7 mL, 205 mmol). Colorless crystals (4.10 g, 66%). Recrystallization from Et_2O–hexane gave colorless crystals: mp 57–58 °C; ^{1}H NMR 1.77 (2H, quintet, J=5.8 Hz), 2.20–2.80 (2H, br), 2.89 (2H, t, J=5.8 Hz), 3.82 (2H, t, J=5.8 Hz), 3.93 (2H, s), 7.89 (3H, s). Anal. Calcd $C_{12}H_{13}F_6NO$: C, 47.85; H, 4.35; N, 4.65. Found: C, 47.76; H, 4.32; N, 4.65.

6.1.15. (2*S*)-3-{[3,5-Bis(trifluoromethyl)benzyl]amino}-2-methylpropan-1-ol (15iii). From **13** (1.20 g, 3.72 mmol) and (2*S*)-3-amino-2-methylpropan-1-ol **14iii**[7] (500 mg, 5.61 mmol). A colorless oil (635 mg, 56%); ^{1}H NMR 0.86 (3H, d, J=6.8 Hz), 1.98 (1H, m), 2.63 (1H, dd, J=11.8, 9.4 Hz), 2.70–2.90 (2H, m), 2.86 (1H, ddd, J=11.8, 4.0, 1.4 Hz), 3.56 (1H, dd, J=10.6, 9.4 Hz), 3.71 (1H, ddd, J=10.6, 4.0, 1.4 Hz), 3.87 (1H, d, J=13.8 Hz), 3.98 (1H, d, J=13.8 Hz), 7.79 (3H, s).

6.1.16. (2*R*)-3-{[3,5-Bis(trifluoromethyl)benzyl]amino}-2-methylpropan-1-ol (15iv). From **13** (2.40 g, 7.45 mmol) and (2*R*)-3-amino-2-methylpropan-1-ol **14iv**[7] (1.00 g, 11.2 mmol). A colorless oil (1.10 g, 47%); ^{1}H NMR spectrum was identical with that of **15iii**.

6.1.17. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(2-hydroxyalkyl)-4-phenylnicotinamides (16, 17, 18*S* and 18*R*). A typical procedure is described for *N*-[3,5-bis(trifluoromethyl)benzyl]-2-chloro-*N*-(2-hydroxyethyl)-4-phenylnicotinamide **16a**: Thionyl chloride (0.70 mL, 9.6 mmol) was added dropwise to a solution of **11a** (318 mg, 1.36 mmol) and DMF (catalytic amount) in THF (10 mL), and the mixture was refluxed for 4 h. The mixture was concentrated, and dissolved in THF (5 mL). The solution was added dropwise to a mixture of **15i** (391 mg, 1.36 mmol), triethylamine (0.57 mL, 4.1 mmol) and THF (5 mL) at 0 °C. After stirring at room temperature for 2 h, the mixture was concentrated. The residue was diluted with AcOEt, and washed with H_2O and brine. The organic layer was dried and concentrated. The residue was subjected to chromatography on silica gel using hexane–AcOEt (1:1) as eluant to give **16a** as a colorless oil (551 mg, 81%, the ratio of *cis–trans* amide isomer: ca. 2:1); ^{1}H NMR 2.00–2.40 (1H, m), 2.82–3.92 (4H, m), 4.16 (1H×1/3, d, J=16.0 Hz), 4.41 (1H×1/3, d, J=16.0 Hz), 4.73 (1H×2/3, d, J=15.0 Hz), 4.87 (1H×2/3, d, J=15.0 Hz), 7.20–8.85 (9H, m), 8.43 (1H, m).

Similarly, compounds **16b**,**c**, **17a**–**c**, **18*S*a**,**b** and **18*R*a**,**b** were prepared from corresponding 3-pyridine carboxylic acids **11a**–**c** and 2-{[3,5-bis(trifluoromethyl)benzyl]amino}alkanols **15i**–**iv**.

6.1.18. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(2-hydroxyethyl)-5-methyl-4-phenylnicotinamide (16b). From **11b** (300 mg, 1.21 mmol) and **15i** (430 mg, 1.33 mmol). Colorless crystals (435 mg, 70%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 146–148 °C; ^{1}H NMR 1.60–1.70 (1H, m), 2.09 (3H, s), 3.02 (1H, dt, J=15.0, 5.6 Hz), 3.25 (1H, dt, J=15.0, 5.6 Hz), 3.60 (2H, m), 4.57 (1H, d, J=15.2 Hz), 4.79 (1H, d, J=15.2 Hz), 7.05–7.50 (5H, m), 7.62 (2H, s), 7.76 (1H, s), 8.33 (1H, s). Anal. Calcd $C_{24}H_{19}ClF_6N_2O_2$: C, 55.77; H, 3.71; N, 5.42. Found: C, 55.79; H, 3.73; N, 5.41.

6.1.19. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(2-hydroxyethyl)-6-methyl-4-phenylnicotinamide (16c). From **11c** (2.00 g, 8.07 mmol) and **15i** (2.86 g, 8.88 mmol). A colorless oil (4.07 g, 98%); the ratio of *cis–trans* amide isomer, ca. 3:2; ^{1}H NMR 1.95–3.80 (5H, m), 2.58 (3H, s), 4.15 (1H×2/5, d, J=16.2 Hz), 4.41 (1H×2/5, d, J=16.2 Hz), 4.75 (1H×3/5, d, J=15.0 Hz), 4.85 (1H×3/5, d, J=15.0 Hz), 7.15 (1H×3/5, s), 7.17 (1H×2/5, d, J=15.0 Hz), 7.23–7.58 (5H, m), 7.74 (2H, s), 7.78 (1H, s).

6.1.20. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(3-hydroxypropyl)-4-phenylnicotinamide (17a). From **11a** (830 mg, 3.55 mmol) and **15ii** (1.07 g, 3.55 mmol). Colorless crystals (1.55 g, 84%, the ratio of *cis–trans* amide isomer: ca. 3:1). Recrystallization from AcOEt–IPE gave colorless crystals: mp 121–122 °C; ^{1}H NMR 1.00–1.70 (2H, m), 2.75–3.20 (2H, m), 3.35–3.55 (3H, m), 4.06 (1H×1/4, d, J=16.2 Hz), 4.31 (1H×1/4, d, J=16.2 Hz), 4.65 (1H×3/4, d, J=15.2 Hz), 4.76 (1H×3/4, d, J=15.2 Hz), 7.20–7.55 (6H, m), 7.72 (2H, s), 7.80 (1H, s), 8.47 (1H, d, J=5.2 Hz). Anal. Calcd $C_{24}H_{19}ClF_6N_2O_2$: C, 55.77; H, 3.71; N, 5.42. Found: C, 55.65; H, 3.70; N, 5.57.

6.1.21. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(3-hydroxypropyl)-5-methyl-4-phenylnicotinamide (17b). From **11b** (300 mg, 1.21 mmol) and **15ii** (400 mg, 1.33 mmol). A colorless oil (626 mg, 97%, the ratio of *cis–trans* amide isomer: ca. 1:1); ^{1}H NMR 1.10–1.80 (2H, m), 1.85–2.00 (1H, m), 2.06 (3H×1/2, s), 2.08 (3H×1/2, s), 2.80–3.30 (3H, m), 3.35–3.70 (1H, m), 4.08 (1H×1/2, d, J=16.4 Hz), 4.39 (1H×1/2, d, J=15.0 Hz), 4.47 (1H×1/2, d, J=16.4 Hz), 4.70 (1H×1/2, d, J=15.0 Hz), 6.90–7.62 (7H, m), 7.72 (1H×1/2, s), 7.77 (1H×1/2, s), 8.28 (1H×1/2, s), 8.31 (1H×1/2, s).

6.1.22. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(3-hydroxypropyl)-6-methyl-4-phenylnicotinamide (17c). From **11c** (938 mg, 4.02 mmol) and **15ii** (1.33 g, 4.42 mmol). A colorless oil (1.95 g, 96%, the ratio of *cis–trans* amide isomer: ca. 3:2); ^{1}H NMR 1.15–1.65 (2H, m), 2.59 (3H, s), 2.75–3.20 (2H, m), 3.25–3.55 (3H, m), 4.06 (1H×2/5, d, J=15.4 Hz), 4.31 (1H×2/5, d, J=15.4 Hz), 4.65 (1H×3/5, d, J=15.2 Hz), 4.74 (1H×3/5, d, J=15.2 Hz), 7.16 (1H, s), 7.20–7.60 (5H, m), 7.72 (2H, s), 7.78 (1H, s).

6.1.23. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*S*)-3-hydroxy-2-methylpropyl]-4-phenylnicotinamide (18*S*a). From **11a** (850 mg, 3.64 mmol) and **15iii** (1.37 g, 4.35 mmol). A colorless oil (1.40 g, 74%, the ratio of *cis–trans* amide isomer: ca. 1:1); ^{1}H NMR 0.53 (3H×1/4, d, J=7.0 Hz), 0.63 (3H×1/4, d, J=7.0 Hz), 0.75 (3H×1/4, d, J=6.8 Hz), 0.81 (3H×1/4, d, J=6.8 Hz), 1.50–1.90 (1H, m), 2.42–3.80 (5H, m), 4.00–4.95 (2H, m), 7.10–7.90 (9H, m), 8.42 (1H, m).

6.1.24. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*S*)-3-hydroxy-2-methylpropyl]-5-methyl-4-phenylnicotinamide (18*S*b). From **11b** (513 mg, 2.07 mmol) and **15iii** (653 mg, 2.07 mmol). A colorless oil (1.06 g, 94%); ^{1}H NMR 0.60–0.82 (3H, m), 1.50–2.00 (2H, m), 2.00–2.15 (3H, m), 2.15–3.92 (4H, m), 4.05–4.92 (2H, m), 7.00–7.85 (8H, m), 8.34 (1H, m).

6.1.25. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*R*)-3-hydroxy-2-methylpropyl]-4-phenylnicotinamide (18*R*a). From **11a** (1.14 g, 4.88 mmol) and **15iv** (1.84 g, 5.83 mmol). A colorless oil (2.14 g, 85%, the ratio of *cis–trans* amide isomer: ca. 1:1); ^{1}H NMR spectrum was identical with that of **18*S*a**.

6.1.26. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*R*)-3-hydroxy-2-methylpropyl]-5-methyl-4-phenylnicotinamide (18*R*b). From **11b** (824 mg, 3.49 mmol) and **15iv** (1.10 g, 3.49 mmol). A colorless oil (1.73 g, 100%.); ^{1}H NMR spectrum was identical with that of **18*S*b**.

6.1.27. 4-[3,5-Bis(trifluoromethyl)benzyl]-6-phenyl-3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-ones (4a–c) and 5-[3,5-bis(trifluoromethyl)benzyl]-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-ones (5a–c). A typical procedure is described for 4-[3,5-bis(trifluoromethyl)benzyl]-6-phenyl-3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one **4a**: NaH (60% in oil) (60 mg, 1.5 mmol) was added to a solution of **16a** (348 mg, 0.69 mmol) in THF (15 mL), and the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and diluted with AcOEt, washed successively with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried and concentrated to afford **4a** as colorless crystals (278 mg, 86%). Recrystallization from EtOH–hexane gave colorless crystals: mp 200–201 °C; ^{1}H NMR 3.70 (2H, t, J=5.8 Hz), 4.47 (2H, t, J=5.8 Hz), 4.88 (2H, s), 7.24 (1H, d, J=5.2 Hz), 7.25–7.55 (5H, m), 7.80 (2H, s), 7.86 (1H, s), 8.44 (1H, d, J=5.2 Hz). MS (electron impact) m/z 466 (M^+) $[(C_{23}H_{16}F_6N_2O_2)]^+$].

Similarly, **4b**, **4c** and **5a–c** were prepared from **16b**, **16c** and **17a–c**, respectively.

6.1.28. 4-[3,5-Bis(trifluoromethyl)benzyl]-7-methyl-6-phenyl-3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one (4b). From **16b** (100 mg, 0.19 mmol). Colorless crystals (74 mg, 80%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 179–181 °C; ^{1}H NMR 2.13 (3H, s), 3.57 (2H, t, J=5.8 Hz), 4.42 (2H, t, J=5.8 Hz), 4.80 (2H, s), 7.16 (2H, m), 7.47 (3H, m), 7.65 (2H, s), 7.81 (1H, s), 8.32 (1H, s).

6.1.29. 4-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-6-phenyl-3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one (4c). From **16c** (2.16 g, 4.18 mmol). Colorless crystals (1.66 g, 83%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 151–153 °C; ^{1}H NMR 2.58 (3H, s), 3.69 (2H, t, J=5.4 Hz), 4.47 (2H, t, J=5.4 Hz), 4.87 (2H, s), 7.11 (1H, s), 7.17–7.56 (5H, m), 7.80 (2H, s), 7.86 (1H, s). Anal. Calcd $C_{24}H_{18}F_6N_2O_2\cdot 1/4H_2O$: C, 59.44; H, 3.85; N, 5.78. Found: C, 59.42; H, 3.82; N, 5.84.

6.1.30. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (5a). From **17a** (1.00 g, 1.93 mmol). Colorless crystals (763 mg, 82%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 188–189 °C; ^{1}H NMR 1.65–1.88 (1H, m), 2.18–2.45 (1H, m), 3.36 (1H, dd, J=15.2, 3.8 Hz), 3.73 (1H, m), 4.17 (1H, d, J=15.2 Hz), 4.32 (1H, dt, J=12.6, 3.6 Hz), 4.67 (1H, ddd, J=12.6, 5.6, 3.6 Hz), 5.50 (1H, d, J=15.2 Hz), 7.16 (1H, d, J=5.2 Hz), 7.20–7.45 (5H, m), 7.71 (2H, s), 7.83 (1H, s), 8.41 (1H, d, J=5.2 Hz). Anal. Calcd $C_{24}H_{18}F_6N_2O_2$: C, 60.00; H, 3.78; N, 5.83. Found: C, 59.92; H, 3.76; N, 5.89.

6.1.31. 5-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (5b). From **17b** (550 mg, 1.03 mmol). Colorless crystals (324 mg, 64%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 180–182 °C; ^{1}H NMR 1.71 (1H, m), 2.07 (3H, m), 2.28 (1H, m), 3.24 (1H, dd, J=15.2, 3.8 Hz), 3.64 (1H, dd, J=15.2, 12.0 Hz), 4.05 (1H, d, J=15.6 Hz), 4.27 (1H, dt, J=12.6, 3.8 Hz), 4.63 (1H, ddd, J=12.6, 5.4, 2.0 Hz), 5.45 (1H, d, J=15.6 Hz), 6.6–7.4 (2H, m), 7.37 (3H, br.s), 7.54 (2H, s), 7.78 (1H, s), 8.29 (1H, s). Anal. Calcd $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67. Found: C, 60.69; H, 4.05; N, 5.63.

6.1.32. 5-[3,5-Bis(trifluoromethyl)benzyl]-9-methyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (5c). From **17c** (1.95 g, 3.67 mmol). Colorless crystals (1.40 g, 77%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 164–165 °C; ^{1}H NMR 1.79 (1H, m), 2.30 (1H, m), 2.56 (3H, s), 3.35 (1H, m), 3.77 (1H, m), 4.14 (1H, d, J=15.2 Hz), 4.31 (1H, m), 4.65 (1H, m), 5.49 (1H, d, J=15.2 Hz), 7.02 (1H, s), 7.20–7.50 (5H, m), 7.72 (2H, s), 7.83 (1H, s). Anal. Calcd $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67. Found: C, 60.43; H, 4.04; N, 5.74.

6.1.33. (3*S*)-5-[3,5-Bis(trifluoromethyl)benzyl]-3,8-dimethyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one [(3*S*)-6b]. NaH (60% in oil) (61 mg, 1.53 mmol) was added to a solution of **18*S*b** (417 mg, 0.76 mmol) in THF (40 mL), and the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and diluted with AcOEt, washed successively with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried and concentrated to afford (3*S*)-**6b** as colorless crystals (251 mg, 65%). Recrystallization from AcOEt–hexane gave colorless crystals: mp 147–148 °C; $[\alpha]_D^{20}=-106.8°$ (c=0.257, $CHCl_3$). Anal. Calcd $C_{26}H_{22}F_6N_2O_2$: C, 61.49; H, 4.36; N, 5.51. Found: C, 61.30; H, 4.52; N, 5.70. In the ^{1}H NMR spectrum ($CDCl_3$) taken on Varian Mercury 300 (300 MHz), a set of major and minor peaks were observed in a ratio of ca. 98:2, which was calculated from the peak area of CH_3-3 and CH_3-8. The major isomer assigned as (*aR*,3*S*)-**6b** showed the following peaks, which are corresponding well to those of TAK-637:[3,4] 0.83 (3H, d, J=6.6 Hz, CH_3-3), 2.07 (3H, s, CH_3-8), 2.40 (1H, m, H-3), 2.97 (1H, d, J=15.5 Hz, H-4a), 3.48 (1H, dd, J=15.5, 10.5 Hz, H-4b), 3.87 (1H, dd, J=12.6, 10.5 Hz, H-2a), 4.06 (1H, d, J=15.3 Hz, –C*H*aHb-Ar), 4.59 (1H, dd, J=12.6, 5.1 Hz, H-2b), 5.44 (1H, d, J=15.3 Hz, –CHa*H*b-Ar), 6.6–7.4 (2H, m, Ar), 7.37 (3H, br.s, Ar), 7.53 (2H, s, Ar), 7.78 (1H, s, Ar), 8.29 (1H, s, H-9); NOEs taken on a Bruker DPX 300 (300 MHz) spectrometer in $CDCl_3$, were observed between a benzylic methylene-Ha and H-3, CH_3-3 and H-2a, CH_3-3 and H-4b, and H-4a and a benzylic methylene-Ha (Fig. 2); long range couplings between H-4b and a benzylic methylene-Hb (J=1.4 Hz), and H-2b and H-4a (J=1.0 Hz) were also observed. The minor isomer assigned as (*aS*,3*S*)-**6b** showed the following peaks in the ^{1}H NMR spectrum, which are corresponding well to those of the minor isomer of TAK-637:[3,4] 1.31 (3H, d, J=7.3 Hz, CH_3-3), 1.98 (3H, s, CH_3-8), 3.35 (1H, dd, J=15.0, 4.5 Hz, H-4a), 3.65 (1H, dd, J=15.0, 6.0 Hz, H-4b), 4.23 (1H, dd, J=13.5, 4.5 Hz, H-2b), 4.35 (1H, dd, J=13.5, 4.5 Hz, H-2a), 8.23 (1H, s, H-9). Other peaks of the minor isomer could not be assigned because of overlapping with those of the major isomer. In the NOESY spectrum of (3*S*)-**6b**, intersite exchange peaks were observed between the two isomers at the positions of CH_3-3, CH_3-8, H-4b, H-2a and H-2b.

6.1.34. (3*S*)-5-[3,5-Bis(trifluoromethyl)benzyl]-3-methyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one [(3*S*)-6a]. Compound **18*S*a** (1.40 g, 2.63 mmol) was treated according to a procedure similar to that described for the preparation of (3*S*)-**6b** to afford (3*S*)-**6a** as colorless crystals (1.06 g, 82%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 142–143 °C; $[\alpha]_D^{20}=-75.1°$ (c=0.381, $CHCl_3$). Anal. Calcd $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.77. Found: C, 60.60; H, 4.00; N, 5.77; ^{1}H NMR (taken on Varian Mercury 300) [(*aR*,3*S*):(*aS*,3*S*)=ca. 98:2]; for (*aR*,3*S*), 0.87 (3H, d, J=6.9 Hz), 2.45 (1H, m), 3.10 (1H, d, J=15.3 Hz), 3.58 (1H, dd, J=15.3, 10.5 Hz), 3.91 (1H, dd, J=12.7, 10.5 Hz), 4.19 (1H, d, J=15.6 Hz), 4.63 (1H, dd, J=12.7, 5.1 Hz), 5.49 (1H, d, J=15.6 Hz), 7.17 (1H, d, J=5.0 Hz), 7.20–7.50 (5H, m), 7.71 (2H, s), 7.83 (1H, s), 8.42 (1H, d, J=5.0 Hz), and for (*aS*,3*S*), following peaks were assigned;1.36 (3H, d, J=7.8 Hz, CH_3-3), 3.64 (1H, dd, J=15.0, 6.6 Hz, H-4b), 4.34 (1H, dd, J=13.5, 4.5 Hz, H-2a), 7.06 (1H, d, J=5.0 Hz, H-8), 8.36 (1H, d, J=5.0 Hz, H-9).

6.1.35. (3*R*)-5-[3,5-Bis(trifluoromethyl)benzyl]-3-methyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one [(3*R*)-6a]. Compound **18*R*a** (2.14 g, 4.14 mmol) was treated according to a procedure similar to that described for the preparation of (3*S*)-**6b** to afford (3*R*)-**6a** as colorless crystals (1.52 g, 74%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 142–143 °C; ^{1}H NMR spectrum was identical with that of (3*S*)-**6a**. $[\alpha]_D^{20}=+75.2°$(c=0.724, $CHCl_3$). Anal. Calcd $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67. Found: C, 60.60; H, 3.86; N, 5.77.

6.1.36. (3*R*)-5-[3,5-Bis(trifluoromethyl)benzyl]-3,8-dimethyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one [(3*R*)-6b]. Compound **18*R*b** (843 mg, 1.55 mmol) was treated according to a procedure similar to that described for the preparation of (3*S*)-**6b** to afford (3*R*)-**6b** as colorless crystals (533 mg, 68%). Recrystallization from AcOEt–hexane gave colorless crystals: mp 147–149 °C; ^{1}H NMR spectrum was identical with that of (3*S*)-**6b**. $[\alpha]_D^{20}=+102.5°$ (c=0.573, $CHCl_3$). Anal. Calcd $C_{26}H_{22}F_6N_2O_2$: C, 61.49; H, 4.36; N, 5.51. Found: C, 61.26; H, 4.33; N, 5.69.

6.2. [^{125}I]-BH-substance P binding in human IM-9 cells

The binding activity was determined according to the protocol previously reported.[1,8]

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References and notes

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5. Compound **1** (*trans*-amide) reached an equilibrium state of *trans*- and *cis*-amide (=ca. 7:1) in solution (e.g., $CDCl_3$) in about ca. 6 h at room temperature. The *cis*-form of **1**, which was separated and isolated in a crystalline form by column chromatography, has weaker NK_1-antagonistic activity (IC_{50}=7.0 nM) than **1**. The presence of atropisomers in the *cis*-form was also shown by HPLC analysis using a chiral column.[1,2]
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9. It should be noted that the *N*-benzylic methylene protons of 7-membered ring analogues of TAK-637 appeared as an AB pattern in the NMR spectrum,[4] suggesting that the conformation of the 7-membered ring in compounds **4a**–**c** changes more rapidly than that in TAK-637 derivatives.
10. For the stereochemistry at $C_{(3)}$ of **6**, note that the sequence of priority is different from that of TAK-637; the methyl group exists in β-configuration for both compounds.
11. The ratio in the NMR spectrum changed slightly depending on the solvent used; i.e., in CD_3OD, it was ca. 96:4, in DMSO-d_6, ca. 97:3, and in pyridine-d_5, ca. 97:3.
12. Coexistence of the two conformers (ca. 98:2) in the solid state of (3*S*)-**6b** may not be ruled out.
13. For a recent NOESY (EXSY) experiment in atropisomers, see: Gibson, K. R.; Hitzel, L.; Mortishire-Smith, R. J.; Gerhard, U.; Jelley, R. A.; Reeve, A. J.; Rowley, M.; Nadin, A.; Owens, A. P. *J. Org. Chem.* **2002**, *67*, 9354–9360.
14. In the ^{1}H NMR spectra, the $C_{(7)}$-phenyl protons of **5b**, (3*S*)-**6b** and (3*R*)-**6b** were observed as a broad signal (2H at 6.6–7.4 ppm) and a broad singlet (3H at 7.37 ppm), whereas those of **5a**, **5c**, (3*S*)-**6a** and (3*R*)-**6a** were observed as multiplets with sharp peaks, suggesting that rotation of the phenyl ring is moderately restricted for **5b**, (3*S*)-**6b** and (3*R*)-**6b**.