Axially Chiral *N*-Benzyl-*N*,7-dimethyl-5-phenyl-1,7-naphthyridine-6-carboxamide Derivatives as Tachykinin NK_1 Receptor Antagonists: Determination of the Absolute Stereochemical Requirements

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A potent and orally active NK_1 antagonist, trans-*N*-[3,5-bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide (**1*t***), was shown to exist as a mixture of separable and stable (*R*)- and (*S*)-atropisomers (**1*t*-A** and **1*t*-B**) originating from the restricted rotation around the $-C_{(6)}-C(=O)-$ bond; the antagonistic activities of **1*t*-A** were ca. 6−13-fold higher than those of **1*t*-B**. Analogues of **1*t*** (**3**), which have (*S*)- and (*R*)-methyl groups at the benzylic methylene portion of **1*t***, were prepared and separated into the diastereomeric atropisomers, **3a-A**, **3a-B** and **3b-A**, **3b-B**, in enantiomerically pure forms. Among the four isomers of **3**, the (*aR*,*S*)-enantiomer (**3a-A**) exhibited the most potent antagonistic activities with an IC_{50} value of 0.80 nM (in vitro inhibition of [^{125}I]BH-SP binding in human IM-9 cells) and ED_{50} values of 9.3 μg/kg (iv) and 67.7 μg/kg (po) (in vivo inhibition of capsaicin-induced plasma extravasation in guinea pig trachea), while the activity of the (*aS*,*R*)-enantiomer (**3b-B**) was the weakest with an IC_{50} value of 620 nM. The structure−activity relationships in this series of antagonists indicate that the (*R*)-configuration at the axial bond and the stacking (or stacking-like) conformation between the two phenyl rings as shown in **1*t*-A** and **3a-A** are essential for high-affinity binding and suggest that the amide moiety functions as a hydrogen bond acceptor in the interaction with the receptor.

Introduction

We recently described[1] the discovery of potent and orally active tachykinin NK_1 receptor antagonists,[2] 6-(*N*-benzyl-*N*-methylcarboxamide) derivatives of pyrido[3,4-*b*]pyridine (1,7-naphthyridine) (e.g., **1*t***; Figure 1), by extensive structure−activity relationship (SAR) studies on a series of *N*-benzylcarboxamides with isoquinolone and related nuclei. Compound **1**, *N*-[3,5-bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide, exists in the form of two separable isomers (rotamers), trans (**1*t***) and cis (**1*c***) with respect to the amide bond, which are interconverted and reach an equilibrium state of a ca. 7:1 ratio in solution. Interestingly, the potency of the trans-rotamer (**1*t***) is ca. 7−20-fold higher than that of the cis-rotamer (**1*c***), indicating a conformational requirement for NK_1 receptor binding.[1a] In the conformational studies on **1*t*** (including **1*c***) and CP-99,994,[3] a representative NK_1 antagonist, two phenyl rings (i.e., the $C_{(5)}$-phenyl and benzylic phenyl in **1*t***) and a heteroatom (i.e., nitrogen or oxygen at the carboxamide moiety in **1*t***) were well-superimposed. This result suggested that these three points are the key sites for NK_1 recognition,[4] and **1*t*** and CP-99,994 bind to similar sites on the NK_1 receptor.[1a] In these studies, two models, in which either the oxygen or the nitrogen at the carboxamide in **1*t*** is superimposed on the exocyclic amine nitrogen in CP-99,994, were indicated, and molecule **1*t*** in each model was shown to have enantiomeric structures (**1*t*-A** and **1*t*-B** in Scheme 1) originating from the axial chirality about the $-C_{(6)}-C(=O)-$ bond. Among these two models, we preferred the one in which the oxygen is superimposed, since the oxygen has higher electron density than the nitrogen and is more likely to function as the hydrogen bond acceptor as reported for the tryptophan ester NK_1 antagonist L-732,138.[5] To further clarify the stereochemistry required for the receptor binding in this class of antagonists, we examined the structure of **1*t*** in more detail.

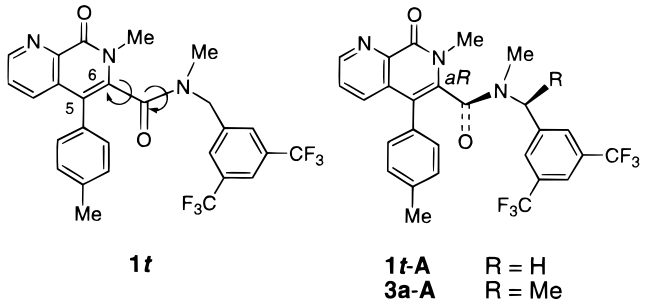

Figure 1. Potent NK_1 antagonist **1*t*** and active atropisomers **1*t*-A** and **3a-A** (for the schematic drawings, see the footnote of Scheme 1).

In this paper, we demonstrate that molecule **1*t*** exists as a mixture of separable and stable axially chiral

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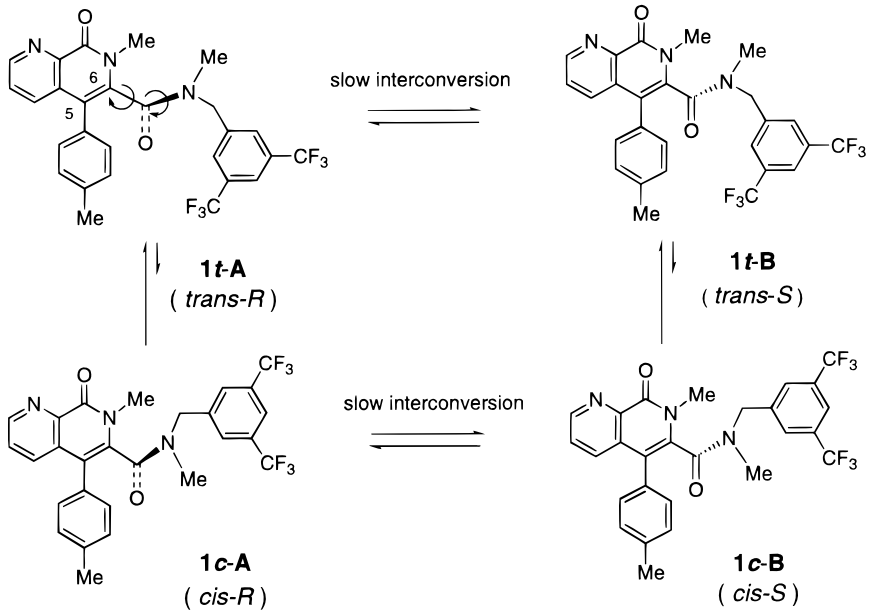
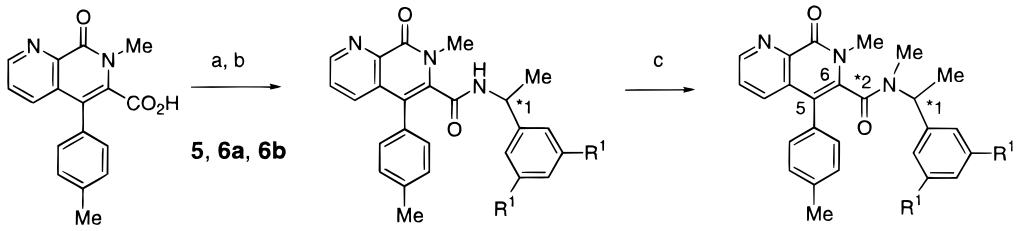
Scheme 1[a]



[a] The four stereoisomers of **1**: trans and cis are used to indicate the relative configuration between the *N*-methyl group and the carbonyl oxygen in the amide moiety, and *R* and *S* denote[12a] the axial chirality originating from the restricted rotation around the $-C_{(6)}-C(=O)-$ bond. In the schematic drawings, the axial chirality is shown by indicating the steric position of the amide oxygen and nitrogen with respect to the plane of the 1,7-naphthyridine ring.

Scheme 2[a]



	chirality *1[d]	R^1
7	*S*	H
8a	*S*	CF_3
8b	*R*	CF_3

	chirality[d] *1	*2	R^1
2A	*S*	*R*	H
2B	*S*	*S*	H
3a-A	*S*	*R*	CF_3
3a-B	*S*	*S*	CF_3
3b-A	*R*	*R*	CF_3
3b-B	*R*	*S*	CF_3

[a] Reagents: (a) $SOCl_2$/1,2-dichloroethane; (b) (*S*)-1-phenylethylamine (**5**) (for **7**), (*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethylamine (**6a**) (for **8a**), and (*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethylamine (**6b**) (for **8b**), Et_3N/1,2-dichloroethane; (c) NaH, MeI/DMF (THF); (d) *1 denotes chirality at the benzylic methylene portion, and *2 denotes chirality about the axial bond $[-C_{(6)}-C(=O)-]$.

isomers (atropisomers), **1*t*-A** and **1*t*-B** (Scheme 1), and that the (*R*)-configuration at the axial chiral center and the stacking (or stacking-like) conformation between the two phenyl rings as shown in **1*t*-A** and **3a-A** (Figure 1) are required for high-affinity NK_1 binding.

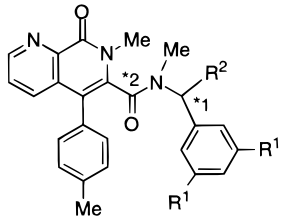
Chemistry

N-[3,5-Bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide (**1**) was prepared by the previously reported method.[1a] The synthesis of chiral methyl analogues of **1*t*** (**2** and **3**) is shown in Scheme 2. First, the 1,7-naphthyridine-6-carboxylic acid **4** was amidated via the acid chloride with 1-[(substituted)phenyl]ethylamines (**5**, **6a**,**b**) to give the secondary amides (**7**, **8a**,**b**, respectively), which, as may be expected, were shown to be stereochemically single isomers by NMR and TLC analyses. These secondary amides were then N-methylated with methyl iodide in the presence of a base to generate the tertiary amides (**2** and **3**) as a mixture of diastereomers, which were separated by crystallization and/or column chromatography. The relative and absolute stereochemistry of these tertiary amides and the stereoselectivity in the methylation reaction are described in Results and Discussion.

Biology

The compounds prepared as described above were evaluated in vitro for inhibition of [^{125}I]Bolton-Hunter

Table 1. NK_1 Antagonistic Activities of 1,7-Naphthyridine-6-carboxamide Derivatives (**1**−**3**)



			chirality			ED$_{50}$ (μg/kg) or % inhibition[b]	
compd no.	R^1	R^2	*1	*2	IC$_{50}$ (nM)[a]	iv	po
1*t* (**A** + **B**)	CF_3	H		*RS*	0.34 ± 0.07	30 (18−54)	110 (76−178)
1*t*-A	CF_3	H		*R*	0.24[c]	7.7 (4.1−12.5)	−[d]
1*t*-B	CF_3	H		*S*	1.4[c]	100 (69−149)	−
1*c* (**A** + **B**)	CF_3	H		*RS*	4.2[c]	220 (130−2160)	−
2A	H	Me	*S*	*R*	130[e]	−	−
2B	H	Me	*S*	*S*	1700[e]	−	−
3a-A	CF_3	Me	*S*	*R*	0.80 ± 0.20	9.3 (3.0−26.2)	67.7 (31.7−111.0)
3a-B	CF_3	Me	*S*	*S*	44 ± 2.2	61.8%[f]	−
3b-A	CF_3	Me	*R*	*R*	19 ± 8	412 (201−1432)	−
3b-B	CF_3	Me	*R*	*S*	620 ± 490	6.9%[f]	−

[a] Inhibition of [^{125}I]BH−SP binding in human IM-9 cells (lymphoblast cells). Mean ± SD value determined by at least three independent experiments (n = 3−6) run in duplicate unless otherwise noted. [b] Capsaicin-induced tracheal plasma extravasation in guinea pigs. To determine the ID$_{50}$ values, 5−8 animals were used at each dose. 95% Confidence limits are given in parentheses. [c] Mean value of two independent experiments run in duplicate. [d] Not tested (−). [e] IC$_{50}$ value determined by a single experiment run in duplicate. [f] Inhibition (%) at 1.0 mg/kg (n = 5 or 6).

(BH)-SP binding in human IM-9 cells[6] and in vivo for inhibition of capsaicin-induced plasma extravasation in the trachea of guinea pigs[7] upon iv and po administration.

Results and Discussion

(a) Atropisomers of *N*-[3,5-Bis(trifluoromethyl)-benzyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide (1). Since the *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methylcarboxamide moiety in **1*t***[1a] is substituted at a sterically hindered position, the rotation around the −C$_{(6)}$−C(=O)− bond is presumed to be restricted, which results in the formation of the separable atropisomers (**1*t*-A** and **1*t*-B**) (Scheme 1). The presence of the atropisomers is, in fact, implied by the following: (1) the NMR spectrum of **1*t***[1a] shows a distinct AB pattern for the methylene protons of the *N*-benzyl group, indicating slow interconversion on the NMR time scale; (2) in the molecular view of **1*t*** as determined by X-ray analysis,[1a] the atropisomers (**1*t*-A** and **1*t*-B**) are observed in the crystalline unit cell (space group: $P2_1/n$); (3) a rather large energy barrier for interconversion between **1*t*-A** and **1*t*-B** (34 kcal/mol), determined on the basis of molecular mechanics calculations using DISCOVER,[8] suggests restricted interconversion; and (4) separability of some sterically hindered aromatic carboxamides into enantiomers due to atropisomerism has been reported.[9] With these points in mind, we analyzed compound **1*t*** by high-performance liquid chromatography (HPLC) using a chiral column.[10] As anticipated, two equal peaks were observed on the chromatogram, and **1*t*-A** and **1*t*-B** were each successfully separated by preparative HPLC at room temperature as oily substances. Compounds **1*t*-A** and **1*t*-B**, which have opposite [α]$_D$ values (−34.2° and +35.0°, respectively), were found to be quite stable in solution; e.g., they were not interconverted in dimethyl sulfoxide (DMSO) after 16 h at 37 °C and underwent racemization only after storage at 50 °C for ca. 3 days ($t_{1/2}$ = 6.4 h). The atropisomers exhibited different affinities for the NK_1 receptor (both in vitro and in vivo (iv)); the potency of **1*t*-A** is ca. 6−13-fold higher than that of **1*t*-B** (Table 1),[11] which indicates that the conformation of **1*t*-A** is preferentially recognized by the NK_1 receptor. From the SAR data obtained for its methyl analogues (i.e., **3**) (see part b, Results and Discussion), it is deduced that the active atropisomer **1*t*-A** has the (*R*)-configuration with the amide oxygen below (and the nitrogen above) the plane of the 1,7-naphthyridine ring.[12] The presence of atropisomers in the *cis*-amide isomer (**1*c*-A** and **1*c*-B**) was also revealed by HPLC analysis. As a consequence, four stereoisomers are present in **1** as shown in Scheme 1.

From a practical point of view, however, separation of the stereoisomers to obtain the active atropisomer **1*t*-A** by preparative HPLC is difficult, and further study using **1*t*** as a racemate would meet with difficulty, especially at the stage of pharmaceutical development. Thus, we designed new chiral analogues of **1*t*** (**3**) with (*R*)- and (*S*)-methyl groups at the benzylic methylene portion, in the hope of selective formation and/or practical preparation of the active atropisomer(s) and to determine the absolute stereochemistry of the atropisomers **1*t*-A** and **1*t*-B**.

(b) Atropisomers of Chiral Methyl Analogues of 1*t* (2 and 3). As an approach to the selective formation of the atropisomer, we investigated N-methylation of (*R*)- and (*S*)-*N*-[1-(substituted)phenylethyl]carboxamides **7** and **8** expecting a kinetically controlled methylation. First, N-methylation of (*S*)-*N*-(1-phenylethyl)carboxamide (**7**) was examined as a model experiment. Diastereomeric atropisomers, **2A** and **2B**, were formed in the reaction, and when the reaction was conducted at −60 °C in dimethyl formamide (DMF), high stereoselectivity with a ratio of ca. 93:7 (determined by NMR) was observed. The ratio changed depending on the temperature; at 0 °C the ratio decreased to ca. 72:28. These isomers were easily separated by crystallization

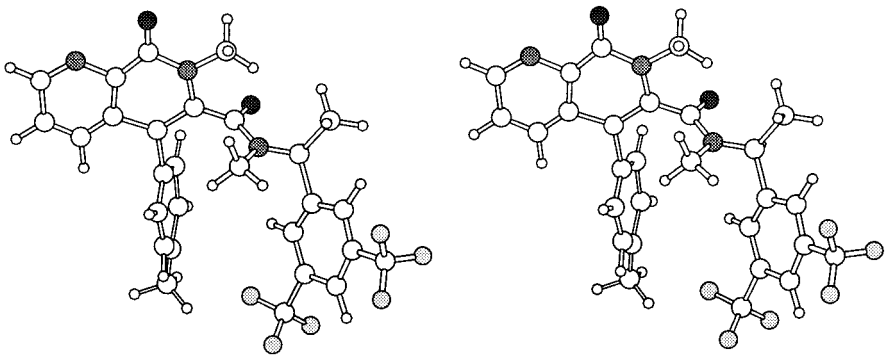


Figure 2. Stereoscopic molecular view of **3a-A** as determined by X-ray crystallographic analysis. The black, shaded, and dotted circles indicate oxygen, nitrogen, and fluorine atoms, respectively.

and/or column chromatography. Stability of these isomers in solution was similar to that of **1*t*-A** and **1*t*-B**; e.g., **2A** and **2B** were stable in ethyl acetate at room temperature for 16 h without interconversion and underwent racemization when heated at 110 °C in toluene for 1 h. The amide rotamers of **2A** and **2B** were not observed by NMR and TLC analyses; they presumably exist predominantly as the preferred trans-isomer due to the steric bulkiness of the *N*-(1-phenylethyl) group. The relative stereochemistry of **2A** and **2B** was determined on the basis of NMR data in comparison with the data obtained for **3a-A** and **3a-B** (see discussion below).

After obtaining these promising data, we next investigated N-methylation of the (*S*)-*N*-[1-[3,5-bis(trifluoromethyl)phenyl]ethyl]carboxamide derivative **8a**. However, contrary to our expectation, the alkylation of **8a** in DMF at −60 °C in the presence of NaH was slow and the selectivity was poor as compared to the reaction of **7**, affording the diastereomeric atropisomers **3a-A** and **3a-B** with a ratio of ca. 47:53 (determined by HPLC) and 35% conversion after a 3-h reaction. When conducted at 0 °C, the reaction was completed in 1 h, but the ratio was unchanged (ca. 45:55). Several attempted modifications of the reaction conditions, such as temperature (−70 to 27 °C), solvents (THF, dichloromethane, toluene), and bases (lithium diisopropylamide, methylmagnesium chloride, potassium *tert*-butoxide), failed to significantly improve the selectivity, and only the addition of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) in the reaction using methyl iodide and potassium *tert*-butoxide in THF at −60 °C resulted in moderate, but undesired (see discussion concerning the activity below), selectivity, giving **3a-A** and **3a-B** in a ratio of ca. 27:73 with a 59% yield after a 1-h reaction. At present, the reason for this notable difference in selectivity between the methylation reactions of **7** and **8a** is not clear. One explanation could be that bulky trifluoromethyl groups at meta-positions in the benzylic phenyl group of **8a** alter the conformation of the intermediary stable anion of **8a** from that of **7**.[13] Although the selectivity was unsatisfactory, separation of the diastereomers (**3a-A** and **3a-B**) by column chromatography was achieved without difficulty, affording **3a-A** and **3a-B** in enantiomerically pure forms. Similarly, by methylation of the (*R*)-*N*-[1-[3,5-bis(trifluoromethyl)phenyl]ethyl]carboxamide derivative **8b**, their enantiomers having an (*R*)-methyl group, **3b-B** and **3b-A**, were prepared.

The stereochemistry of **3a-A** was determined by single-crystal X-ray analysis (Figure 2), which revealed that **3a-A** has the (*R*)-configuration at the axial chiral center, with the amide nitrogen disposed above the plane of the adjacent 1,7-naphthyridine ring and the amide oxygen below the ring, and the (*S*)-configuration at the benzylic methylene portion, and allowed elucidation of the relative and absolute configuration of the stereoisomers **3a-B**, **3b-A**, and **3b-B**: (*aS*,*S*), (*aR*,*R*), and (*aS*,*R*), respectively. In the crystal structure of **3a-A**, a similar stacking (or stacking-like) conformation between the $C_{(5)}$-phenyl and the *N*-benzylic phenyl groups as observed in the X-ray analysis of **1*t***[1a] is also seen.

The conformations of the three compounds with the (*aR*)-configuration, **1*t*-A** (*aR*), **3a-A** (*aR*,*S*), and **3b-A** (*aR*,*R*), were analyzed using MO calculation. Figure 3 shows their most stable conformations as determined by the analysis. Here again, a stacking (or stacking-like) conformation between the two phenyl groups is the most stable for **1*t*-A** and **3a-A**, whereas an extended conformation between the two phenyl groups is the most stable for **3b-A**. This conformational difference between **3a-A** and **3b-A** seemed to be reflected in the difference in activity (described below). The ^{1}H NMR analysis of the (*aR*,*S*)-isomer **3a-A** and its (*aS*,*S*)-diastereomer **3a-B** (in $CDCl_3$) provided the solution conformations in good agreement with those obtained by the conformational analysis. That is, the aromatic ring protons ($C_{(4)}$-H, $C_{(5)}$-phenyl protons (4H) and benzylic phenyl protons (2H)) and the methyl protons on the $C_{(5)}$-phenyl of **3a-A** were observed in the upper field compared to those of **3a-B** (Δ 0.11−0.34 ppm), suggesting a stacking (or stacking-like) conformation between the two phenyl groups in **3a-A**, and also the upward field shift of the chemical shift (δ = 0.936 ppm) of the methyl protons at the benzylic methylene portion of **3a-B** as compared to **3a-A** (δ = 1.597 ppm) suggests that **3a-B** has a conformation in which the methyl group is over the plane of the $C_{(5)}$-phenyl ring and consequently the benzylic phenyl group is in the extended arrangement.

The stability of **3a-A** and **3a-B** in solution was similar to that of **1*t*-A** and **1*t*-B**: **3a-A** and **3a-B** were stable in DMSO at room temperature for 16 h without interconversion and underwent racemization when heated at 50 °C in DMSO for ca. 160 h ($t_{1/2}$ = 4.5 h).

The NK_1 antagonistic activities (in vitro and in vivo) of the 1,7-naphthyridine-6-carboxamide stereoisomers (**2** and **3**) are shown in Table 1. The in vitro SARs of the four stereoisomers of **3** (**3a-A**, **3a-B**, **3b-A**, and **3b-**

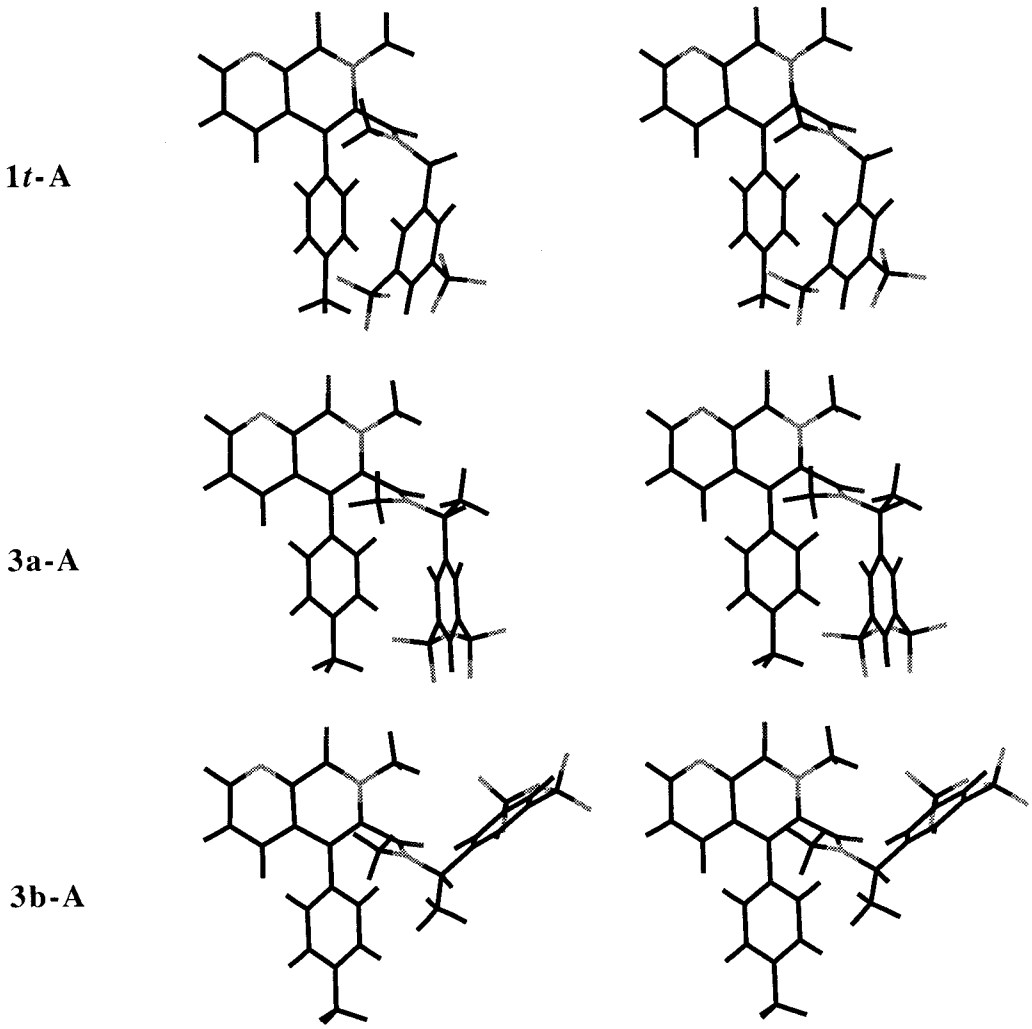


Figure 3. Stereoscopic view of the most stable conformations of the three compounds with the (*aR*)-configuration, **1*t*-A** (*aR*) (top), **3a-A** (*aR,S*) (middle), and **3b-A** (*aR,R*) (bottom), as determined by the conformational analysis using MO calculation. The shaded lines indicate heteroatoms (nitrogen, oxygen, and fluorine). In **3a-A**, a stacking-like conformation between the two phenyl rings shown in this figure is more stable than its extended conformation by 2.67 kcal/mol, while in **3b-A**, an extended conformation shown in this figure is more stable than its stacking-like conformation by 0.73 kcal/mol.

B) clearly indicate the stereochemistry required for high-affinity binding to the NK_1 receptor in this series of antagonists. Among these isomers, the (*aR,S*)-isomer **3a-A** showed the most potent activity with an IC_{50} value of 0.80 nM; the activity is ca. 1/3-fold weaker than that of **1*t*-A**, suggesting that the introduction of the methyl group at the benzylic methylene portion of **1*t*** has a slightly deleterious effect on receptor binding. The affinity of the (*aS,R*)-enantiomer **3b-B** was the weakest with an IC_{50} value of 620 nM, and the isomers **3a-B** (*aS,S*) and **3b-A** (*aR,R*), which are presumed to have the extended arrangement of the two phenyl rings as described above, showed moderate activities with IC_{50} values on the 10^{-8} M level. The in vivo (iv) activity of these isomers corresponds well to their in vitro potency; **3a-A** was the most potent with an ED_{50} value of 9.3 μg/kg, and **3b-B** was the weakest. Upon oral administration, **3a-A** exhibited significantly potent activity with an ED_{50} value of 67.7 μg/kg, suggesting good oral availability of **3a-A**.

As anticipated from our preceding study,[1a] compounds **2A** and **2B**, which are unsubstituted at the benzylic phenyl, showed weak in vitro activity. However, it is noteworthy that the preference of the absolute stereochemistry for the receptor binding is also seen with these compounds: i.e., **2A** (*aR,S*) > **2B** (*aS,S*).

Conclusions

This study has demonstrated that the 1,7-naphthyridine-6-carboxamides **1**−**3** exist as a mixture of separable and stable atropisomers originating from the restricted rotation around the $-C_{(6)}-C(=O)-$ bond. The SARs for these atropisomers, along with the conformational analysis of **3** by NMR and MO calculation, indicate that the (*R*)-configuration at the axial bond and the stacking (or stacking-like) conformation between the two phenyl rings (the $C_{(5)}$-phenyl and benzylic phenyl) as shown in **1*t*-A** and **3a-A** are important for NK_1 receptor binding. These results enable us to further refine our pharmacophore models previously reported[1] and suggest that the $-C_{(6)}-C(=O)-N(Me)-$ moiety in this class of antagonists functions not only as a spacer between the two phenyl rings but also as the hydrogen bond acceptor in the interaction with the receptor. From a synthetic point of view, however, selective preparation of the active atropisomers remains to be explored. Approaches toward the active atropisomers

by asymmetric induction at the axial chiral center are currently under investigation, and the results will be reported elsewhere.[14]

Experimental Section

Chemistry. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were taken on a Varian Gemini 200 (200 MHz) spectrometer in $CDCl_3$ unless otherwise noted; ^{1}H NMR spectra of **3a-A** and **3a-B** were taken on a Bruker DPX-300 (300 MHz) spectrometer. Chemical shifts are 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, m = multiplet, dd = double doublet, bs = broad singlet, bt = broad triplet. Optical rotations were determined on a JASCO DIP-370 digital polarimeter at 20 °C at the sodium D-line; the concentrations are reported g/100 mL. Circular dichroism (CD) spectra were obtained at 25 °C with a JASCO J-720 spectropolarimeter. The sample cell was 1 cm, and the slit was programmed for a spectral bandwidth of 1.0 nm. Cutoff was indicated when the dynode voltage reached ca. 400 V. The concentrations given with the CD spectra are g/100 mL. Mass spectra were obtained on a JEOL JMS-AX505W spectrometer. Elemental analyses were within ±0.4% of the theoretical values for the elements indicated unless otherwise noted. Extracted solutions were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4. The yields reported are not optimized.

Separation of Atropisomers (1*t*-A and 1*t*-B) of *trans*-*N*-[3,5-Bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide (1*t*). Compound **1*t***[1a] was separated into the atropisomers (**1*t*-A** and **1*t*-B**) by preparative high-performance liquid chromatography (HPLC) using Chiralpak AD (10.0 mm ϕ × 250 mm) (DAICEL Chemical Industries, Ltd., Japan) under detection at 254 nm using a mixture of hexane−EtOH (90:10) as the eluant at a flow rate of 2.4 mL/min at 28 °C to give **1*t*-A** and **1*t*-B** as oily substances. **1*t*-A**: ca. 90% ee; retention time = 28.2 min; $[\alpha]_D = -34.2°$ (c = 0.1, $CHCl_3$). **1*t*-B**: ca. 90% ee; retention time = 22.7 min; $[\alpha]_D = +35.0°$ (c = 0.1, $CHCl_3$).

(*S*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethylamine Hydrochloride (6a) and Its (*R*)-Isomer (6b). The separation of(±)-*N*-(benzyloxycarbonyl)-1-[3,5-bis(trifluoromethyl)phenyl]-ethylamine (7.27 g, 18.6 mmol) was carried out by HPLC [column, Chiralcel OD (DAICEL Chemical Industries, Ltd., Japan), 20.0 mm ϕ × 250 mm; eluant, hexane−2-propanol = 95:5; flow rate, 8.0 mL/min; detection, UV 254 nm], followed by hydrogenation and treatment with 4 N HCl−EtOAc to give **6a** (2.56 g, 47%) and **6b** (2.63 g, 48%), each as colorless crystals. **6a**: recrystallization from EtOH−hexane gave colorless crystals; mp ca. 220 °C (sublimated); $[\alpha]_D = -3.3°$ (c = 0.250, MeOH); CD[15] (c = 0.002 56, MeOH) $[\theta]_{315} = +14\,043$, $[\theta]_{253} = +22\,838$ [lit.[16] $[\alpha]_D = -9.8°$ (neat, 0.5 dm) (71% ee); CD[15] (MeOH) $[\theta]_{318} = +18\,000$, $[\theta]_{252} = +33\,000$ (molecular ellipticity adjusted to 100% ee)]; ^{1}H NMR (DMSO-d_6) 1.58 (3H, d, J = 6.6), 4.68 (1H, m), 8.14 (1H, s), 8.34 (2H, s), 8.81 (3H, m). Anal. ($C_{10}H_{10}ClF_6N$) C, H, N. **6b**: recrystallization from EtOH−hexane gave colorless crystals; mp ca. 220 °C (sublimated); $[\alpha]_D = +3.2°$ (c = 0.252, MeOH); CD[15] (c = 0.002 28, MeOH) $[\theta]_{315} = -13\,500$, $[\theta]_{252} = -21\,765$; ^{1}H NMR (DMSO-$d_6$) identical to that of **6a**. Anal. ($C_{10}H_{10}ClF_6N \cdot {}^1/_2H_2O$) C, H, N.

(*S*)-7,8-Dihydro-7-methyl-5-(4-methylphenyl)-8-oxo-*N*-(1-phenylethyl)-1,7-naphthyridine-6-carboxamide (7). Thionyl chloride (0.74 mL, 10.1 mmol) and DMF (catalytic amount) were added to a solution of 7,8-dihydro-7-methyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxylic acid (**4**)[1a] (590 mg, 2.00 mmol) in 1,2-dichloroethane (20 mL) at room temperature, and the mixture was refluxed for 3 h. After evaporation of the solvent, the residue was dissolved in 1,2-dichloroethane (30 mL). To this solution were added (*S*)-1-phenylethylamine (**5**) (0.31 mL, 2.40 mmol) and Et_3N (0.84 mL, 6.03 mmol), and the mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the resulting crystals were collected by filtration and washed successively with H_2O, ethyl ether, and diisopropyl ether (IPE) to give **7** as colorless crystals (530 mg, 67%). Recrystallization from MeOH−IPE gave colorless crystals: mp 287−288 °C; ^{1}H NMR 1.25 (3H, d, J = 7.0), 2.44 (3H, s), 3.47 (3H, s), 5.01 (1H, m), 7.0−7.6 (12H, m), 8.61 (1H, m). Anal. ($C_{25}H_{23}N_3O_2 \cdot {}^1/_2H_2O$) C, H, N.

(*S*)-*N*-[1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-7,8-dihydro-7-methyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide (8a). Compound **4** (1.40 g, 3.52 mmol) was treated according to a procedure similar to that described for the preparation of **7** using **6a** in place of **5** to afford **8a** as colorless crystals (1.12 g, 60%). Recrystallization from EtOAc−IPE gave colorless crystals: mp 197−199 °C; $[\alpha]_D = -19.0°$ (c = 0.25, $CHCl_3$); ^{1}H NMR 1.40 (3H, d, J = 7.0), 2.38 (3H, s), 3.07 (1H, m), 3.50 (3H, s), 5.10 (1H, m), 7.05−7.30 (3H, m), 7.36 (1H, d, J = 6.6), 7.49 (1H, d, J = 8.0), 7.79 (1H, s), 7.89 (2H, s), 8.13 (1H, d, J = 8.6), 8.62 (1H, d, J = 3.2). Anal. ($C_{27}H_{21}F_6N_3O_2$) C, H, N.

(*R*)-*N*-[1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-7,8-dihydro-7-methyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide (8b). Compound **4** (840 mg, 2.11 mmol) was treated according to a procedure similar to that described for the preparation of **7** using **6b** in place of **5** to afford **8b** as colorless crystals (910 mg, 81%). Recrystallization from EtOAc−IPE gave colorless crystals: mp 197−199 °C; $[\alpha]_D = +18.2°$ (c = 0.248, $CHCl_3$); ^{1}H NMR identical to that of **8a**. Anal. ($C_{27}H_{21}F_6N_3O_2$) C, H, N.

(*aR*,*S*)-7,8-Dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-*N*-(1-phenylethyl)-1,7-naphthyridine-6-carboxamide (2A) and Its (*aS*,*S*)-Isomer (2B). A mixture of **7** (450 mg, 1.13 mmol), NaH (60% dispersion in oil) (99 mg, 2.48 mmol), and DMF (20 mL) was stirred at room temperature for 30 min. The mixture was cooled to 0 °C, and iodomethane (0.5 mL, 8.0 mmol) was added to it. The resulting mixture was stirred at room temperature for 30 min, added to H_2O, and then extracted with EtOAc. The extract was washed with H_2O, dried, and then concentrated. The concentrate, which contained **2A** and **2B** in a ratio of ca. 72:28 as determined by ^{1}H NMR, was subjected to chromatography on silica gel using EtOAc−MeOH (9:1) as the eluant to give **2A** (142 mg, 31%) from the more polar fraction and **2B** (18.6 mg, 4%) from the less polar fraction, each as colorless crystals. **2A**: recrystallization from acetone−ethyl ether gave colorless crystals; mp 233−234 °C; $[\alpha]_D = -54.2°$ (c = 0.184, MeOH); ^{1}H NMR 1.52 (3H, d, J = 6.8), 2.40 (3H, s), 2.54 (3H, s), 3.69 (3H, s), 5.82 (1H, q, J = 6.8), 6.47 (2H, d, J = 7.4), 7.0−7.3 (5H, m), 7.35−7.55 (3H, m), 7.62 (1H, dd, J = 8.2, 1.8), 8.90 (1H, dd, J = 4.4, 1.8). Anal. ($C_{26}H_{25}N_3O_2$) C, H, N. **2B**: recrystallization from EtOAc−IPE gave colorless crystals; mp 229−231 °C; $[\alpha]_D = +36.0°$ (c = 0.1785, MeOH); ^{1}H NMR 0.85 (3H, d, J = 6.8), 2.39 (3H, s), 2.45 (3H, s), 3.66 (3H, s), 5.86 (1H, q, J = 6.8), 7.12−7.52 (10H, m), 7.69 (1H, dd, J = 8.4, 2.0), 8.90 (1H, dd, J = 4.0, 2.0); MS (electron impact) m/z 411 (M^+). When the above reaction was conducted at −60 °C, the product ratio (**2A**:**2B**) changed to ca. 93:7.

(*aR*,*S*)-*N*-[1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide (3a-A) and Its (*aS*,*S*)-Isomer (3a-B). Compound **8a** (460 mg, 0.86 mmol) was treated at 0 °C according to a procedure similar to that described for the preparation of **2** to form **3a-A** and **3a-B** in a ratio of ca. 45:55 (determined by HPLC). These two compounds were separated by column chromatography on silica gel using EtOAc−MeOH (9:1) as the eluant to afford **3a-A** (56 mg, 12%) from the more polar fraction and **3a-B** (109 mg, 23%) from the less polar fraction, each as colorless crystals. **3a-A**: recrystallization from EtOAc−IPE gave colorless crystals; mp 164−165 °C; $[\alpha]_D = -50.9°$ (c = 0.242, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.597 (3H, d, J = 7.1), 2.349 (3H, s), 2.590 (3H, s), 3.675 (3H, s), 5.878 (1H, q, J = 7.1), 6.962 (1H, dd, J = 7.8, 1.9), 7.106 (1H, dd like), 7.189 (1H, dd like), 7.314 (1H, dd, J = 7.8, 1.9), 7.368 (2H, s like), 7.449 (1H, dd, J = 8.4, 4.3), 7.550 (1H, dd, J = 8.4, 1.7), 7.781 (1H, s like), 8.900 (1H, dd, J = 4.3, 1.7); MS

(electron impact) *m*/*z* 547 (M^+). Anal. ($C_{28}H_{23}F_6N_3O_2$) C, H, N. **3a-B**: recrystallization from EtOAc−IPE gave colorless crystals; mp 194−196 °C; $[\alpha]_D = +43.7°$ ($c = 0.207$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 0.936 (3H, d, $J = 7.1$), 2.428 (3H, s), 2.458 (3H, s), 3.655 (3H, s), 5.920 (1H, q, $J = 7.1$), 7.185 (1H, dd, $J = 7.8, 1.9$), 7.303 (1H, dd like), 7.347 (1H, dd like), 7.422 (1H, dd, $J = 7.8, 1.9$), 7.491 (1H, dd, $J = 8.4, 4.3$), 7.709 (1H, dd, $J = 8.4, 1.7$), 7.709 (2H, s like), 7.828 (1H, s like), 8.919 (1H, dd, $J = 4.3, 1.7$); MS (electron impact) *m*/*z* 547 (M^+). Anal. ($C_{28}H_{23}F_6N_3O_2$) C, H, N.

(*aR*,*R*)-*N*-[1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide (3b-A) and Its (*aS*,*R*)-Isomer (3b-B). Compound **8b** (840 mg, 1.57 mmol) was treated at 0 °C according to a procedure similar to that described for the preparation of **2** to form **3b-A** and **3b-B** in a ratio of ca. 55:45 (determined by HPLC). These two compounds were separated by column chromatography on silica gel using EtOAc−MeOH (9:1) as the eluant to afford **3b-B** (38 mg, 4%) from the more polar fraction and **3b-A** (136 mg, 16%) from the less polar fraction, each as colorless crystals. **3b-A**: recrystallization from EtOAc−IPE gave colorless crystals; mp 194−196 °C; $[\alpha]_D = -43.7°$ ($c = 0.212$, $CHCl_3$); ^{1}H NMR identical to that of **3a-B**. Anal. ($C_{28}H_{23}F_6N_3O_2$) C, H, N. **3b-B**: recrystallization from EtOAc−IPE gave colorless crystals; mp 164−165 °C; $[\alpha]_D = +51.1°$ ($c = 0.242$, $CHCl_3$); ^{1}H NMR identical to that of **3a-A**; MS (electron impact) *m*/*z* 547 (M^+).

All the isomers (**3a-A**, **3a-B**, **3b-A**, and **3b-B**) were shown to have >99.9% ee [determined by chiral HPLC (Chiralcel OD, 4.6 mm ϕ × 250 mm; eluant, hexane−ethanol = 85:15; flow rate, 0.6 mL/min; detection, UV 247 nm)] and >99.9% diastereomeric excess [determined by HPLC (Puresil 5-μm C18, 120 Å, 4.6 mm ϕ × 150 mm; eluant, 50 mM KH_2PO_4 (pH = 6.5)−CH_3CN = 1:1; flow rate, 0.8 mL/min; detection, UV 247 nm)].

Single-Crystal X-ray Analysis of 3a-A. Crystals of **3a-A** were grown from EtOAc−ethyl ether. Data were collected on a diffractometer, Rigaku AFC5R, and corrected for Lorentz and polarization factors. A Ψ-scan absorption correction was applied. The structure was solved by direct methods with the aid of TEXSAN[17] and refined by CRYLSQ[18] in the XTAL package. The parameters refined include the coordinates and anisotropic thermal parameters for non-hydrogen atoms. Hydrogen atoms were included using a riding model (dH = 1.09 Å). Thermal parameters of hydrogen atoms were taken from their bonded atoms as Uiso and fixed through the next several cycles of refinement. The two trifluoromethyl groups were treated as groups respectively and only the isotropic thermal parameters were refined due to their highly disordered nature. The authors presume that this disordered structure and small volume of the crystal lead to a large final *R*-factor of 0.16. In the asymmetric unit of the crystal structure, two molecules (**I** and **II** in the Supporting Information) with slightly different positions of the 3,5-bis(trifluoromethyl)phenyl ring were observed. Among them, the stereoscopic view of molecule **I** is shown in Figure 2. The crystal data and data collection details are summarized in Table 2. The atomic coordinates, thermal parameters, bond distances, bond angles, and torsion angles are available as Supporting Information.

Molecular Modeling Studies. The systematic conformational search (SCS) was performed using Search/Compare Module in Insight II (ver. 95.5.6, Molecular Simulations Inc., San Diego, CA). Preliminary search were carried out by SCS standard mode under the following conditions. Increments of bond rotation were set to 30° and 180° for all rotatable single bonds and an amide bond, respectively. Scale radii values for van der Waals were set to 0.7, 0.65, and 0.5 for vicinal atoms, hydrogen bonds, and the other atoms, respectively. After preliminary search, SCS energy mode calculations were executed to obtain stable conformations within 10 kcal/mol above the lowest energy. Local minimum conformers were obtained by full energy minimization using AM1 calculation (MOPAC ver. 6.00, QCPE Program by J. J. Stewart) for representative conformations which were selected by an in-house program from the previous systematic search results.

Rotational barriers were estimated by Discover CVFF force field (ver. 2.9.7, Molecular Simulations Inc., San Diego, CA) using torsional forcing as a constraint. During those calculations, the force constant of the constraint was set to 100 kcal/mol/Å^2, and increments of bond rotation were set to 10° and 180° for all rotatable single bonds and an amide bond, respectively. The calculated energy was plotted against the torsion angle around the $-C_{(6)}-C(C{=}O)-$ bond.

[^{125}I]BH-SP Binding in Human IM-9 Cells. The binding activities were determined according to the protocol previously reported.[1a]

Inhibitory Effect on Capsaicin-Induced Plasma Extravasation in the Trachea of Guinea Pigs. The inhibitory effect was determined according to the protocol previously reported.[1a]

Table 2. Crystal Data and Summary of Data Collection

formula	$C_{28}H_{23}F_6N_3O_2$
formula weight	547.44
crystal system	monoclinic
space group	$P2_1$
molecules/unit cell	4
cell dimensions	$a = 10.435(2)$ Å
	$b = 18.166(1)$ Å
	$c = 14.309(1)$ Å
	$\beta = 103.274(8)°$
	$V = 2640.0(5)$ Å^3
calculated density (g/cm^3)	1.377
absorption coefficient (cm^{-1})	10.08
crystal size (mm)	0.60 × 0.30 × 0.02
radiation	Cu Kα ($\lambda = 1.5418$ Å)
data collection range	$3° \le 2\theta \le 120°$
scan mode	$2\theta-\omega$
scan speed (deg/min)	16
unique reflections	4071
observed reflections ($F \ge 3\sigma F$)	2352
R, *Rw*	0.162, 0.101
weighting factor	$1/\sigma(F)^2$

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Supporting Information Available: Crystallographic data for **3a-A** (15 pages). Ordering information is given on any current masthead page.

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