Enantioselective synthesis of an axially chiral 1,7-naphthyridine-6-carboxamide derivative having potent antagonist activity at the NK_1 receptor

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A new and highly potent NK_1 antagonist, (*aR*,9*R*)-3 [(*aR*,9*R*)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7*H*-[1,4]diazocino[2,1-*g*][1,7]naphthyridine-6,13-dione], was atropdiastereoselectively synthesized in good yield by cyclization of the chiral intermediate 6b.

In our preceding papers,[1] we described the discovery[1a,b] and stereochemical characterization[1c] of the potent NK_1 antagonist[2] **1** {*N*-[3,5-bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-1,7-naphthyridine-6-carboxamide}. Since **1** has a tertiary carboxamide group at the sterically hindered C_6-position, it exhibits two notable stereochemical properties (Fig. 1). First, the *trans* and *cis* amide conformational isomers (rotamers) of **1** are separable at room temperature;[1a] the compound isolated by conventional work-up is the *trans*-isomer (*trans*-**1**), while the thermodynamically unstable *cis*-isomer (*cis*-**1**) can also be isolated as a minor product by careful separation procedures. Both isomers interconvert and reach an equilibrium state of a *ca.* 7:1 ratio in solution. Second, *trans*-**1** and *cis*-**1** exist as a mixture of two separable and stable enantiomers [(*trans*,*aR*)-**1**, (*trans*,*aS*)-**1** and (*cis*,*aR*)-**1**, (*cis*,*aS*)-**1**, respectively][3] arising from restricted rotation around the C_6–C(O) bond (Fig. 1).[1c] Such stereoisomerism due to restricted rotation is known as atropisomerism among biaryl compounds and some sterically hindered aromatic carboxamides.[4] The atropisomers, (*trans*,*aR*)-**1** and (*trans*,*aS*)-**1**, which were separated by preparative high performance liquid chromatography (HPLC) using a chiral column,‡ have significant stability in solution; *e.g.* they were not interconverted in DMSO at 37 °C for 16 h and underwent racemization only after storage at 50 °C for *ca.* 70 h. Among these four isomers of **1**, the active isomer was shown to be (*trans*,*aR*)-**1**. From a practical perspective, however, separation of the active isomer (*trans*,*aR*)-**1** is difficult, and further studies using *trans*-**1** as a racemate would encounter difficulties, especially at the stage of pharmaceutical development.

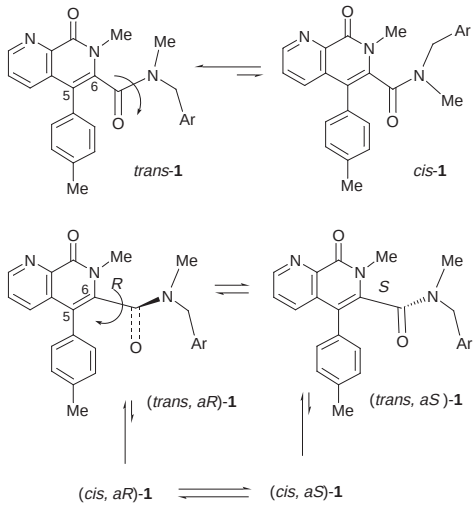
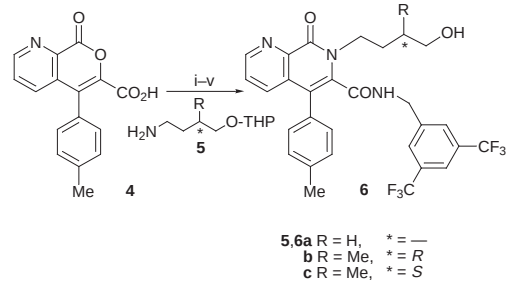


Fig. 1 The stereoisomers of **1**

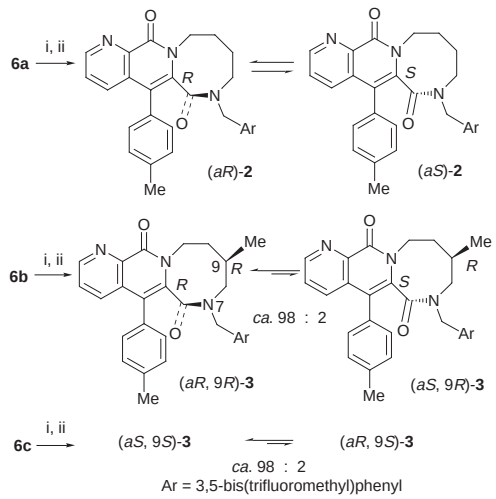
Thus, in the search for new compounds with an improved stereochemical profile, we designed cyclic analogues of **1**, and analogues with an eight-membered ring (*e.g.* **2** and **3**) (Scheme 2) became target molecules based on the results of conformational studies on *trans*-**1**. Here we describe the atropdiastereoselective synthesis of the potent NK_1 receptor antagonist (*aR*,9*R*)-**3** {(*aR*,9*R*)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7*H*-[1,4]-diazocino[2,1-*g*][1,7]naphthyridine-6,13-dione} by cyclization of the chiral intermediate **6b**.

General synthesis of tricyclic analogues of **1** (**2** and **3**) is outlined in Schemes 1 and 2. The key intermediates **6a–c** [7-(hydroxyalkyl)-1,7-naphthyridine-6-carboxamide derivatives] were prepared from the pyrano[3,4-*b*]pyridine-6-carboxylic acid **4**.[5] First, the acid **4** was amidated with 3,5-bis(trifluoromethyl)benzylamine *via* the acid chloride to provide the amide. Treatment of the amide with the appropriate amines **5a–c**,[6] followed by deprotection with TsOH and dehydration with DBU gave **6a–c** (Scheme 1). Cyclization of **6a–c** was accomplished by mesylation followed by treatment with NaH in THF to give **2** and **3** in good yields (Scheme 2).

For the atropisomers in the cyclic analogues of **1** (**2** and **3**), we initially supposed that the flipping of this new ring would be too rapid to enable the separation of stable isomers at room temperature.[7] However, chiral HPLC analysis of **2** showed two peaks at room temperature, and **2** was separated by preparative HPLC using a chiral column to give the atropisomers (*aR*)-**2** and (*aS*)-**2**, which have opposite $[\alpha]_D$ values (+45.6 and −41.3, respectively) and show considerable stability in solution; *e.g.* they are gradually interconverted in DMSO to *ca*. 70% ee at 37 °C over 40 h and undergo racemization after storage at 50 °C for *ca.* 60 h. These results indicate that **2** exists as a racemate, making development as a clinical candidate difficult. Thus, we



Scheme 1 *Reagents and conditions*: i, $SOCl_2$, THF, reflux, 1.5 h; ii, 3,5-bis(trifluoromethyl)benzylamine, Et_3N, THF, room temp., 0.5 h (71% from **4**); iii, **5**, THF–MeOH, room temp., 16 h ; iv, DBU, toluene–MeCN, reflux, 1 h; v, TsOH, MeOH, room temp., 0.5 h



Scheme 2 *Reagents and conditions*: i, MsCl, Et_3N, THF, 0 °C, 0.5 h; ii, NaH, THF, reflux, 1 h [isolated yields from **6**: 79% for **2**, 69% for (*aR*,9*R*)-**3** and 66% for (*aS*,9*S*)-**3**]

next designed the C_9 methyl analogues of **2** (*i.e.* **3**) as target compounds, expecting asymmetric induction from the C_9 chiral center to obtain the desirable chirality arising from atropisomerism, and achieved the stereoselective synthesis of the atropisomer by cyclization of an intermediate with a chiral methyl group, **6b** (Scheme 2). The product ratio of the atropisomer (*aR*,9*R*)-**3** to its isomer (*aS*,9*R*)-**3** was *ca.* 98:2, and a single recrystallization step gave (*aR*,9*R*)-**3** with > 99% de. The minor isomer (*aS*,9*R*)-**3**, with 98.6% de, was isolated as a powdery substance by repeated preparative HPLC at 0 °C using the mother liquor. Both atropisomers, (*aR*,9*R*)-**3** and (*aS*,9*R*)-**3**, were found to be gradually interconverted in solution to reach the same equilibrium state [(*aR*,9*R*)-**3**:(*aS*,9*R*)-**3** = *ca.* 98:2] (*e.g.* in EtOH at 37 °C in *ca.* 60 h).

Single crystal X-ray analysis of (*aR*,9*R*)-**3**[8] revealed that the N_7–C_8–C_9–C_{10} moiety in the eight-membered ring is disposed above the plane of the adjacent 1,7-naphthyridine ring, while the amide oxygen (C_6=O) is below the ring (*i.e. aR* stereochemistry). The relative spatial orientation of the C_9 methyl group and the *N*-[3,5-bis(trifluoromethyl)benzyl] group in (*aR*,9*R*)-**3** was shown to be such that the two groups are disposed in opposite directions. This is presumed to be a thermodynamically stable form which is important for the high atropdiastereoselectivity in the cyclization of **6b**.

The enantiomer of (*aR*,9*R*)-**3** [*i.e.* (*aS*,9*S*)-**3**], with > 99% de, was similarly obtained by the cyclization of the corresponding enantiomeric intermediate **6c** followed by a single recrystallization step (Scheme 2).

Compound (*aR*,9*R*)-**3** exhibited excellent NK_1 antagonistic activities§ both *in vitro* (IC_{50} = 0.45 nM) and *in vivo* (ED_{50} = 4.3 μg kg^{-1}). The structure–activity relationships in the isomers of **3** [for the atropisomer (*aS*,9*R*)-**3**: IC_{50} = 20 nM and ED_{50} = 26 μg kg^{-1}¶ and for the enantiomer (*aS*,9*S*)-**3**: IC_{50} = 340 nM and ED_{50} = > 300 μg kg^{-1}] indicate that the stereochemistry around C_{5a}–C_6(O)–N_7–CH_2Ar is the important factor for receptor recognition.

In summary, the axially chiral compound (*aR*,9*R*)-**3** and its enantiomer (*aS*,9*S*)-**3** were atropdiastereoselectively synthesized by cyclization of the chiral intermediates **6b** and **6c**, respectively. Compound (*aR*,9*R*)-**3** exhibited excellent NK_1 antagonistic activities both *in vitro* and *in vivo*.

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Notes and References

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‡ Chiralpack AD, DAICEL Chemical Industries, Ltd., Japan.
§ The NK_1 antagonistic activities were measured *in vitro* for inhibition of [^{125}I] Bolton-Hunter-SP binding in human IM-9 cells (ref. 9) and *in vivo* for inhibition of capsaicin-induced plasma extravasation in the trachea of guinea pigs (ref. 10).
¶ Since the purity of (*aS*,9*R*)-**3** is 98.6% de [*i.e.* it contains *ca.*1% of the active isomer (*aR*,9*R*)-**3**], its intrinsic antagonistic activities may be lower than those observed.

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