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Potent NK_1 Receptor Antagonists: Synthesis and Antagonistic Activity of Various Heterocycles with an *N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl Substituent

Yoshinori IKEURA,*[,a] Toshimasa TANAKA,[a] Yutaka KIYOTA,[a] Shinji MORIMOTO,[a] Masaki OGINO,[a] Takenori ISHIMARU,[b] Izumi KAMO,[a] Takayuki DOI,[a] and Hideaki NATSUGARI[a]

Pharmaceutical Research Division,[a] Takeda Chemical Industries, Ltd., 2–17–85, Jusohonmachi, Yodogawa-ku, Osaka 532, Japan and Discovery Research Division,[b] Takeda Chemical Industries, Ltd., 10 Wadai, Tsukuba-shi, Ibaraki 305, Japan. Received April 28, 1997; accepted June 30, 1997

Various *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl heterocycles (1, 2 and 3) modified at rings A and B in the isoquinolone (1a) and pyrido[3,4-*b*]pyridine (2a) nuclei were prepared and evaluated for NK_1 receptor antagonistic activities. The structure–activity relationship studies on this series, along with conformational analysis, showed that (i) for ring A, 6-membered heterocycles are preferable to 5-membered heterocycles (a *ca.* 300-fold difference in potency), (ii) the 6-membered ring seems to function as an anchor by fixing the pendant phenyl group in a desirable orientation for receptor binding, and (iii) since compounds with aromatic rings (2) and those with aliphatic rings (3) as ring B both show good potency, this ring does not seem to be essential for receptor recognition. Among the compounds synthesized, the tetrahydropyridine derivatives 3a, 3b and 3f exhibited excellent inhibitory effects both *in vitro* and *in vivo*, with potent activity upon oral administration (ED_{50} = 0.20—0.27 mg/kg) (capsaicin-induced plasma extravasation in guinea pig trachea).

Key words tachykinin; substance P; NK_1 receptor antagonist; *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl-heterocycle; conformational analysis

Substance P (SP), a member of the tachykinin family, has been shown to elicit a wide variety of biological responses in both the central nervous system and peripheral tissues, including the transmission of pain and stress signals, inflammation and the contraction of smooth muscles.[1] The biological responses induced by SP are primarily mediated by binding to the NK_1 receptor. Recently, orally active non-peptide NK_1 antagonists with a wide variety of distinct chemical structures (*e.g.*, SR140333,[2] RPR100893,[3] CP-122,721,[4] CGP49823,[5] GR205171,[6] LY303870,[7] L-741,671[8] and L-742,694[9]) have been disclosed, and their clinical potential in the treatment of various pathological states, such as pain, inflammation, rheumatoid arthritis, asthma, emesis and migraine, has been proposed.

In our preceding paper,[10] we reported the discovery of a novel type of highly potent and orally active NK_1 antagonist, the *N*-benzylcarboxamide derivatives of isoquinolone (**1a**) and pyrido[3,4-*b*]pyridine (1,7-naphthyridine) (**2a**), through extensive structure–activity relationship (SAR) studies starting from an isoquinolone-urea lead. The SAR and conformational studies on **2a-2** and CP-99,994, a representative NK_1 antagonist,[11] indicated that the spatial orientation of two phenyl rings (*i.e.*, benzylic phenyl and pendant phenyl) and the hetero atom in the carboxamide moiety are important for NK_1 receptor recognition.[10] In the hope of obtaining NK_1 antagonists with a better pharmacokinetic profile and learning more about the receptor recognition, we have done further studies on compounds related to **1a** and **2a**. This paper describes the synthesis and the SAR of a series of *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl heterocycles (**1**, **2** and **3**) obtained by modification of rings A and B in **1a** and **2a** (Fig. 1).

Chemistry

The *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl derivatives of various cyclic and non-cyclic compounds having a diphenylmethane moiety (**1**) were generally synthesized from the corresponding carboxylic acids **4** by amidation with *N*-methyl-3,5-bis(trifluoromethyl)benzylamine (Chart 1). The quinoline-amide **1c** was prepared from the quinoline-ester **5** *via* **6** by reaction with methylamine, followed by alkylation with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH. The starting carboxylic acids **4** and the quinoline-ester **5** were prepared by procedures based on literature protocols.[10,12–17]

Chart 2 shows the methods used for the preparation of the carboxamide derivatives of isoquinolone-related heterocycles (**2**), in which the carboxylic acids **14** were chosen as key intermediates. The intermediates **14** were synthesized *via* synthetic routes a and b from the benzoyl-carboxylic acids **8** which were obtained by the Friedel–Crafts reaction or Grignard reaction of the anhydrides **7**. In route a, condensation of **8** with sarcosine ethyl ester gave the amides **9**, which were cyclized and dehydrated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the esters **11**. Alkaline hydrolysis of **11** gave the acids **14**. In the case of preparing **14d**, route b was used. Thus, **8d** [2-(4-fluorobenzoyl)-3-pyridinecarboxylic acid] was condensed with *N*-methylaminoacetonitrile to provide the amide **10d**, which was cyclized and dehydrated with DBU to afford the nitrile **12d**. Alkaline hydrolysis of **12d** gave the amide **13d**, which was treated with $NaNO_2$ in concentrated HCl–AcOH to give the acid **14d**. The acids **14a—h** thus obtained were converted to the carboxamide derivatives **2a—h** by reaction with *N*-methyl-3,5-bis(trifluoromethyl)benzylamine *via* the acid chlorides.

The tetrahydro derivatives of the pyridopyridine-

* To whom correspondence should be addressed.

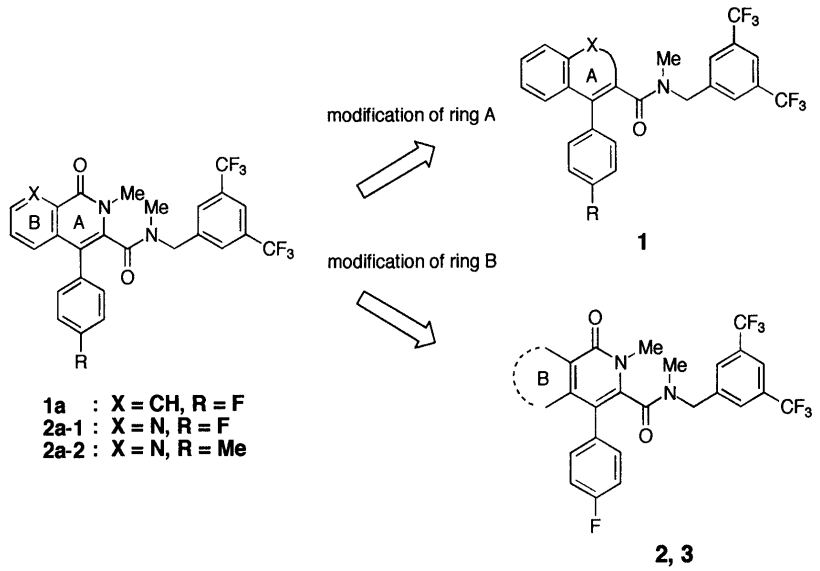
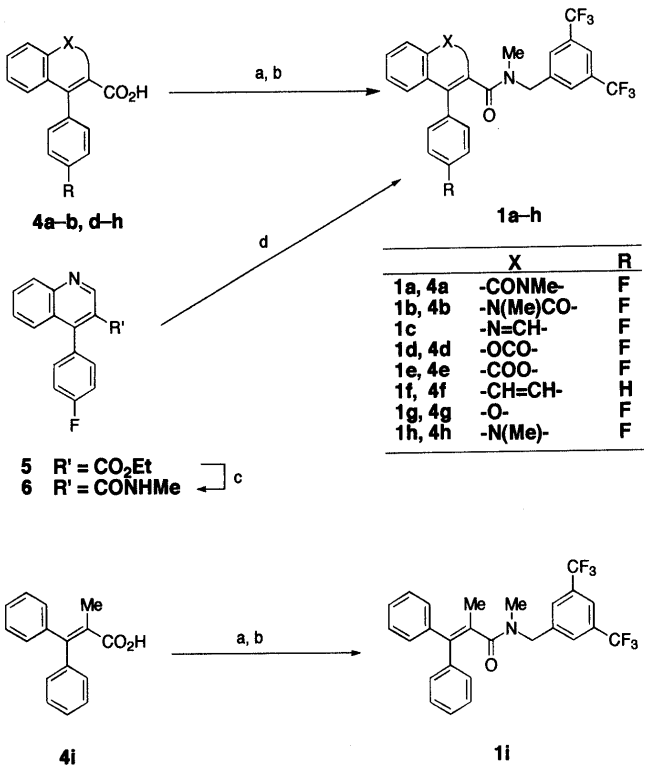


Fig. 1



	X	R
1a, 4a	-CONMe-	F
1b, 4b	-N(Me)CO-	F
1c	-N=CH-	F
1d, 4d	-OCO-	F
1e, 4e	-COO-	F
1f, 4f	-CH=CH-	H
1g, 4g	-O-	F
1h, 4h	-N(Me)-	F

(a) $(COCl)_2$, DMF/THF; (b) *N*-methyl-3,5-bis(trifluoromethyl)benzylamine, Et_3N/THF; (c) $MeNH_2$/MeOH; (d) 3,5-bis(trifluoromethyl)benzyl bromide, NaH/DMF.

Chart 1

carboxamides **2a—d** (**3a—f**) (Table 2) were prepared by reduction of the pyridine nucleus. As a typical example, the preparation of **3b** is shown in Chart 3. The amide **2b** was converted to **3b** by methylation with MeI followed by two-step reduction (*i.e.*, $NaBH_4$ and H_2/Pd–C). As an alternative route, the amide **2b** was first hydrogenated over Pt–C to afford the tetrahydro derivative **3c**, which was then methylated with MeI in the presence of NaH to give **3b**.

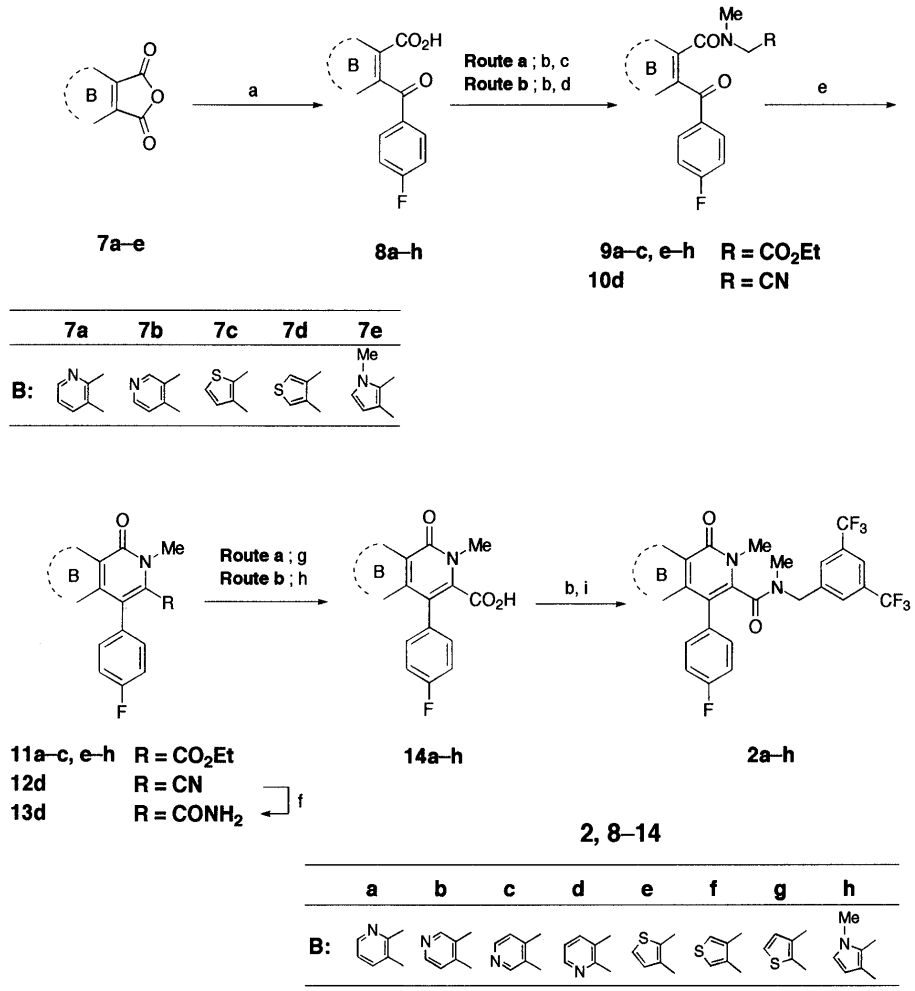
The carboxamide derivatives (**1**, **2** and **3**) thus prepared exist as two conformational isomers (rotamers), *trans* and *cis* with respect to the amide bond. In the case of the carboxamide derivatives with isoquinolone (**1a**) and related heterocycles (**2** and **3**), two rotamers were usually formed in a ratio of *ca.* 7 : 1 (*trans* : *cis*), as observed by HPLC, TLC and/or NMR analysis. Due to the steric hindrance around the amide bond, interconversion of the rotamers is relatively slow, and each rotamer could be isolated by careful separation procedures. However, since the minor (*cis*) rotamer is unstable in solution, being easily interconverted to the major (*trans*) one, all the crystalline products isolated by conventional work-up and used in this study have the *trans* configuration.[18] On the other hand, the carboxamide derivatives with other nuclei (**1b—i**) showed single spots upon TLC analysis, while the rotamers were observed in a ratio of *ca.* 3 : 1—5 : 1 by NMR at room temperature. The ratio remained unchanged for the products obtained before and after recrystallization, suggesting that the rotamers are interconverted in solution too rapidly to be separated at room temperature. In this study, compounds **1b—i** were used without further investigation with regard to stereochemistry.

Biology

The compounds prepared were preliminarily evaluated *in vitro* for inhibition of [^{125}I]Bolton–Hunter (BH)-SP binding in human IM-9 cells[19] followed by *in vivo* screening (inhibition of capsaicin-induced plasma extravasation in the trachea of guinea pigs[20]) of the compounds that showed good *in vitro* activity.

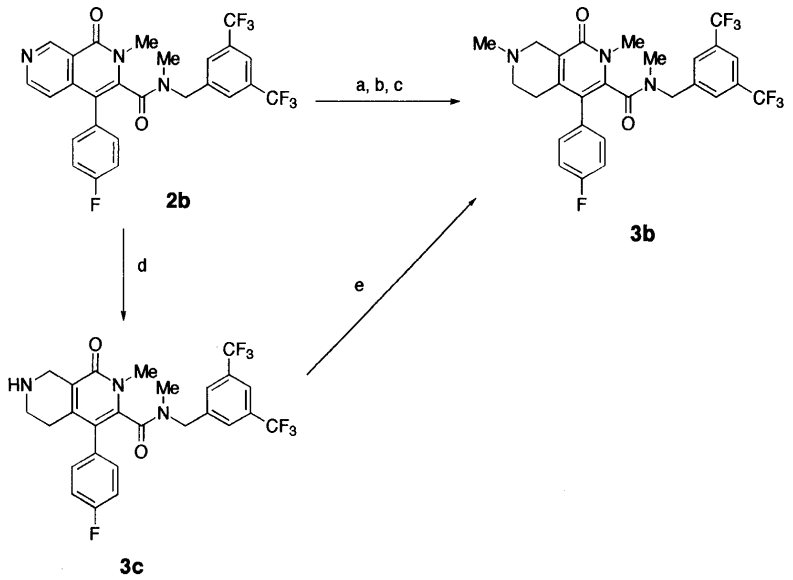
Results and Discussion

(a) Modification of Ring A (Compounds 1) Biological data for the carboxamide derivatives of various cyclic and non-cyclic compounds having a diphenylmethane moiety (**1**) are shown in Table 1. The amide moiety in **1** is fixed as *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methylamide, which has been shown to exhibit good antagonistic activity from SAR studies on the isoquinolone (**1a**) and the



(a) 4-F-Ph–$AlCl_3$ or 4-F-PhMgBr/THF; (b) $SOCl_2$, DMF/THF; (c) sarcosine ethyl ester hydrochloride, Et_3N/THF; (d) *N*-methylaminoacetonitrile hydrochloride, Et_3N/CH_2Cl_2; (e) DBU/toluene; (f) aqueous NaOH/EtOH; (g) aqueous NaOH/THF–EtOH; (h) $NaNO_2$/AcOH-concentrated HCl; (i) *N*-methyl-3,5-bis(trifluoromethyl)benzylamine, Et_3N/THF.

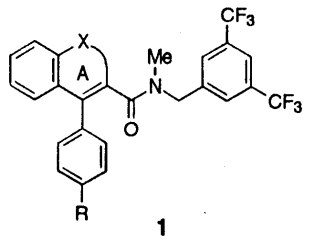
Chart 2



(a) MeI/dioxane; (b) $NaBH_4$/MeOH; (c) H_2/Pd–C/MeOH, (d) H_2/Pt–C/AcOH; (e) NaH, MeI/THF.

Chart 3

Table 1. Biological Properties of Various Diphenylmethane Derivatives with an *N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl Substituent (**1**)



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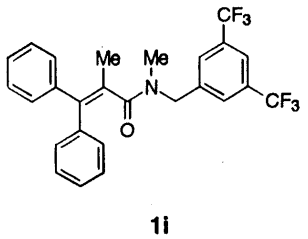


1i

Compd. No.	X	R	IC_{50} [a] (nM)	ED_{50} (mg/kg) or % inh [b] i.v.	*p.o.*
1a	–CONMe–	F	0.35	0.063 (0.042—0.086)	1.0 (0.51—3.37)
1b	–NMeCO–	F	0.44	13.3±20.3% [c]	—[d]
1c	–N=CH–	F	0.21	0.068 (0.011—0.156)	22.4±8.4% [e]
1d	–OCO–	F	0.41	22.5±17.7% [c]	—
1e	–COO–	F	0.48	0.19 (0.086—1.740)	—
1f	–CH=CH–	H	9.3 [f]	—	—
1g	–O–	F	180	—	—
1h	–NMe–	F	110	—	—
1i			175	—	—

a) Inhibition of [^{125}I]BH-SP binding in human IM-9 cells (lymphoblast cells). IC_{50} values represent the mean of two independent experiments run in duplicate unless otherwise noted. *b*) Capsaicin-induced trachea extravasation in guinea pigs (n=3—12). *c*) Inhibition (%) at 0.1 mg/kg. *d*) —: not tested. *e*) Inhibition (%) at 0.3 mg/kg. *f*) Determined by a single experiment run in duplicate.

1,7-naphthyridine (**2a**) amide series.[10] Replacement of ring A in **1a** with 6-membered heterocycles [*i.e.*, quinolone (**1b**), quinoline (**1c**), coumarin (**1d**) and isocoumarin (**1e**)] did not affect *in vitro* potency; all the compounds had fairly strong activities comparable to that of **1a**, whereas replacement with a benzene ring [*i.e.*, naphthalene (**1f**)[21]] led to a decrease in activity. Surprisingly, replacement with 5-membered heterocycles [*i.e.*, benzofuran (**1g**) and indole (**1h**)] caused a more than 300-fold decrease in activity, and ring opening (**1i**)[21] also resulted in a significant decrease in activity.

In an attempt to rationalize these striking differences in affinity among the 6-membered ring derivatives (**1a—f**), the 5-membered ring derivatives (**1g—h**) and the non-cyclic derivative (**1i**), we first examined the most stable conformations of the selected compounds (**1a**, **1h** and **1i**). A systematic conformational search around the rotatable bonds followed by energy minimization using the Discover force field[22] afforded similar most stable conformations with stacking of the two phenyl rings. We initially supposed that these conformations would differ in the spatial arrangement of the two phenyl rings and the amide hetero atom, which we postulated to be a key for receptor recognition as described in our preceding paper.[10] Contrary to our expectation, however, superimposition of the most stable conformations of **1a**, **1h** and **1i** (Fig. 2) showed that these three points in each conformation overlap significantly, although dissimilarity is observed for other parts of the molecule, such as the other (fused) benzene ring, which are presumably not key determinants for the receptor recognition (see discussion, item (b)).

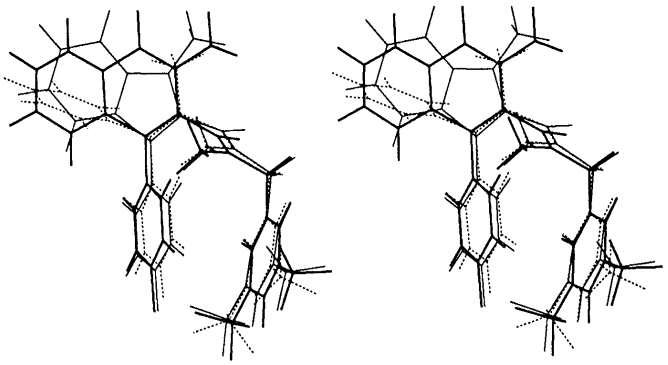
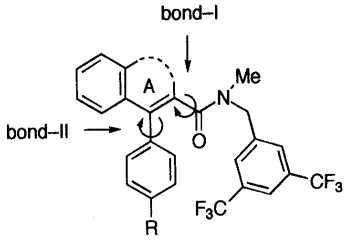


Fig. 2. Stereoscopic View of the Overlapping of the Three Most Stable Conformers of **1a** (Bold Line), **1h** (Solid Line), and **1i** (Dotted Line)



1a : A =  , R = F

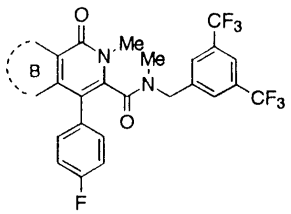
1h : A =  , R = F

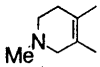
1i : A =  , R = H

Fig. 3

Since these results obtained from the conformational analysis were inconclusive, we next examined the conformational flexibility of **1a**, **1h** and **1i** using Discover.[22] The conformational flexibility was estimated from the rotational barriers around two bonds, *i.e.*, the bond between ring A and the amide moiety (bond-I) and the bond between ring A and the pendant phenyl (bond-II) (Fig. 3). The estimated rotational barriers around bond-I in **1a**, **1h** and **1i** were 34, 27 and 28 kcal/mol, respectively, indicating that the rotation is restricted similarly in these three compounds. On the other hand, the barriers around bond-II in **1a**, **1h** and **1i** were 28, 11 and 13 kcal/mol, respectively, indicating that the rotation around bond-II at room temperature is restricted only in **1a**. These results imply that the restricted rotation around bond-II in **1a** gives rise to a beneficial effect on receptor binding by virtue of lowering the entropy loss of binding. In other words, the rather high conformational entropy in **1h** and **1i** arising from the rotational freedom around bond-II has a deleterious effect on receptor binding.[23] Consequently, the 6-membered ring in **1a—f** may function as an anchor by fixing the pendant phenyl ring in the desirable orientation. Futhermore, considering the relatively weak *in vitro* activity of the naphthalene **1f**, compared with the 6-membered heterocycles **1a—e**, a hetero atom (nitrogen or oxygen) in ring A may play an additional role, *e.g.*, as a hydrogen-bond acceptor.

Table 2. Biological Properties of Isoquinolone-Related Heterocycles with an *N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl Substituent (**2**, **3**)



Compd. No.	Ring B	IC_{50}[a] (nM)	ED_{50} (mg/kg) or % inh[b] i.v.	*p.o.*
2a-1		0.21±0.03[c]	0.017 (0.013—0.024)	0.068 (0.029—0.249)
2b		0.28	0.068 (0.045—0.141)	0.24 (0.14—0.35)
2c		2.65	—[d]	—
2d		0.93	—	—
2e		0.18±0.12[c]	0.0093 (0.0043—0.0159)	2.5 (1.4—4.0)
2f		0.48	0.063 (0.042—0.115)	7.2±8.6%[e]
2g		0.45	51.5±6.2%[f]	—
2h		0.22	0.057 (0.037—0.090)	0.70 (0.55—0.98)
3a		0.42	0.021 (0.00011—0.06172)	0.21 (0.15—0.32)
3b		0.06	0.050 (0.0087—0.1346)	0.27 (0.15—0.43)
3c		0.12	0.055 (0.0034—1.2424)	—
3d		2.55	—	—
3e		8.00	—	—
3f		0.28	0.031 (0.018—0.055)	0.20 (0.15—0.29)

a, *b*) See corresponding footnotes of Table 1. *c*) Mean±S.E.M. value of three independent experiments run in duplicate. *d*) —: not tested. *e*) Inhibition (%) at 0.3 mg/kg. *f*) Inhibition (%) at 0.1 mg/kg.

In the *in vivo* (i.v.) evaluation, the quinoline **1c** and the isocoumarin **1e** showed potent activities, with that of **1c** being comparable to that of **1a**. Unfortunately, however, **1c** was only weakly active upon oral administration.

The basic role of ring A for receptor binding was thus clarified. Although 6-membered heterocycles are in general preferable for inherent receptor binding, the 2-pyridone ring in **1a**, which exhibited moderate potency upon oral administration, seemed to be the most favorable from the pharmacokinetic profile standpoint. In our preceding paper,[10] we reported that replacement of the benzene ring in the isoquinolone nucleus of **1a** with a pyridine ring (**2a**) significantly improved the antagonistic activities both *in vitro* and *in vivo* (i.v. and *p.o.*). In order to investigate the influence of ring B of **1a** in more detail, its replacement with other heterocycles was examined.

(b) Modification of Ring B (Compounds 2 and 3) Biological data for the carboxamide derivatives having pyridine (**2a—d**), thiophene (**2e—g**), pyrrole (**2h**) and tetrahydropyridine (**3a—f**) rings in place of ring B in **1a** are shown in Table 2. Among the pyridine derivatives, **2a—b** with the nitrogen at the 1 or 2 position exhibited fairly good activities both *in vitro* and *in vivo* (i.v.), while **2c—d** with the nitrogen at the 3 or 4 position showed slightly weaker activities. The thiophene and pyrrole derivatives (**2e—h**) were all potent both *in vitro* and *in vivo* (i.v.). In the *in vivo* (i.v.) evaluation, the thiophene derivative **2e** exhibited more potent activity than **2a—1**, corresponding well to its excellent *in vitro* potency.

Some of the compounds which showed potent *in vivo* activity upon i.v. administration were evaluated *in vivo* using oral administration. Compound **2b** exhibited a potent inhibitory effect, whereas compounds **2e** and **2f** were only weakly active due to low oral bioavailability, presumably caused by metabolic instability.

Expecting to improve the pharmacokinetic profiles by changing molecular characteristics such as basicity and lipophilicity, we prepared the tetrahydro derivatives of the pyridopyridines **2a—d** (**3**) and evaluated them for biological activity (Table 2). Of interest is the overall trend observed here; the activities of the tetrahydropyridine derivatives **3** correlate well with those of the corresponding parent pyridine derivatives **2** both *in vitro* and *in vivo* (i.v.). Compounds **3a—c** were as potent as **2a-1** and **2b**, and the potency of **3d** was rather weak, like that of **2c**. Interestingly, compared with **2d**, the *N*-methyl derivative **3e** was less potent, while the NH derivative **3f** exhibited more potent activity. Among these tetrahydropyridine derivatives, **3a**, **3b** and **3f** showed significantly potent activities, comparable to that of **2a-1**, upon oral administration.[24]

These results indicate that replacement of ring B in **1a** with heterocycles is well tolerated and in some cases leads to improvement of the activity. Considering that both aromatic (**2**) and non-aromatic (**3**) derivatives show good to excellent binding affinities, this region (ring B) does not seem to be essential for the inherent receptor recognition.[25] Furthermore, the following assumptions can be made: (1) since the pyridine (**2a—b**) and tetrahydropyridine (**3a—b** and **3f**) derivatives exhibited high potency upon oral administration, the basic nitrogen in ring B may confer favorable pharmacokinetic profiles on the molecules and (2) in the SAR studies on the 4-pyridine series (**2d**, **3e** and **3f**), the unsubstituted tetrahydropyridine **3f** was more potent than **3e** and **2d**, suggesting that the torsion angle of the phenyl ring at the 8 position, which is an important factor for receptor recognition, may be affected by the substituents on the nitrogen (H, Me and lone pair).

In summary, we have demonstrated the effect of modification of rings A and B, in **1a** and **2a**, on the antagonistic activity. The following features should be emphasized: (1) for ring A, 6-membered heterocycles are generally preferable for receptor binding, presumably functioning as an anchor by fixing two phenyl rings in the desired position, and among the 6-membered rings, the 2-pyridone ring (**1a**) seems to be the most favorable from the pharmacokinetic profile standpoint; (2) regarding ring B, since the derivatives with various aromatic rings (**2**) and those with various aliphatic rings (**3**) both show good potency, this region (ring B) does not seem to be essential for the inherent receptor recognition but seems to play some additional role in interaction with the receptor; and (3) some of the tetrahydropyridine derivatives, **3a**, **3b** and **3f**, exhibited a potent inhibitory effect, comparable to that of **2a-1**, upon oral administration. On the basis of the SAR described here, studies on this series of carboxamides are in progress to select a candidate for further pharmacological evaluation, and the results will be published in due course.

Experimental

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 with tetramethylsilane as the internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublets of doublet, br s = broad singlet, br t = broad triplet. IR spectra were obtained on a Hitachi IR-215 spectrometer. Mass spectra were obtained on a JEOL JMS-AX505W spectrometer. Elemental analyses were within $\pm$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 were not optimized.

4-(4-Fluorophenyl)-1,2-dihydro-1-methyl-2-oxo-3-quinolinecarboxylic Acid (4b) Compound **4b** was prepared according to a procedure similar to that described in the literature.[12] Recrystallization from EtOAc–diisopropyl ether (IPE) gave colorless crystals: mp 207—208 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s), 7.10—7.31 (6H, m), 7.57 (1H, d, J = 8.8 Hz), 7.72—7.84 (1H, m). *Anal.* Calcd for $C_{17}H_{12}FNO_3$: C, 68.68; H, 4.07; N, 4.71. Found: C, 68.53; H, 4.08; N, 4.80.

4-(4-Fluorophenyl)-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid (4d) Compound **4d** was prepared according to a procedure similar to that described in the literature.[12] Recrystallization from EtOH–hexane gave colorless crystals: mp 183—185 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.0—7.4 (6H, m), 7.50 (1H, d, J = 8.8 Hz), 7.73 (1H, m). *Anal.* Calcd for $C_{16}H_9FO_4$: C, 67.61; H, 3.91. Found: C, 67.28; H, 3.36.

3-(4-Fluorophenyl)-2-benzofurancarboxylic Acid (4g) Compound **4g** was prepared according to a procedure similar to that described in the literature.[13] Recrystallization from EtOAc—IPE gave colorless crystals: mp 254—255 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.03 (1H, br s, COOH), 7.16 (2H, t-like, J = 8.7 Hz), 7.27—7.65 (6H, m). *Anal.* Calcd for $C_{15}H_9FO_3$: C, 70.31; H, 3.54. Found: C, 70.09; H, 3.60.

3-(4-Fluorophenyl)-1-methyl-1*H*-indole-2-carboxylic Acid (4h) Compound **4h** was prepared according to a procedure similar to that described in the literature.[14] Recrystallization from diethyl ether—hexane gave colorless crystals: mp 212—213 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.09 (3H, s), 7.10—7.20 (3H, m), 7.40—7.52 (5H, m). *Anal.* Calcd for $C_{16}H_{12}FNO_2$: C, 71.37; H, 4.49; N, 5.20. Found: C, 71.14; H, 4.53; N, 5.25.

Carboxylic acids **4a**,[10] **4e**,[10] **4f**,[15] and **4i**[16] were prepared according to the procedures described in the literature.

***N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methylcarboxamide Derivatives of 4 (1). By Amidation** As a typical example, the preparation of **1e** is described. Oxalyl chloride (0.052 ml, 0.60 mmol) and dimethyl formamide (DMF, catalytic amount) were added to a solution of **4e** (142 mg, 0.50 mmol) in tetra hydrofuran (THF, 5 ml) at room temperature, and the mixture was stirred for 30 min. After evaporation of the solvent, the residue was dissolved in THF (5 ml). To the solution were added *N*-methyl-3,5-bis(trifluoromethyl)benzylamine (150 mg, 0.58 mmol) and Et_3N (0.077 ml, 0.55 mmol), and the mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was diluted with EtOAc and washed successively with H_2O, 1 N HCl, H_2O, aqueous $NaHCO_3$ and H_2O. The extract was dried and concentrated to give **1e** as colorless crystals (187 mg, 72%).

By Methylation As a typical example, the preparation of **1b** is described. A mixture of *N*-[3,5-bis(trifluoromethyl)benzyl]-4-(4-fluorophenyl)-1,2-dihydro-1-methyl-2-oxo-3-quinolinecarboxamide (prepared from **4b** and 3,5-bis(trifluoromethyl)benzylamine by amidation) (150 mg, 0.29 mmol), NaH (60% dispersion in oil) (19 mg, 0.48 mmol) and DMF (10 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

Table 3. Physicochemical and Spectral Data for Various Diphenylmethane Derivatives with an *N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl Substituent (**1**)

Compd. No.	Method[a]	Yield[b] (%)	mp (°C) (Solv.)[c]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ
1b	B	40	149—150 (EE–H)	$C_{27}H_{19}F_7N_2O_2$	60.45 (60.69	3.57 3.44	5.22 5.20)	2.75 (3H × 1/4, s), 2.85 (3H × 3/4, s), 3.80 (3H × 1/4), 3.83 (3H × 3/4, s), 4.23 (1H × 1/4, d, J = 16 Hz), 4.36 (1H × 3/4, d, J = 15 Hz), 4.62 (1H × 1/4, d, J = 16 Hz), 4.97 (1H × 3/4, d, J = 15 Hz), 7.00—7.30 (5H, m), 7.40—7.70 (5H + 1H × 1/4, m), 7.78 (1H × 3/4, s)
1c	B	70	141—142 (EE–IPE)	$C_{26}H_{17}F_7N_2O$	61.67 (61.74	3.38 3.37	5.53 5.50)	2.66 (3H × 5/6, s), 2.85 (3H × 1/6, s), 4.00—5.20 (2H, m), 7.07 (2H, t-like, J = 8.8 Hz), 7.30—7.40 (2H, m), 7.50—7.85 (6H, m), 8.20 (1H, m), 8.92 (1H, br s)
1d	A	71	160—161 (H–IPE)	$C_{26}H_{16}F_7NO_3$	59.66 (59.64	3.08 3.08	2.68 2.66)	2.78 (3H × 1/5, s), 2.89 (3H × 4/5, s), 4.25 (1H × 1/5, d, J = 16 Hz), 4.45 (1H × 4/5, d, J = 15 Hz), 4.65 (1H × 1/5, d, J = 16 Hz), 4.88 (1H × 4/5, d, J = 15 Hz), 7.05—7.28 (5H, m), 7.40—7.66 (5H, m), 7.80 (1H, s)
1e	A	72	132—133 (EE–IPE)	$C_{26}H_{16}F_7NO_3$	59.66 (59.49	3.08 3.39	2.68 2.49)	2.82 (3H × 1/6, s), 2.96 (3H × 5/6, s), 4.61 (2H, s), 7.02—7.38 (5H, m), 7.52 (2H, s), 7.58—7.76 (2H, m), 7.82 (1H, s), 8.34—8.44 (1H, m)
1f	A	63	88—89 (EE–H)	$C_{27}H_{19}F_6NO$	66.53 (66.58	3.93 3.99	2.87 2.63)	2.60 (3H × 3/4, s), 2.73 (3H × 1/4, s), 3.83 (1H × 1/4, d, J = 17 Hz), 4.29 (1H × 3/4, d, J = 16 Hz), 4.56 (1H × 1/4, d, J = 17 Hz), 4.89 (1H × 3/4, d, J = 16 Hz), 7.2—8.0 (14H, m)
1g	A	75	123—124 (EE–H)	$C_{25}H_{16}F_7NO_2$	60.61 (60.43	3.26 3.23	2.83 2.96)	2.86 (3H × 3/4, s), 3.03 (3H × 1/4, s), 4.59 (2H × 1/4, s), 4.81 (2H × 3/4, s), 7.05—7.90 (11H, m)
1h	A	87	Oil		—[d]	—	—	2.55 (3H × 3/4, s), 2.99 (3H × 1/4, s), 3.81 (3H × 1/4, s), 3.86 (3H × 3/4, s), 4.64—4.90 (2H, m), 6.97—7.55 (8H, m), 7.70—7.90 (3H, m)
1i	B	34	108—110 (EE–H)	$C_{26}H_{21}F_6NO$	65.41 (65.63	4.43 4.67	2.93 2.73)	2.00 (0.75 H, s), 2.04 (2.25H, s), 2.72 (0.75H, s), 2.74 (2.25H, s), 3.90—4.90 (2H, m), 7.07—7.20 (6H, m), 7.20—7.40 (4.5H, m), 7.54 (1.5H, s), 7.77 (1H, s)

a) A: amidation, B: alkylation. *b*) Yield of final step. *c*) Recrystallization solvent: EA = ethyl acetate, EE = ethyl ether, IPE = isopropyl ether, H = hexane. *d*)—: not determined.

whole was stirred at room temperature for 30 min, added to H_2O and then extracted with EtOAc. The extract was washed successively with 2 N HCl, aqueous $NaHCO_3$ and H_2O, and then dried and concentrated. The concentrate was subjected to chromatography on silica gel using hexane–EtOAc (1 : 1) as the eluant to give **1b** as colorless crystals (61 mg, 40%). Similarly **1d**, **f**—**i** were prepared by amidation or alkylation. The physicochemical properties of **1b**, **d**—**i** are listed in Table 3.

Ethyl 4-(4-Fluorophenyl)-3-quinolinecarboxylate (5) Compound **5** was prepared according to a procedure similar to that described in the literature.[17] Recrystallization from diethyl ether–hexane gave colorless crystals: mp 117—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 7.2 Hz), 4.16 (2H, q, J = 7.2 Hz), 7.15—7.35 (4H, m), 7.45—7.60 (2H, m), 7.81 (1H, m), 8.20 (1H, d, J = 8.8 Hz), 9.36 (1H, s). *Anal.* Calcd for $C_{18}H_{14}FNO_2$: C, 73.21; H, 4.78; N, 4.74. Found: C, 73.14; H, 4.76; N, 4.87.

4-(4-Fluorophenyl)-*N*-methyl-3-quinolinecarboxamide (6) A solution of **5** (200 mg, 0.677 mmol) in 40% $MeNH_2$–MeOH (3 ml) was stirred at room temperature for 14 h. The reaction mixture was concentrated to give **6** as colorless crystals (149 mg, 78.5%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 143—144 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.74 (3H, d, J = 5.2 Hz), 5.37 (1H, br s), 7.2—7.9 (7H, m), 8.17 (1H, d, J = 8.0 Hz), 9.16 (1H, s). *Anal.* Calcd for $C_{17}H_{13}FN_2O$: C, 72.85; H, 4.67; N, 9.99. Found: C, 72.63; H, 4.62; N, 9.77.

***N*-[3,5-Bis(trifluoromethyl)benzyl]-4-fluorophenyl-*N*-methyl-3-quinolinecarboxamide (1c)** A mixture of **6** (100 mg, 0.36 mmol), NaH (60% dispersion in oil) (22 mg, 0.55 mmol) and DMF (5 ml) was stirred at room temperature for 1 h. The mixture was cooled to 0 °C, and 3,5-bis(trifluoromethyl)benzyl bromide (160 mg, 0.52 mmol) was added to it. The whole was stirred at room temperature for 1 h, added to H_2O and then extracted with EtOAc. The extract was washed successively with aqueous $NaHCO_3$ and H_2O, dried and concentrated to give **1c** as colorless crystals (128 mg, 70%). The physicochemical properties of **1c** are listed in Table 3.

4-(4-Fluorobenzoyl)-3-pyridinecarboxylic Acid (8b) and 3-(4-Fluorobenzoyl)-4-pyridinecarboxylic Acid (8c) A mixture of 3,4-pyridinedicarboxylic acid anhydride (**7b**) (8.5 g, 57.0 mmol) and fluorobenzene (170 ml), to which $AlCl_3$ (12.0 g, 90.0 mmol) had been added at room temperature, was refluxed for 3 h. After having been cooled, the mixture was poured into concentrated HCl–ice water and then treated with aqueous $NaHCO_3$ to adjust the pH to 4. The resulting crystals were collected by filtration and washed with H_2O to give **8c** as colorless crystals (1.51 g, 11%). Recrystallization from MeOH–EtOAc gave colorless crystals: mp 305—310 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 7.36 (2H, d, J = 8.8 Hz), 7.76 (2H, t-like, J = 8.0 Hz), 7.88 (1H, d, J = 5.2 Hz), 8.73 (1H, s), 8.94 (1H, d, J = 5.2 Hz). *Anal.* Calcd for $C_{13}H_8FNO_3$: C, 63.68; H, 3.29; N, 5.71. Found: C, 63.88; H, 3.45; N, 5.49. The mother liquor and washings after isolation of **8c** were combined and extracted with EtOAc. The extract was washed with brine, dried and concentrated to give **8b** as colorless crystals (2.27 g, 16%). Recrystallization from MeOH–EtOAc gave colorless crystals: mp 217—219 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.35 (2H, t-like, J = 8.5 Hz), 7.53 (1H, d, J = 5.0 Hz), 7.75 (2H, m), 8.92 (1H, d, J = 5.0 Hz), 9.17 (1H, s). *Anal.* Calcd for $C_{13}H_8FNO_3$: C, 63.68; H, 3.29; N, 5.71. Found: C, 63.61; H, 3.45; N, 5.57.

2-(4-Fluorobenzoyl)-3-pyridinecarboxylic Acid (8d) A solution of 1-bromo-4-fluorobenzene (13.6 ml, 125 mmol) in THF (100 ml) was added dropwise to a stirred mixture of Mg (3.91 g, 161 mmol), I_2 (catalytic amount) and THF (15 ml) at room temperature. After having been stirred for 30 min, the mixture was added dropwise to a stirred suspension of 2,3-pyridinedicarboxylic acid anhydride (**7a**) (18.6 g, 125 mmol) in THF (150 ml) at 0 °C. The whole was stirred for 1 h at room temperature, poured into 1 N HCl–ice water, treated with 1 N NaOH to adjust the pH to 2—3 and then extracted with EtOAc. The extract was washed with brine, dried and concentrated to give a mixture of **8d** and 3-(4-fluorobenzoyl)-2-pyridinecarboxylic acid as a colorless oil. This mixture was subjected to chromatography on silica gel with EtOAc to give **8d** as colorless crystals (10.5 g, 34%). Recrystallization from MeOH–Et_2O gave colorless crystals: mp 179—181 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.12 (2H, t-like), 7.55 (1H, dd, J = 8.2, 4.8 Hz), 7.81 (2H, dd-like), 8.39 (1H, dd, J = 8.2, 1.6 Hz), 8.84 (1H, dd, J = 5.0, 1.6 Hz). *Anal.* Calcd for $C_{13}H_8FNO_3$: C, 63.68; H, 3.29; N, 5.71. Found: C, 63.34; H, 3.48; N, 5.62.

3-(4-Fluorobenzoyl)-2-thiophenecarboxylic Acid (8e) and 2-(4-Fluorobenzoyl)-3-thiophenecarboxylic Acid (8g) A mixture of 2,3-thiophenedicarboxylic acid anhydride (**7c**) (1.98 g, 12.8 mmol) and fluorobenzene

(30 ml), to which $AlCl_3$ (2.7 g, 20.2 mmol) had been added at room temperature, was refluxed for 3.5 h. After having been cooled, the mixture was poured into concentrated HCl–ice water and extracted with EtOAc. The extract was washed with brine, dried and concentrated to give **8e** as colorless crystals (2.73 g, 85%). Recrystallization from Et_2O–IPE gave colorless crystals: mp 152 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.10—7.30 (3H, m), 7.66 (1H, d, J=5.2 Hz), 7.80—7.95 (2H, m). *Anal.* Calcd for $C_{12}H_7FO_3S$: C, 57.60; H, 2.82. Found: C, 57.41; H, 3.13. The mother liquor after isolation of **8e** was evaporated to give an oily residue which contained **8g**, and the residue was used without further purification.

4-(4-Fluorobenzoyl)-3-thiophenecarboxylic Acid (8f) 3,4-Thiophenedicarboxylic acid anhydride (**7d**) (0.74 g, 4.80 mmol) was treated according to a procedure similar to that described for the preparation of **8e** to afford **8f** as colorless crystals (784 mg, 65%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 161—162 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.18 (2H, t-like, J=8.6 Hz), 7.76 (1H, d, J=3.3 Hz), 7.80—7.95 (2H, m), 8.39 (1H, d, J=3.3 Hz), 9.90 (1H, br s). *Anal.* Calcd for $C_{12}H_7FO_3S$: C, 57.60; H, 2.82. Found: C, 57.39; H, 2.87.

3-(4-Fluorobenzoyl)-1-methyl-1*H*-pyrrole-2-carboxylic Acid (8h) 1-Methyl-1*H*-pyrrole-2,3-dicarboxylic acid anhydride (**7e**) (390 mg, 2.58 mmol) was treated according to a procedure similar to that described for the preparation of **8e** to afford **8h** as colorless crystals (556 mg, 87%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 140—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.11 (3H, s), 6.51 (1H, d, J=2.9 Hz), 6.85 (1H, d, J=2.9 Hz), 7.20 (2H, t-like, J=8.6 Hz), 7.80—7.90 (2H, m). *Anal.* Calcd for $C_{13}H_{10}FNO_3$: C, 63.16; H, 4.08; N, 5.67. Found: C, 62.95; H, 4.23; N, 5.59.

***N*-[[4-(4-Fluorobenzoyl)-3-pyridinyl]carbonyl]-*N*-methylglycine Ethyl Ester (9b)** Thionyl chloride (0.5 ml, 6.85 mmol) and DMF (catalytic amount) were added to a solution of **7b** (500 mg, 2.04 mmol) in THF (10 ml) at room temperature, and the mixture was refluxed for 1 h. After evaporation of the solvent, the residue was dissolved in THF (15 ml). To this solution were added sarcosine ethyl ester hydrochloride (570 mg, 3.71 mmol) and Et_3N (0.89 ml, 6.39 mmol), and the mixture was stirred at room temperature for 14 h. After evaporation of the solvent, the residue was diluted with EtOAc and washed successively with H_2O, aqueous $NaHCO_3$ and H_2O. The organic layer was dried and concentrated to give **9b** as a colorless oil (705 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.0 Hz), 3.07 (3H, s), 4.16 (2H, s), 4.22 (2H, q, J=7.0 Hz), 7.16 (2H, t-like, J=8.0 Hz), 7.27—7.37 (1H, m), 7.81—7.87 (2H, m), 8.75—8.82 (2H, m).

***N*-[[3-(4-Fluorobenzoyl)-4-pyridinyl]carbonyl]-*N*-methylglycine Ethyl Ester (9c)** Compound **8c** (1.70 g, 6.93 mmol) was treated according to a procedure similar to that described for the preparation of **9b** to give **9c** as a colorless oil (2.27 g, 95%). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.0 Hz), 3.00 (3H, s), 4.20 (2H, s), 4.24 (2H, q, J=7.0 Hz), 7.18 (2H, t-like, J=8.0 Hz), 7.40—7.48 (1H, m), 7.85—7.92 (2H, m), 8.77—8.86 (2H, m).

***N*-[[3-(4-Fluorobenzoyl)-2-thienyl]carbonyl]-*N*-methylglycine Ethyl Ester (9e)** Oxalyl chloride (1.7 ml, 19.5 mmol) and DMF (catalytic amount) were added to a solution of **8e** (3.21 g, 12.8 mmol) in THF (60 ml) at room temperature, and the mixture was stirred at room temperature for 30 min. After evaporation of the solvent, the residue was dissolved in THF (20 ml). The solution was added to a mixture of sarcosine ethyl ester hydrochloride (2.5 g, 16.3 mmol), Et_3N (4.0 ml, 28.7 mmol) and THF (50 ml), and the mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was diluted with H_2O and extracted with EtOAc. The extract was washed successively with 2 N HCl, aqueous $NaHCO_3$ and H_2O, then dried and concentrated. The concentrate was subjected to chromatography on silica gel with hexane–EtOAc (1 : 1) to give **9e** as a colorless oil (0.98 g, 22%). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.1 Hz), 2.99 (3H, br s), 4.05 (2H, s), 4.19 (2H, q, J=7.1 Hz), 7.05—7.30 (3H, m), 7.45 (1H, m), 7.80—7.95 (2H, m).

***N*-[[4-(4-Fluorobenzoyl)-3-thienyl]carbonyl]-*N*-methylglycine Ethyl Ester (9f)** Compound **8f** (1.06 g, 4.24 mmol) was treated according to a procedure similar to that described for the preparation of **8f** to give **8g** as an oil (1.22 g, 82%), which was used without further purification.

***N*-[[2-(4-Fluorobenzoyl)-3-thienyl]carbonyl]-*N*-methylglycine Ethyl Ester (9g)** Compound **8g** (2.33 g, 9.31 mmol) was treated according to a procedure similar to that described for the preparation of **9e** to give **9g** as an oil (1.4 g, 44%), which was used without further purification.

***N*-[[3-(4-Fluorobenzoyl)-1-methyl-1*H*-pyrrol-2-yl]carbonyl]-*N*-methylglycine Ethyl Ester (9h)** Compound **8h** (556 mg, 2.25 mmol) was treated according to a procedure similar to that described for the preparation of **9e** to give **9h** as an oil (409 mg, 53%). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (0.9H, t, J=7.3 Hz), 1.31 (2.1H, t, J=7.1 Hz), 2.93 (2.1H, s), 3.08 (0.9H, s), 3.30—3.90 (1H, m), 3.69 (0.9H, s), 3.74 (2.1H, s), 4.00—4.50 (1H, m), 4.12 (0.6H, q, J=7.3 Hz), 4.23 (1.4H, q, J=7.1 Hz), 6.40 (0.3H, d, J=2.6 Hz), 6.44 (0.7H, d, J=2.8 Hz), 6.63 (0.3H, d, J=2.6 Hz), 6.66 (0.7H, d, J=2.8 Hz), 7.12 (2H, t-like, J=8.8 Hz), 7.78—7.92 (2H, m).

Ethyl 4-(4-Fluorophenyl)-1,2-dihydro-2-methyl-1-oxo-2,7-naphthyridine-3-carboxylate (11b) A mixture of **9b** (3.99 g, 11.6 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (4.0 ml, 26.7 mmol) and toluene (250 ml) was refluxed for 4.5 h, while the water formed was removed azeotropically using a Dean–Stark apparatus. After having been cooled, the mixture was poured into 1 N HCl, treated with aqueous $NaHCO_3$ to adjust the pH to 4—5 and extracted with EtOAc–THF. The extract was washed with brine, dried and concentrated. The concentrate was subjected to chromatography on silica gel with EtOAc–hexane (3 : 1) to give **11b** as colorless crystals (1.70 g, 45%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 150—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.0 Hz), 3.61 (3H, s), 4.10 (2H, q, J=7.0 Hz), 7.03 (1H, d, J=5.6 Hz), 7.13—7.34 (4H, m), 8.69 (1H, d, J=5.6 Hz), 9.69 (1H, s). *Anal.* Calcd for $C_{18}H_{15}FN_2O_3$: C, 66.25; H, 4.63; N, 8.58. Found: C, 66.16; H, 4.66; N, 8.44.

Ethyl 4-(4-Fluorophenyl)-1,2-dihydro-2-methyl-1-oxo-2,6-naphthyridine-3-carboxylate (11c) Compound **9c** (2.20 g, 6.39 mmol) was treated according to a procedure similar to that described for the preparation of **11b** to give **11c** as colorless crystals (0.79 g, 38%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 181—183 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.0 Hz), 3.63 (3H, s), 4.09 (2H, q, J=7.0 Hz), 7.14—7.38 (4H, m), 8.26 (1H, d, J=5.4 Hz), 8.63 (1H, s), 8.75 (1H, d, J=5.4 Hz). *Anal.* Calcd for $C_{18}H_{15}FN_2O_3$: C, 66.25; H, 4.63; N, 8.58. Found: C, 66.01; H, 4.58; N, 8.60.

Ethyl 4-(4-Fluorophenyl)-6,7-dihydro-6-methyl-7-oxothieno[2,3-*c*]pyridine-5-carboxylate (11e) A mixture of **9e** (0.98 g, 2.80 mmol), DBU (1.5 ml, 10.0 mmol) and toluene (50 ml) was refluxed for 3 h, while the water formed was removed azeotropically using a Dean–Stark apparatus. After having been cooled, the mixture was poured into 2 N HCl and extracted with EtOAc. The extract was washed with H_2O, dried and concentrated. The concentrate was subjected to chromatography on silica gel with EtOAc–hexane (1 : 1) to give **11e** as colorless crystals (354 mg, 38%). Recrystallization from EtOAc–hexane gave colorless crystals: mp 145—147 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.2 Hz), 3.65 (3H, s), 4.10 (2H, q, J=7.2 Hz), 6.92 (1H, d, J=5.1 Hz), 7.13 (2H, t-like, J=8.6 Hz), 7.25—7.40 (2H, m), 7.67 (1H, d, J=5.1 Hz). *Anal.* Calcd for $C_{17}H_{14}FNO_3S$: C, 61.62; H, 4.26; N, 4.23. Found: C, 61.50; H, 4.35; N, 4.08.

Ethyl 7-(4-Fluorophenyl)-4,5-dihydro-5-methyl-4-oxothieno[3,4-*c*]-pyridine-6-carboxylate (11f) Compound **9f** (1.22 g, 3.49 mol) was treated according to a procedure similar to that described for the preparation of **11e** to give **11f** as colorless crystals (819 mg, 71%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 128—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.2 Hz), 3.52 (3H, s), 4.07 (2H, q, J=7.2 Hz), 7.05—7.20 (3H, m), 7.30—7.45 (2H, m), 8.42 (1H, d, J=2.6 Hz). *Anal.* Calcd for $C_{17}H_{14}FNO_3S$: C, 61.62; H, 4.26; N, 4.23. Found: C, 61.57; H, 4.14; N, 4.20.

Ethyl 7-(4-Fluorophenyl)-4,5-dihydro-5-methyl-4-oxothieno[3,2-*c*]-pyridine-6-carboxylate (11g) Compound **9g** (1.40 g, 4.01 mmol) was treated according to a procedure similar to that described for the preparation of **11e** to give **11g** as colorless crystals (1.27 g, 96%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 127—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.2 Hz), 3.63 (3H, s), 4.10 (2H, q, J=7.2 Hz), 7.14 (2H, t-like, J=8.7 Hz), 7.35—7.50 (2H, m), 7.36 (1H, d, J=5.3 Hz), 7.73 (1H, d, J=5.3 Hz). *Anal.* Calcd for $C_{17}H_{14}FNO_3S \cdot 1/5\ H_2O$: C, 60.96; H, 4.33; N, 4.18. Found: C, 60.84; H, 4.37; N, 4.16.

Ethyl 4-(4-Fluorophenyl)-6,7-dihydro-1,6-dimethyl-7-oxo-1*H*-pyrrolo-[2,3-*c*]pyridine-5-carboxylate (11h) Compound **9h** (409 mg, 1.18 mmol) was treated according to a procedure similar to that described for the preparation of **11e** to give **11h** as a colorless oil (362 mg, 93%). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.2 Hz), 3.60 (3H, s), 4.07 (2H, q, J=7.2 Hz), 4.20 (3H, s), 6.03 (1H, d, J=2.9 Hz), 6.98 (1H, d, J=2.9 Hz), 7.00—7.40 (4H, m).

4-(4-Fluorophenyl)-1,2-dihydro-2-methyl-1-oxo-2,7-naphthyridine-3-carboxylic Acid (14b) A mixture of **11b** (1.60 g, 4.90 mmol), EtOH

(20 ml), THF (20 ml) and 1 N NaOH (20 ml) was refluxed for 2 h and concentrated. The concentrate was treated with 1 N HCl to adjust the pH to 3—4, saturated with NaCl and extracted with THF–EtOAc. The extract was dried and concentrated to give **14b** as colorless crystals (0.92 g, 63%). Recrystallization from THF–MeOH gave colorless crystals: mp 246—247 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 3.54 (3H, s), 7.00 (1H, d, J=5.6 Hz), 7.33—7.38 (4H, m), 8.69 (1H, d, J=5.6 Hz), 9.46 (1H, s). *Anal.* Calcd for $C_{16}H_{11}FN_2O_3 \cdot 1/4H_2O$: C, 63.47; H, 3.83; N, 9.25. Found: C, 63.37; H, 3.80; N, 9.30.

4-(4-Fluorophenyl)-1,2-dihydro-2-methyl-1-oxo-2,6-naphthyridine-3-carboxylic Acid (14c) Compound **14c** was prepared from **11c** in 95% yield as colorless crystals. Recrystallization from THF–MeOH gave colorless crystals: mp 294—295 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.55 (3H, s), 7.31—7.45 (4H, m), 8.13 (1H, d, J=5.2 Hz), 8.47 (1H, s), 8.73 (1H, d, J=5.2 Hz). *Anal.* Calcd for $C_{16}H_{11}FN_2O_3 \cdot 1/4H_2O$: C, 63.47; H, 3.83; N, 9.25. Found: C, 63.48; H, 3.82; N, 9.35.

4-(4-Fluorophenyl)-6,7-dihydro-6-methyl-7-oxothieno[2,3-*c*]pyridine-5-carboxylic Acid (14e) Compound **14e** was prepared from **11e** in 86% yield as colorless crystals. Recrystallization from EtOAc–IPE gave colorless crystals: mp 205 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s), 6.93 (1H, d, J=5.3 Hz), 7.14 (2H, t-like, J=8.6 Hz), 7.37—7.49 (2H, m), 7.70 (1H, d, J=5.3 Hz). *Anal.* Calcd for $C_{15}H_{10}FNO_3S$: C, 59.40; H, 3.32; N, 4.62. Found: C, 59.24; H, 3.42; N, 4.55.

7-(4-Fluorophenyl)-4,5-dihydro-5-methyl-4-oxothieno[3,4-*c*]pyridine-6-carboxylic Acid (14f) Compound **14f** was prepared from **11f** in 77% yield as colorless crystals. Recrystallization from EtOAc–IPE gave colorless crystals: mp 217—218 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (3H, s), 7.06 (1H, d, J=3.3 Hz), 7.12 (2H, t-like, J=8.8 Hz), 7.40—7.50 (2H, m), 8.40 (1H, d, J=3.3 Hz). *Anal.* Calcd for $C_{15}H_{10}FNO_3S$: C, 59.40; H, 3.32; N, 4.62. Found: C, 59.10; H, 3.37; N, 4.45.

7-(4-Fluorophenyl)-4,5-dihydro-5-methyl-4-oxothieno[3,2-*c*]pyridine-6-carboxylic Acid (14g) Compound **14g** was prepared from **11g** in 65% yield as colorless crystals. Recrystallization from EtOAc–THF–IPE gave colorless crystals: mp 233 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s), 5.08 (1H, br s), 7.14 (2H, t-like, J=8.8 Hz), 7.33 (1H, d, J=5.4 Hz), 7.43—7.55 (2H, m), 7.70 (1H, d, J=5.4 Hz). *Anal.* Calcd for: C, 59.40; H, 3.32; N, 4.62. Found: C, 59.07; H, 3.51; N, 4.35.

4-(4-Fluorophenyl)-6,7-dihydro-1,6-dimethyl-7-oxo-1*H*-pyrrolo[2,3-*c*]-pyridine-5-carboxylic Acid (14h) Compound **14h** was prepared from **11h** in 46% yield as colorless crystals. Recrystallization from EtOAc–IPE gave colorless crystals: mp 267—270 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s), 4.20 (3H, s), 6.02 (1H, d, J=2.8 Hz), 6.98 (1H, d, J=2.8 Hz), 7.09 (2H, t, J=8.8 Hz), 7.38—7.50 (2H, m). *Anal.* Calcd for $C_{16}H_{13}FN_2O_3$: C, 64.00; H, 4.36; N, 9.33. Found: C, 63.72; H, 4.50; N, 9.24.

***N*-(Cyanomethyl)-2-(4-fluorobenzoyl)-*N*-methyl-3-pyridinecarboxamide (10d)** Thionyl chloride (2.2 ml, 30.2 mmol) and DMF (catalytic amount) were added to a suspension of **8d** (1.50 g, 6.12 mmol) in CH_2Cl_2 (23 ml) at room temperature, and the mixture was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (20 ml). The solution was added to a mixture of *N*-methylaminoacetonitrile hydrochloride (717 mg, 6.73 mmol), Et_3N (4.70 ml, 33.7 mmol) and CH_2Cl_2 (20 ml), and the mixture was stirred at room temperature for 16 h. After evaporation of the solvent, the residue was diluted with H_2O and then extracted with EtOAc. The extract was washed successively with aqueous $NaHCO_3$ and H_2O, dried and concentrated to give **10d** as a colorless oil (1.80 g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 3.02 (3H, s), 4.52 (2H, s), 7.15 (t-like), 7.55 (1H, m), 7.81 (1H, d, J=7.6 Hz), 8.08 (2H, m), 8.73 (1H, dd, J=4.8, 1.6 Hz).

8-(4-Fluorophenyl)-5,6-dihydro-6-methyl-5-oxo-1,6-naphthyridine-7-carbonitrile (12d) A mixture of **10d** (1.80 g, 6.05 mmol), DBU (1.03 ml, 6.89 mmol) and toluene (80 ml) was refluxed for 7 h, while the water formed was removed azeotropically using a Dean–Stark apparatus. After evaporation of the solvent, the resulting crystals were collected by filtration and washed successively with H_2O and EtOAc to give **12d** as colorless crystals (1.55 g, 92%). Recrystallization from CH_2Cl_2–EtOAc gave colorless crystals: mp 258—259 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (3H, s), 7.24 (2H, t-like), 7.44—7.62 (3H, m), 8.79 (1H, dd, J=8.4, 1.8 Hz), 8.99 (1H, dd, J=4.4, 1.8 Hz). *Anal.* Calcd for $C_{16}H_{10}FN_3O$: C, 68.81; H, 3.61; N, 15.05. Found: C, 68.79; H, 3.63; N, 15.04.

8-(4-Fluorophenyl)-5,6-dihydro-6-methyl-5-oxo-1,6-naphthyridine-7-carboxamide (13d) A mixture of **12d** (1.00 g, 3.58 mmol), EtOH (10 ml) and 1 N NaOH (10 ml) was refluxed for 1 h. After evaporation of the solvent, the resulting crystals were collected by filtration and washed successively with H_2O and Et_2O to give **13d** as colorless crystals (1.00 g, 94%). Recrystallization from MeOH–Et_2O gave colorless crystals: mp 300—301 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, s), 5.42—5.67 (2H, b), 7.16 (2H, t-like), 7.45 (3H, m), 8.75 (1H, dd, J=8.0, 1.8 Hz), 8.90 (1H, dd, J=4.4, 1.8 Hz). *Anal.* Calcd for $C_{16}H_{12}FN_3O_2$: C, 64.64; H, 4.07; N, 14.13. Found: C, 64.34; H, 4.04; N, 14.28.

8-(4-Fluorophenyl)-5,6-dihydro-6-methyl-5-oxo-1,6-naphthyridine-7-carboxylic Acid (14d) A stirred mixture of **13d** (900 mg, 3.03 mmol) and concentrated HCl (25 ml) was treated portionwise with $NaNO_2$ (10 g, 0.14 mol) at room temperature, and the mixture was stirred for 20 h. After evaporation of the solvent, the residue was diluted with H_2O, treated with aqueous NaOH to adjust the pH to 10 and then washed with Et_2O. The aqueous layer was treated with concentrated HCl to adjust the pH to 3, saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated to give **14d** as colorless crystals (561 mg, 62%). Recrystallization from MeOH–Et_2O gave colorless crystals: mp 237 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 3.54 (3H, s), 7.25 (2H, t-like), 7.37 (2H, m), 7.58 (1H, dd, J=8.2, 4.4 Hz), 8.62 (1H, dd, J=8.2, 1.8 Hz), 8.88 (1H, dd, J=4.4, 1.8 Hz). *Anal.* Calcd for $C_{16}H_{11}FN_2O_3 \cdot 1/4H_2O$: C, 63.47; H, 3.75; N, 9.25. Found: C, 63.53; H, 3.73; N, 9.04.

***N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methylcarboxamide Derivatives of Isoquinolone-Related Heterocycles (2)** As a typical example, the preparation of **2b** is described. Thionyl chloride (0.90 ml, 12.3 mmol) and DMF (catalytic amount) were added to a solution of **14b** (0.27 g, 0.91 mmol) in benzene (27 ml) and THF (4.5 ml) at room temperature, and the mixture was refluxed for 1.5 h. After evaporation of the solvent, the residue was dissolved in THF (18 ml). The solution was added to a mixture of *N*-methyl-3,5-bis(trifluoromethyl)benzylamine (0.36 g, 1.23 mmol), Et_3N (0.50 ml, 3.59 mmol) and THF (20 ml), and the whole was stirred at room temperature for 14 h. After evaporation of the solvent, the residue was diluted with EtOAc and washed successively with H_2O, 1 N HCl, H_2O, aqueous $NaHCO_3$ and H_2O. The organic layer was dried and concentrated. The concentrate was subjected to chromatography on silica gel with EtOAc to give **2b** as colorless crystals (240 mg, 49%). Similarly, **2c—h** were prepared from **14c—h**, respectively. The physicochemical properties of **2b—h** are listed in Table 4.

***N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methylcarboxamide Derivatives of Tetrahydropyridopyridines (3). Method A** As a typical example, the preparation of **3b** is described. A mixture of **2b** (240 mg, 0.45 mmol), iodomethane (4 ml, 64.3 mmol) and dioxane (4 ml) was refluxed for 1.5 h. Evaporation of the solvent gave 3-[*N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methylaminocarbonyl]-4-(4-fluorophenyl)-1,2-dihydro-2,7-dimethyl-1-oxopyrido[3,4-*c*]pyridinium iodide as yellow crystals (303 mg, 100%). This quaternary salt (300 mg, 0.56 mmol) was dissolved in MeOH (15 ml). The stirred solution was treated portionwise with $NaBH_4$ (150 mg, 3.97 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After evaporation of the solvent, the residue was diluted with EtOAc, washed with H_2O, dried and concentrated. To this residue were added MeOH (15 ml) and 10% Pd–C (50% H_2O) (150 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 5 h. The catalyst was removed by filtration, and the filtrate was concentrated. The concentrate was subjected to chromatography on silica gel with EtOAc–MeOH (7:3) to give **3b** as colorless crystals (107 mg, 44%).

Method B As a typical example, the preparation of **3c** is described. A mixture of **2b** (270 mg, 0.50 mmol), 5% Pt–C (270 mg) and AcOH (15 ml) was stirred under a hydrogen atmosphere at room temperature for 4.5 h. The catalyst was removed by filtration, and the filtrate was concentrated. The concentrate was diluted with EtOAc, and the whole was washed successively with aqueous $NaHCO_3$ and H_2O. The organic layer was dried and concentrated to give **3c** as colorless crystals (170 mg, 62%).

Method C As a typical example, the preparation of **3b** is described. A solution of **3c** (68 mg, 0.13 mmol) in THF (3 ml) was treated with NaH (60% dispersion in oil) (6.0 mg, 0.15 mmol) and iodomethane (1.50 ml, 24.1 mmol). The mixture was stirred at room temperature for 15 h, diluted with EtOAc, washed with H_2O, dried and concentrated to give **3b** as colorless crystals (39 mg, 56%). Similarly, **3a**, **d—f** were prepared according to Method A, B or C. The physicochemical properties of **3a—f** are listed in Table 5.

Molecular Modeling Studies Systematic conformational search was performed using the Search/Compare Module in Insight II (ver. 95.0, Molecular Simulations Inc., San Diego, California, U.S.A.). The increments of rotation were set to 10 and 180 degrees for rotatable single and amide bonds, respectively. The most stable conformations were

Table 4. Physicochemical and Spectral Data for Isoquinolone-Related Heterocycles with an *N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methylcarbamoyl Substituent (**2**)

Compd. No.	Yield[a] (%)	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ
2b	35	179—181 (EA–IPE)	$C_{26}H_{18}F_7N_3O_2$	58.11 (57.96	3.38 3.44	7.82 7.61)	2.82 (3H, s), 3.60 (3H, s), 4.27 (1H, d, J=14.6 Hz), 4.80 (1H, d, J=14.6 Hz), 6.95—7.35 (5H, m), 7.55 (2H, s), 7.85 (1H, s), 8.67 (1H, d, J=5.8 Hz), 9.68 (1H, s)
2c	54	136—138 (EA–IPE)	$C_{26}H_{18}F_7N_3O_2$	58.11 (58.23	3.38 3.53	7.82 7.76)	2.82 (3H, s), 3.61 (3H, s), 4.31 (1H, d, J=14.6 Hz), 4.77 (1H, d, J=14.6 Hz), 6.95—7.37 (4H, m), 7.56 (2H, s), 7.85 (1H, s), 8.25 (1H, d, J=5.4 Hz), 8.61 (1H, s), 8.75 (1H, d, J=5.4 Hz)
2d	78	149—150 (EA–IPE)	$C_{26}H_{18}F_7N_3O_2$	58.11 (57.90	3.38 3.40	7.82 7.88)	2.78 (3H, s), 3.61 (3H, s), 4.41 (1H, d, J=14.6 Hz), 4.66 (1H, d, J=14.6 Hz), 6.97 (2H, t-like), 7.33 (2H, m), 7.45 (1H, dd, J=8.0, 4.2 Hz), 7.59 (2H, s), 7.85 (1H, s), 8.75 (1H, dd, J=8.0, 1.6 Hz), 8.89 (1H, dd, J=4.4, 1.6 Hz)
2e	61	196—197 (EA–IPE)	$C_{25}H_{17}F_7N_2O_2S$	55.35 (55.13	3.16 3.29	5.16 4.97)	2.73 (3H, s), 3.63 (3H, s), 4.37 (1H, d, J=15 Hz), 4.76 (1H, d, J=15 Hz), 6.85—7.10 (2H, m), 6.93 (1H, d, J=5.3 Hz), 7.20—7.40 (2H, m), 7.57 (2H, s), 7.68 (1H, d, J=5.3 Hz), 7.84 (1H, s)
2f	31	188—189 (EA–IPE)	$C_{25}H_{17}F_7N_2O_2S$	55.35 (55.58	3.16 3.36	5.16 5.04)	2.75 (3H, s), 3.61 (3H, s), 4.38 (1H, d, J=15 Hz), 4.75 (1H, d, J=15 Hz), 6.99 (2H, t-like , J=8.4 Hz), 7.34 (1H, d, J=5.6 Hz), 7.35—7.46 (2H, m), 7.56 (2H, s), 7.73 (1H, d, J=5.6 Hz), 7.84 (1H, s)
2g	61	130—132 (EE–H)	$C_{25}H_{17}F_7N_2O_2S\cdot$ 1/5 hexane	56.22 (56.17	3.57 3.49	5.01 5.07)	2.78 (3H, s), 3.50 (3H, s), 4.37 (1H, d, J=15 Hz), 4.71 (1H, d, J=15 Hz), 6.90—7.15 (2H, m), 7.08 (1H, d, J=3.3 Hz), 7.30—7.45 (2H, m), 7.55 (2H, s), 7.82 (1H, s), 8.44 (1H, d, J=3.3 Hz)
2h	27	160—161 (EE–H)	$C_{26}H_{20}F_7N_3O_2$	57.89 (58.05	3.74 3.53	7.79 7.72)	2.66 (3H, s), 3.57 (3H, s), 4.21 (3H, s), 4.45 (1H, d, J=14.5 Hz), 4.67 (1H, d, J=14.5 Hz), 6.05 (1H, d, J=3.0 Hz), 6.96 (2H, t-like, J=8.4 Hz), 7.00 (1H, d, J=3.0 Hz), 7.31—7.42 (2H, m), 7.58 (2H, s), 7.82 (1H, s)

a) Yield of final step. *b*) Recrystallization solvent: EA=ethyl acetate, EE=ethyl ether, IPE=isopropyl ether, H=hexane.

Table 5. Physicochemical and Spectral Data for Tetrahydro Derivatives of the Pyridopyridines **2a—d** (**3**)

Compd. No.	Method[a]	Yield[b] (%)	mp (°C) (Solv.)[c]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ
3a	A	10	155—157 (EA–IPE)	$C_{27}H_{24}F_7N_3O_2$	58.38 (57.99	4.35 4.57	7.56 7.48)	1.68 (2H, m), 1.74—2.32 (2H, m), 2.66 (3H, s), 3.04 (3H, s), 3.05 (2H, m), 3.48 (3H, s), 4.21 (1H, d, J=14.4 Hz), 4.72 (1H, d, J=14.4 Hz), 6.83—7.27 (4H, m), 7.51 (2H, s), 7.81 (1H, s)
3b	A	44	156—157 (EA–IPE)	$C_{27}H_{24}F_7N_3O_2$	58.38 (58.27	4.35 4.49	7.56 7.53)	1.93—2.73 (4H, m), 2.48 (3H, s), 2.75 (3H, s), 3.24 (1H, d, J=17 Hz), 3.75 (1H, d, J=17 Hz), 4.18 (1H, d, J=14.3 Hz), 4.77 (1H, d, J=14.3 Hz), 6.84—7.25 (4H, m), 7.50 (2H, s), 7.81 (1H, s)
3c	B	86	178—180 (EA–EE)	$C_{26}H_{22}F_7N_3O_2$	57.67 (57.29	4.10 4.28	7.76 7.62)	1.92 (1H, d-like, J=17 Hz), 2.3—2.5 (1H, m), 2.7—2.9 (1H, m), 2.77 (3H, s), 3.0—3.1 (1H, m), 3.50 (3H, s), 3.81 (1H, d, J=18 Hz), 3.98 (1H, d, J=18 Hz), 4.19 (1H, d, J=14.4 Hz), 4.77 (1H, d, J= 14.4 Hz), 6.8—7.2 (4H, m), 7.50 (2H, s), 7.81 (1H, s)
3d	A	61	156—158 (EA–IPE)	$C_{27}H_{24}F_7N_3O_2$	58.38 (58.14	4.35 4.52	7.56 7.49)	2.97 (3H, s), 2.58—2.78 (5H, m), 2.78 (3H, s), 3.06 (1H, d, J=17 Hz), 3.50 (3H, s), 4.17 (1H, d, J=14.5 Hz), 4.79 (1H, d, J=14.5 Hz), 6.86—7.25 (4H, m), 7.50 (2H, s), 7.82 (1H, s)
3e	C	88	230—232 (EA–EE)	$C_{27}H_{24}F_7N_3O_2\cdot$ 1/2H_2O	57.45 (57.46	4.46 4.30	7.44 7.25)	1.81 (2H, m), 2.16 (3H, s), 2.58 (3H, s), 2.62 (2H, m), 3.01 (2H, m), 3.44 (3H, s), 4.32 (1H, d, J=14.4 Hz), 4.57 (1H, d, J=14.4 Hz), 6.8—7.3 (4H, m), 7.54 (2H, s), 7.82 (1H, s)
3f	B	70	226—228 (EA–IPE)	$C_{26}H_{22}F_7N_3O_2\cdot$ 3/4H_2O	56.31 (56.51	4.20 4.21	7.58 7.39)	1.86 (2H, m), 2.64 (2H, m), 2.78 (3H, s), 3.17 (2H, m), 3.42 (3H, s), 3.82 (1H, b), 4.16 (1H, d, J=14.2 Hz), 4.79 (1H, d, J=14.2 Hz), 6.9—7.3 (4H, m), 7.49 (2H, s), 7.80 (1H, s)

a) See Experimental section. *b*, *c*, *d*) See corresponding footnotes of Table 3.

created by energy minimization using the Discover force field (ver. 95.0, Molecular Simulation Inc.) from the lowest energy conformations obtained in a previous systematic conformational search. Rotational barriers were estimated by energy minimization using torsional forcing as constraints in Discover. All these procedures were carried out on an INDIGO^2 workstation from Silicon Graphics Inc.

[^{125}I]BH-SP Binding in Human IM-9 Cells and in Rat Forebrain The binding activities were determined according to the protocol previously reported.[10]

Guinea Pig Ileum Contraction Assay The assay using SP or NKA was performed according to the protocol previously reported.[10]

Inhibitory Effect on Capsaicin-Induced Plasma Extravasation in the Trachea of Guinea Pigs The inhibitory effect was determined according to the protocol in the literature[20] with minor modifications. Guinea pigs (Std. Hartley, male) ($n=3$—12) were anesthetized with 35 mg/kg of pentobarbital injected intraperitoneally, and the test sample was administered intravenously (i.v.). Five minutes after administration, a solution of capsaicin (150 μg/kg) and Evans blue dye (20 mg/kg) in ethanol–saline (3 : 7) was administered (i.v.) to cause the reaction. In the case of the oral administration test, the sample was administered 60 min prior to reaction induction. Ten minutes after the reaction was induced, test animals were killed by cutting the interior vena cava, and the pulmonary artery was perfused with 50 ml of physiological saline. The trachea was excised, and its wet weight was measured. Evans blue dye was extracted by incubation in 1 ml of acetone–0.3% sodium sulfate (7 : 3) overnight. After centrifugation at 2800 rpm for 20 min, the concentration of Evans blue dye in the supernatant was quantified by measuring the absorbance at 620 nm. Plasma extravasation was expressed in terms of the amount of extracted Evans blue dye (μg) relative to the weight of the trachea (g). The efficacy of the sample was evaluated by calculating the % inhibition in accordance with the following formula: % inhibition $=[1-(A-B)/(C-B)]\times 100$, in which A, B and C represent the amount of Evans blue dye (μg/g) obtained in the test animal, in the group not treated with capsaicin (blank) (mean value) and in the control group (mean value), respectively.

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References and Notes

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25) We prepared some carboxamide derivatives without the ring B based on this assumption and found that they also showed good NK_1 antagonistic activity.[25a] The details will be reported in due course. *a*) European Patent Publication No.: EP0 733 632 A1 (publication date 1996. 9. 25).