Novel, Potent, and Orally Active Substance P Antagonists: Synthesis and Antagonist Activity of *N*-Benzylcarboxamide Derivatives of Pyrido[3,4-*b*]pyridine

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A series of 4-phenylisoquinolone derivatives were synthesized and evaluated for NK_1 (substance P) antagonist activity. Highly potent antagonists, 4-phenyl-3-isoquinolone-*N*-benzylcarboxamides (**11**), were discovered from the structure–activity relationship studies on the isoquinolone–urea lead **1a**. Optimization of the activity in this series resulted in the development of 5-phenyl-6-pyrido[3,4-*b*]pyridine-*N*-benzylcarboxamides (**30**) which are highly potent *orally* active NK_1 antagonists. Among the compounds synthesized, *N*-[3,5-bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-8-oxo-5-(substituted phenyl)-6-pyrido[3,4-*b*]pyridinecarboxamides (**30a,f,g**) showed excellent antagonist activities with IC_{50} values (*in vitro* inhibition of [^{125}I]-BH-SP binding in human IM-9 cells) of 0.21–0.34 nM and ED_{50} values (*in vivo* inhibition of capsaicin-induced plasma extravasation in guinea-pig trachea, iv) of 0.017–0.030 mg/kg. These compounds exhibited significantly potent activity upon oral administration with ED_{50} values of 0.068–0.17 mg/kg. Conformational studies on **30g** indicated that the two stable conformers of **30g** are quite similar to those of CP-99,994.

Introduction

Substance P (SP),[1] Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2,[2] is a neuropeptide belonging to the tachykinin family which includes neurokinins A and B (NKA and NKB). These tachykinins possess the common C-terminal amino acid sequence "-Phe-X-Gly-Leu-Met-NH_2" and have been shown to elicit a wide variety of physiological responses both in the central nervous system and peripheral tissues, including the transmission of pain and stress signals, inflammation, and the contraction of smooth muscles. The biological responses induced by the tachykinins (SP, NKA, and NKB) are mediated by three distinct receptors, NK_1, NK_2, and NK_3, respectively. Hence, stable receptor antagonists could have clinical potential in the treatment of various pathological states such as pain, inflammation, rheumatoid arthritis, asthma, and migraine.[3]

Since the discovery of the first selective *non-peptide* NK_1 antagonist CP-96,345,[4] study in this area has been highlighted, and reports of several antagonists which belong to other structural classes have rapidly followed, *e.g.*, RP67580,[5] CP-99,994,[6] SR140333,[7] CGP49823,[8] RPR100893,[9] L-732,138,[10] FK224,[11] and FK888[12] (Figure 1). It is noteworthy that some of the antagonists (*e.g.*, SR140333 and RPR100893) have been reported to have highly potent antagonist activity upon *oral* administration, implying that they have the potential for clinical use.

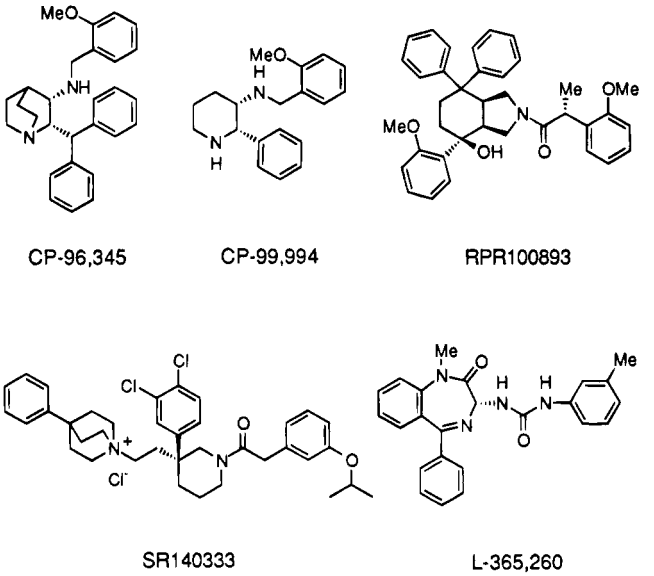

Figure 1.

In our search for a new non-peptide NK_1 antagonist, we first focused[13] on the similarity between SP and cholecystokinin (CCK) as well as between their receptors; both neuropeptides possess hydrophobic amino acid sequences, and the receptors of both peptides are members of the G-protein-coupled receptor superfamily. A report[14] which dealt with certain hydrophobic peptides that act as ligands for both SP and CCK receptors also attracted our attention. Thus, our synthesis started by taking into consideration the structural features of the non-peptide CCK antagonist L-365,260[15] (Figure 1) which is characterized as a heterocycle consisting of a diphenylmethane moiety linked to a phenyl ring *via* a spacer. Among the compounds synthesized along this line, a derivative of isoquinolone, *N*-(1,2-dihydro-2,6,7-

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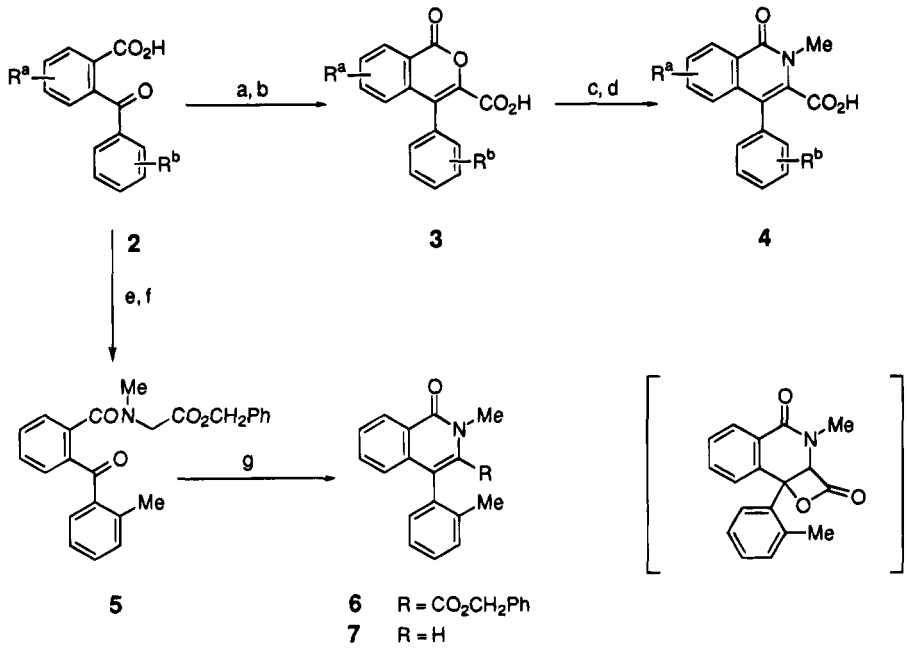
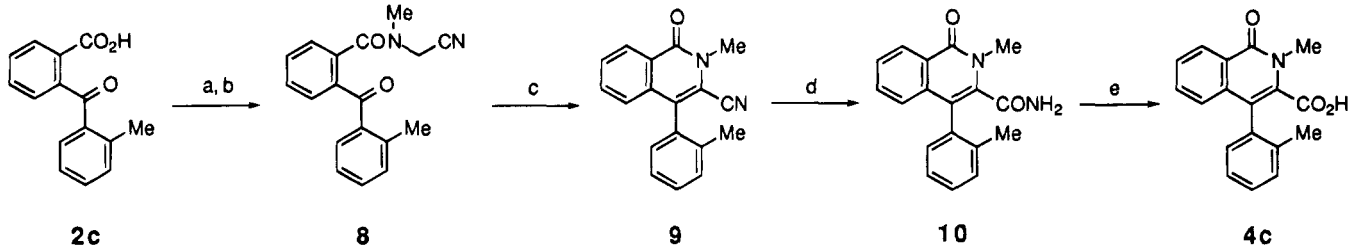
Scheme 1[a]



[a] Reagents: (a) $BrCH(CO_2Et)_2$, K_2CO_3/DMF/acetone; (b) concentrated HCl–AcOH; (c) $MeNH_2$/MeOH; (d) 4 N HCl–EtOAc; (e) $(COCl)_2$, DMF/THF; (f) sarcosine benzyl ester hydrochloride, Et_3N/THF; (g) DBU/toluene.

Scheme 2[a]



[a] Reagents: (a) $SOCl_2$, DMF/CH_2Cl_2; (b) (*N*-methylamino)acetonitrile hydrochloride, Et_3N/CH_2Cl_2; (c) DBU/toluene; (d) aqueous NaOH/EtOH; (e) $NaNO_2$/concentrated HCl–AcOH.

trimethyl-1-oxo-4-phenyl-3-isoquinolinyl)-*N'*-(3-methylphenyl)urea (**1a**), was found to possess weak binding affinity for the human NK_1 receptor (IC_{50} = 0.84 μM). The disclosure of CP-96,345 and RP67580 during the course of our optimization study from **1a** further stimulated our synthetic work, since both of these antagonists were found to possess structural features related to those we had envisioned.

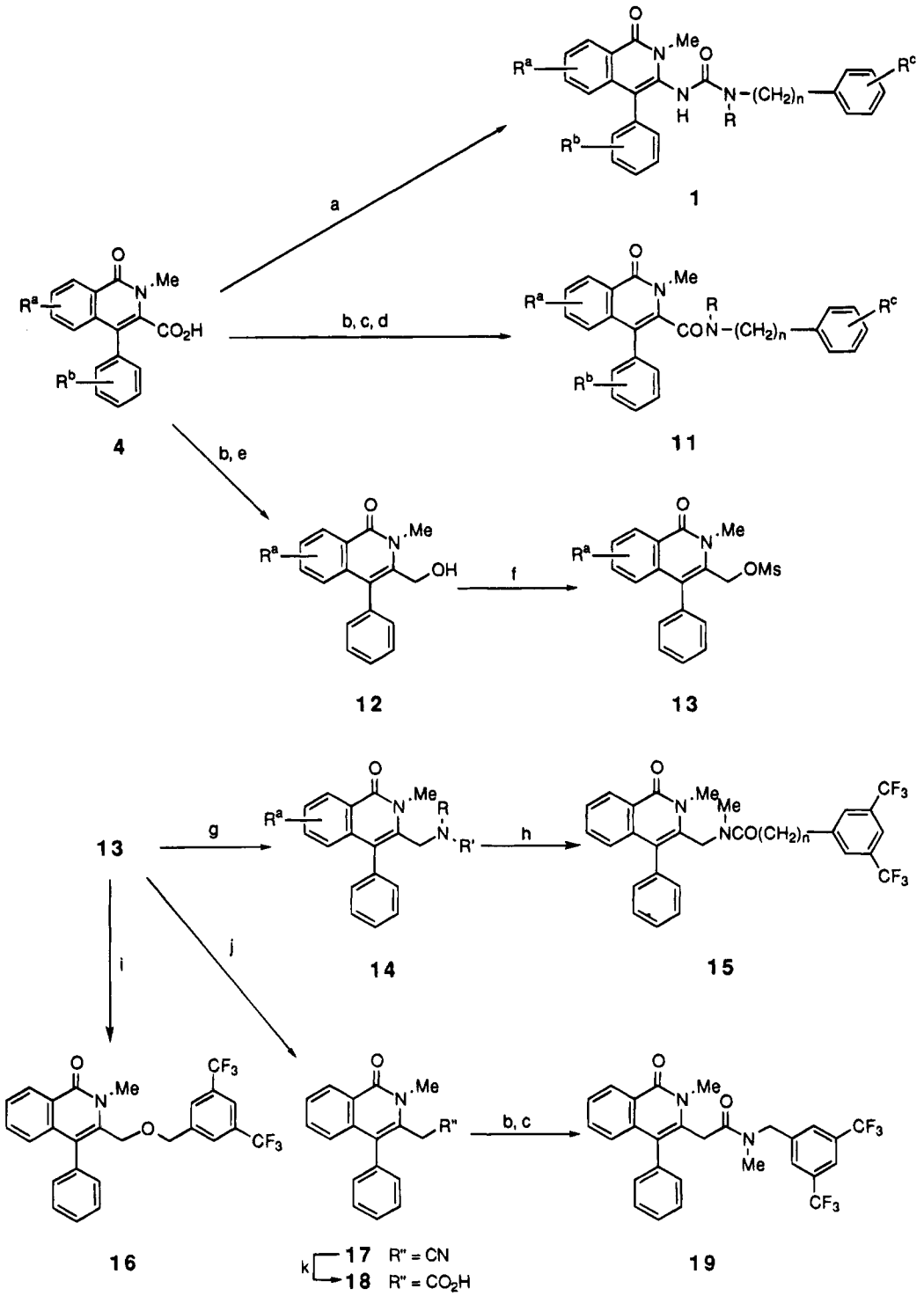
In this paper, we describe our synthetic studies starting from the lead compound **1a** and resulting in the discovery of a novel class of highly potent, selective, and orally active NK_1 antagonists, *N*-benzylcarboxamide derivatives of isoquinolone (**11**) and pyrido[3,4-*b*]pyridine (**30**). Conformational studies on **30g**, whose results may prove useful as an aid in better understanding the interactions between the antagonists and the NK_1 receptor, are also described.

Chemistry

The 4-phenylisoquinolone derivatives having various substituents at the 3-position were synthesized using the 4-phenylisoquinolone-3-carboxylic acids **4** as the key intermediates. The preparation of **4** is outlined in Schemes 1 and 2. The first method (**2** → **3** → **4**) is based on the protocol in the literature.[16,17] Alkylation of the 2-benzoylbenzoic acids **2** with diethyl bromomalonate followed by refluxing in concentrated HCl–AcOH gave the isocoumarin-3-carboxylic acids **3**. Treatment of **3** with methylamine followed by dehydration with HCl in EtOAc gave **4**.[18] In this method, however, when R is 2-methyl [*i.e.*, 2-(2-methylbenzoyl)benzoic acid (**2c**)], the ring closure reaction of the ester with concentrated HCl–AcOH did not proceed, affording the starting material **2c** instead of **3c**. Attempted dehydration of the glycine ester amide of **2c** (**5**) afforded **6** only in a trace amount, the undesired decarboxylation product **7** being the main product presumably formed *via* the 4-membered ring intermediate.[19] The synthesis of **4c** was accomplished *via* the 3-cyanoisoquinolone **9** (Scheme 2). Condensation of **2c** with (*N*-methylamino)acetonitrile provided the amide **8**, which was cyclized and dehydrated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the 3-cyanoisoquinolone **9**. Alkaline hydrolysis of **9** gave the amide **10**, which was treated with $NaNO_2$ in concentrated HCl–AcOH to give the acid **4c**.

The synthesis of the 4-phenylisoquinolone derivatives, having various substituents at the 3-position, from the carboxylic acids **4** is shown in Scheme 3. The urea derivatives **1** were synthesized by reaction of **4** with diphenyl phosphorazidate (DPPA) followed by treatment with the appropriate amines. The isoquinolone–amide derivatives **11** were prepared from **4**, *via* the acid chlorides, by reaction with the appropriate amines. The *N*-alkyl derivatives (**11**; R = Me, Et) were also prepared from **11** (R = H) by alkylation. Reduction of **4** with $NaBH_4$ *via* the acid chlorides gave the hydroxymethyl

Scheme 3[a]

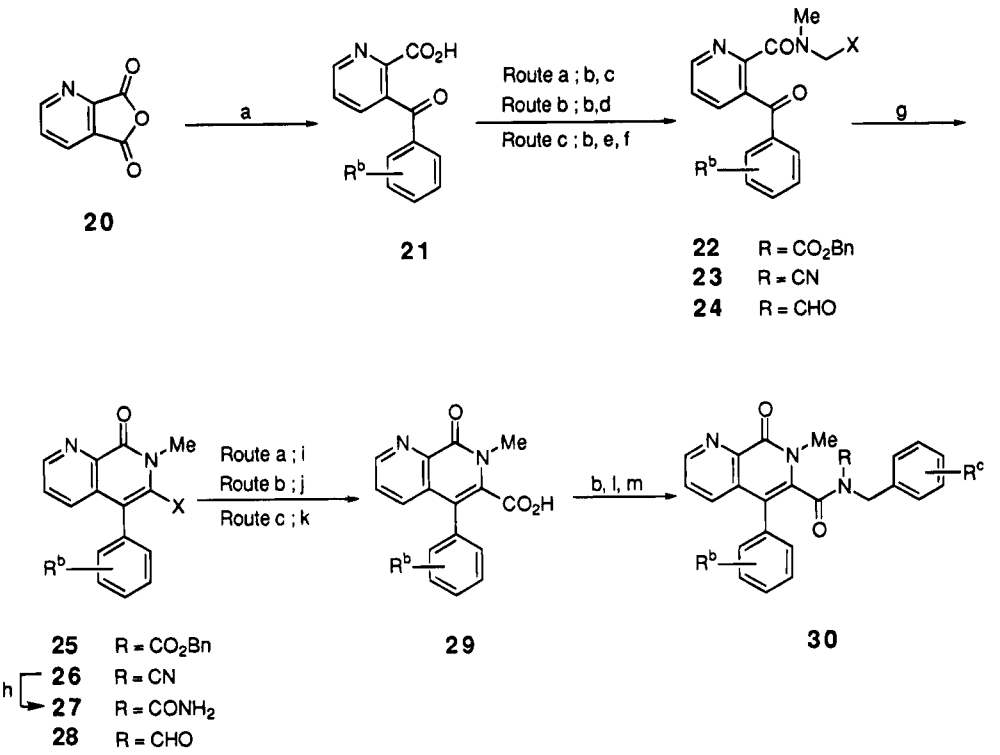


[a] Reagents: (a) DPPA, Et_3N, $RNH(CH_2)_nPhR^c$/benzene; (b) $(COCl)_2$, DMF/THF; (c) $RNH(CH_2)_nPhR^c$, Et_3N/CH_2Cl_2; (d) MeI (or EtI), NaH/DMF [for (**11**; R = H)]; (e) $NaBH_4$/1,2-dimethoxyethane/THF; (f) MsCl, Et_3N/CH_2Cl_2; (g) RR'NH; (h) $3,5\text{-}(CF_3)_2Ph(CH_2)_nCOCl$, Et_3N/THF (**14f**; R' = H); (i) 3,5-bis(trifluoromethyl)benzyl alcohol, NaH/DMF; (j) NaCN/DMSO; (k) concentrated HCl–AcOH.

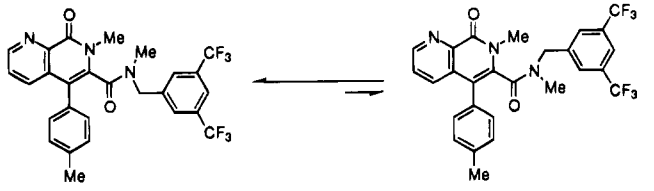
derivatives **12**, which were converted to the isoquinolone–amine derivatives **14** and the isoquinolone–ether derivative **16** by reaction with the appropriate amines and 3,5-bis(trifluoromethyl)benzyl alcohol, respectively, *via* the mesylates **13**. Treatment of **14f** (R = Me, R' = H) with the acid chlorides gave the amides **15**. The mesylate **13a** was converted to the 3-acetic acid derivative **18** by reaction with NaCN followed by acid hydrolysis. The amide derivative of **18** (**19**) was synthesized *via* the acid chloride by reaction with *N*-methyl-3,5-bis(trifluoromethyl)benzylamine.

Scheme 4 shows the preparation of the pyrido[3,4-*b*]-pyridinecarboxamide derivatives **30**, in which the carboxylic acids **29** were chosen as the key intermediates. The intermediates **29** were synthesized from the 3-benzoyl-2-pyridinecarboxylic acids **21** *via* synthetic routes a–c. The acids **21** were obtained by the Friedel–Crafts reaction (method A) or Grignard reaction (method B) of 2,3-pyridinedicarboxylic anhydride (**20**). In routes a and b, **21** was converted to **29** by methods similar to those used in the preparation of **4**. In route c, condensation of **21** with (*N*-methylamino)acetaldehyde dimethyl acetal followed by acid hydrolysis gave the aldehydes **24**. The aldehydes **24** were cyclized and dehydrated with

Scheme 4[a]



[a] Reagents: (a) $AlCl_3/R^bPh$ or $R^bPhMgBr/THF$; (b) $SOCl_2$, DMF/THF; (c) sarcosine benzyl ester hydrochloride, Et_3N/CH_2Cl_2; (d) (*N*-methylamino)acetonitrile hydrochloride, Et_3N/CH_2Cl_2; (e) (*N*-methylamino)acetaldehyde dimethyl acetal, Et_3N/CH_2Cl_2; (f) aqueous HCl/THF; (g) DBU/toluene; (h) aqueous NaOH/EtOH; (i) H_2/Pd–C/MeOH; (j) $NaNO_2$/AcOH–concentrated HCl; (k) $KMnO_4$/0.3 N NaOH/^{t}BuOH; (l) (*N*-substituted) benzylamines, Et_3N/CH_2Cl_2; (m) MeI, NaH/DMF [for (**30**; R = H)].



30g *trans* (*Z*) **30g'** *cis* (*E*)

Figure 2. Conformational isomers, **30g** and **30g'**. *Cis* and *trans* conformers are assigned with respect to the amide bond, and *Z* and *E* are assigned according to the sequence rule.

DBU to afford the pyrido[2,3-*b*]pyridine-3-carboxaldehydes **28**, which were oxidized with $KMnO_4$ to afford **29**. The acids **29**, thus obtained, were converted to the amide derivatives **30** by reaction with benzylamines *via* the acid chlorides.

An important structural feature should be noted for the *N*-substituted *N*-benzylcarboxamide derivatives of isoquinolone (**11**; R = Me, Et) and pyrido[3,4-*b*]pyridine (**30**; R = Me). These exist in two conformational isomers (rotamers), *cis* and *trans*, with respect to the amide bond (Figure 2).[20] In the amidation reaction of **4** and **29** with *N*-substituted benzylamines, the two conformers were usually formed in a ratio of *ca.* 7:1 as observed by TLC and/or HPLC. Since the minor conformer is unstable in solution, being easily interconverted to the major one, the product isolated in a crystalline form by conventional workup of the reaction mixture is usually the major conformer: physicochemical and biological data for **11** and **30** in the tables and Experimental Section are those for the major conformer unless otherwise noted. The physicochemical properties of the rotamers were examined in detail using compound **30g** and the isomer **30g'**. Single-crystal X-ray structural analysis of **30g** revealed that the major isomer has the *trans* conformation at the amide bond. A stereoscopic view of **30g** as determined by X-ray analysis is shown in Figure 3. The minor conformer **30g'** was separated and isolated in a crystalline form in a low yield by column chromatography (SiO_2) followed by a rapid and careful workup (*e.g.*, evaporation of solvent at low temperature). NMR studies on **30g** and **30g'** in $CDCl_3$ at 25 °C indicated that both isomers interconverted and reached the same equilibrium state (**30g/30g'** = *ca.* 7:1) in about 6 h.

Biology

The antagonist activities of the compounds prepared were preliminarily evaluated for *in vitro* inhibition of [^{125}I]Bolton-Hunter (BH)-SP binding in human IM-9 cells,[21] followed by *in vivo* screening (inhibition of capsaicin-induced plasma extravasation in the trachea of guinea pigs[22]) for the compounds showing good *in vitro* activity. Selected compounds were assayed for the ability to inhibit SP-induced contraction in guinea pig ileum preparations.

Results and Discussion

(a) Isoquinolone–Urea Derivatives (1). The biological data for the isoquinolone–urea derivatives, which have structures related to the lead compound **1a**, are shown in Table 1. Substitution of the phenyl group at the urea nitrogen with a benzyl group ($n = 0 \rightarrow 1$) (**1b**) resulted in a 6-fold increase in affinity, and *N*-methylation at the urea nitrogen (R) remarkably improved the affinity (**1b** *vs* **1f**). The substituent effects in the three phenyl rings (R^a, R^b, R^c) were examined with compounds **1c–j**. The compounds having a 4-fluoro atom (**1d,e**) on the 4-phenyl ring (R^b) showed substantially the same level of potency as the unsub-

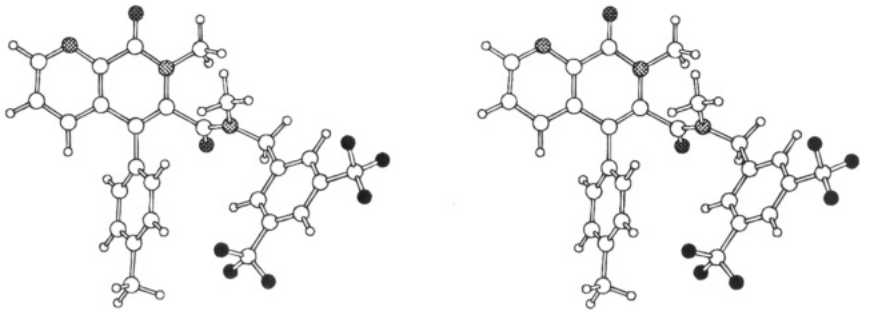
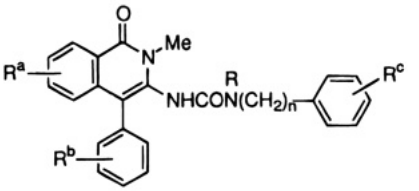


Figure 3. Stereoscopic molecular view of **30g** as determined by X-ray crystallographic analysis.

Table 1. Physicochemical and Biological Properties of Isoquinolone–Urea Derivatives (**1**)



compd no.	R^a	R^b	R^c	R	*n*	yield[a] (%)	mp (°C)	recrystn solvent[b]	formula	IC_{50}[c] (nM)	% inhibition[d] 3.0 mg/kg, iv
1a	6,7-Me_2	H	3-Me	H	0	43	>300	E	$C_{26}H_{25}N_3O_2$	840	–[e]
1b	6,7-Me_2	H	H	H	1	53	234–236	T	$C_{26}H_{25}N_3O_2$	140	–
1c	H	H	H	Me	1	55	203–206	EA–EE	$C_{25}H_{23}N_3O_2 \cdot 0.5H_2O$	1100	–
1d	H	4-F	H	Me	1	65	225–228	EA–EE	$C_{25}H_{22}FN_3O_2$	1500	–
1e	H	4-F	2-Cl	Me	1	65	226–228	EA–EE	$C_{25}H_{21}ClFN_3O_2$	480	–
1f	6,7-Me_2	H	H	Me	1	59	174–176	A–EE	$C_{27}H_{27}N_3O_2$	16	57.3 ± 6.6*[f]
1g	6,7-Me_2	H	2-MeO	Me	1	48	270–272	EA–EE	$C_{28}H_{29}N_3O_3$	23	–
1h	6,7-Me_2	H	2-Cl	Me	1	68	ca.207	T–IPE	$C_{27}H_{26}ClN_3O_2$	4.2	58.5 ± 9.4*[f]
1i	6,7-Me_2	H	3,5-Me_2	Me	1	60	184–185	EA–IPE	$C_{29}H_{31}N_3O_2 \cdot 0.1H_2O$	28	–
1j	6,7-Me_2	H	3,5-$(CF_3)_2$	Me	1	70	ca.230	EA–IPE	$C_{29}H_{25}F_6N_3O_2$	54	–
1k	6,7-Me_2	H	H	Et	1	77	153–155	T–IPE	$C_{28}H_{29}N_3O_2 \cdot 0.4H_2O$	66	–
1l	6,7-Me_2	H	H	Me	2	59	184–188	EA–EE	$C_{28}H_{29}N_3O_2$	3600	–

[a] Yield of final step. [b] E = ethyl alcohol, T = tetrahydrofuran, EA = ethyl acetate, EE = ethyl ether, A = acetone, IPE = isopropyl ether, H = hexane, M = methyl alcohol, DC = dichloromethane. [c] Inhibition of [^{125}I]BH-SP binding in human IM-9 cells (lymphocyte). IC_{50} values were determined by a single experiment run in duplicate unless otherwise noted. [d] Capsaicin-induced trachea extravasation in guinea pigs ($n = 6$). [e] –: not tested. [f] Mean ± SEM values are given for $n = 6$ determinations. Dunnett's test: * $p < 0.05$.

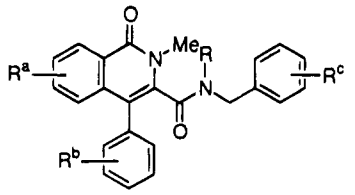
stituted derivative (**1c**). Introduction of methyl groups at the 6,7-positions (**1f**) of the isoquinolone ring (R^a) significantly improved the affinity. In particular, the compound having a 2-chloro atom (**1h**) on the phenyl ring (R^c) in the side chain showed the most favorable activity among the urea derivatives, with an IC_{50} value in the nanomolar range. Substitution with trifluoromethyl groups at the 3,5-positions in R^c (**1j**) did not improve the activity, whereas the same substitution in the isoquinolone–amide (**11**) and pyrido[3,4-*b*]pyridine–amide (**30**) derivatives led to significant enhancement of activity as described below. Substitution with an ethyl group at the urea nitrogen (**1k**) decreased the activity, and elongation of the tether length to two methylenes ($n = 2$) (**1l**) caused a significant loss of activity.

Compounds **1f** and **1h** were subjected to *in vivo* (iv) evaluation. To our disappointment, however, these urea derivatives were only weakly active in the *in vivo* test, presumably due to low solubility (**1f** and **1h** are insoluble in plasma) and/or metabolic unstability.

The above results indicate that the tether length (*n*: $1 \gg 0, 2$) and the substituent at the urea nitrogen (R: Me > Et ≫ H) play important roles in the activity, suggesting that the distance and the relative spatial orientation between the lipophilic moieties (the diphenylmethane moiety and the phenyl ring in the side chain) are important for binding to the NK_1 receptor. Thus, the spacer portion [urea: $-NHCON(Me)CH_2-$] was further modified to amide (**11**, **15**, and **19**), amine (**14**), and ether (**16**) groups.

(b) Modification of the Spacer Portion (11, 14–16, and 19). The biological data for the isoquinolone–amide derivatives (**11**) are shown in Table 2. *N*-Methylation at the amide nitrogen (R) significantly increased the inhibitory activity (**11a** *vs* **11c**, **11k** *vs* **11j**) in a manner similar to that observed in the urea series (**1**). This is similar to the structure–activity relationship (SAR) in the tryptophan–amide series[23] but in contrast to the SAR in the CP-96,345 series, in which *N*-methylation of the benzylamino group caused loss of activity.[4c] Effects of substituents on the phenyl ring (R^c) in the side chain were evaluated with **11f–j**. These compounds were all potently active, with IC_{50} values in the range of 10^{-8}–10^{-9} M. In particular, introduction of trifluoromethyl groups at the 3,5-positions (**11i,j**) in R^c led to marked improvement of the inhibitory potency; this effect is similar to that reported for the SP antagonists of quinuclidine ethers[24] and *N*-acyl-L-tryptophans.[10a] As for the R^b substitutent on the 4-phenyl ring, the compound having a 4-fluoro atom (**11n**) tended to be more potent than the unsubstituted derivative (**11i**) and the 2-methyl derivative (**11j**). As for the R^a substitutent on the isoquinolone ring, the unsubstituted derivative (**11i**) was more active than the 6-chloro derivative (**11l**), and substitution with methyl groups at the 6,7-positions (**11m**), which led to enhancement of activity in the urea series (**1**), resulted in a

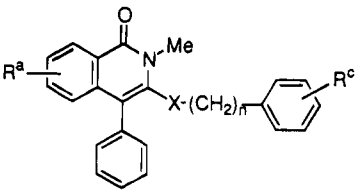
Table 2. Physicochemical and Biological Properties of Isoquinolone–Amide Derivatives (**11**)



compd no.	R^a	R^b	R^c	R	yield[a] (%)	mp (°C)	recrystn solvent[b]	formula	IC_{50}[c] (nM)	ED_{50} (mg/kg) or % inh[d] iv	po
11a	H	H	2-MeO	H	93	220–221	EA	$C_{25}H_{22}N_2O_3$	860[e]	–[f]	–
11b	H	2-Me	2-MeO	H	74	237–239	EA	$C_{26}H_{24}N_2O_3$	470[e]	–	–
11c	H	H	2-MeO	Me	87	147–148	EA	$C_{26}H_{24}N_2O_3$	30[e]	–	–
11d	H	2-Me	2-MeO	Me	85[g]	153–155	EA	$C_{27}H_{26}N_2O_3$	16[e]	–	–
11e	H	2-Me	2-MeO	Et	69[g]	119–120	EE–H	$C_{28}H_{28}N_2O_3$	34	–	–
11f	H	2-Me	H	Me	45	172–174	EA	$C_{26}H_{24}N_2O_2 \cdot 0.2H_2O$	34	–	–
11g	H	2-Me	2-Cl	Me	65[g]	143–144	EA	$C_{26}H_{23}ClN_2O_2$	19[e]	–	–
11h	H	2-Me	3,5-Me_2	Me	71[g]	135–136	EA–H	$C_{28}H_{28}N_2O_2$	32[e]	–	–
11i	H	H	3,5-$(CF_3)_2$	Me	51	145–146	EE	$C_{27}H_{20}F_6N_2O_2$	1.2[e]	45.7 ± 1.6%***[h]	–
11j	H	2-Me	3,5-$(CF_3)_2$	Me	97[g]	76–78	H	$C_{28}H_{22}F_6N_2O_2$	1.3	0.18 (0.14–0.27)[i]	0.81 (0.39–1.51)
11k	H	2-Me	3,5-$(CF_3)_2$	H	48	169–170	EA–H	$C_{27}H_{20}F_6N_2O_2$	2.5[e]	1.1 (0.54–4.26)	–
11l	6-Cl	H	3,5-$(CF_3)_2$	Me	75	165–166	EE	$C_{27}H_{19}ClF_6N_2O_2$	3.4	–	–
11m	6,7-Me_2	H	3,5-$(CF_3)_2$	Me	61[g]	148–149	EE–H	$C_{29}H_{24}F_6N_2O_2$	8.4	0.49 (0.21–0.79)	–
11n	H	4-F	3,5-$(CF_3)_2$	Me	67	99–101	IPE–H	$C_{27}H_{19}F_7N_2O_2$	0.4[e]	0.063 (0.042–0.086)	1.0 (0.51–3.37)

[a] Yield from **4** by amidation unless otherwise noted. [b–d,f] See corresponding footnotes of Table 1. [e] Mean value of two independent experiments run in duplicate. [g] Yield from **11** (R = H) by alkylation. [h] Inhibition (%) at 0.3 mg/kg. Dunnett's test: *** $p < 0.001$. [i] 95% confidence limits are given in parentheses.

Table 3. Physicochemical and Biological Properties of Amine (**14**), Ether (**16**), and Amide (**15**, **19**) Derivatives of Isoquinolone



compd no.	R^a	R^c	X	n	yield[a] (%)	mp (°C)	recrystn solvent[b]	formula	IC_{50}[c] (nM)	% inh[d] 3.0 mg/kg, iv
14a	H	2-MeO	CH_2NH	1	57	145–146	EA–EE	$C_{25}H_{24}N_2O_2 \cdot 0.3H_2O$	460	–[e]
14b	H	3,5-$(CF_3)_2$	$CH_2N(Me)$	1	51	135–136	EA–IPE	$C_{27}H_{22}F_6N_2O$	600	–
14c	6,7-Me_2	2-MeO	CH_2NH	1	90	159–160	EA–IPE	$C_{27}H_{28}N_2O_2$	13	36.3 ± 11.2
14d	6,7-Me_2	2-MeO	$CH_2N(Me)$	1	43	91–92	EE–H	$C_{28}H_{30}N_2O_2$	800	–
14e[f]	6,7-Me_2	3,5-$(CF_3)_2$	CH_2NH	1	64	powder	–	$C_{28}H_{25}ClF_6N_2O$	250	–
16	H	3,5-$(CF_3)_2$	CH_2O	1	18	133–134	EA–IPE	$C_{26}H_{19}F_6NO_2$	23[g]	–
19	H	3,5-$(CF_3)_2$	$CH_2CON(Me)$	1	69	193–194	EA–IPE	$C_{28}H_{22}F_6N_2O_2$	68	–
15a	H	3,5-$(CF_3)_2$	$CH_2N(Me)CO$	0	72	229–230	EA–IPE	$C_{27}H_{20}F_6N_2O_2$	19 ± 7[h]	–
15b	H	3,5-$(CF_3)_2$	$CH_2N(Me)CO$	1	37	219–220	EA–IPE	$C_{28}H_{22}F_6N_2O_2$	110	–

[a–e] See corresponding footnotes of Table 1. [f] This compound was prepared as the hydrochloride. [g] Mean value of two independent experiments run in duplicate. [h] Mean ± SD value of three independent experiments run in duplicate.

decrease in activity. Among the amide derivatives, **11n** showed the most potent activity with an IC_{50} value in the subnanomolar range, which is comparable to that of (±)-CP-99,994 [25] (IC_{50} = 0.2 nM).

The biological data for the compounds having various other functional groups in the spacer portion (X) are shown in Table 3. The amine derivatives (**14a–e**) and the ether derivative (**16**), which we had anticipated would possess highly potent activities considering their structural similarity to CP-96,345, showed only weak to moderate activities with IC_{50} values on the 10^{-7}–10^{-8} M level. The amide derivatives (**15a,b**, and **19**), whose structures are related to **11i**, were also found to have low potency.

In the *in vivo* (iv) evaluation, the amide derivatives (**11j,k,m,n**) exhibited potent activity corresponding relatively well to *in vitro* potency. Although the best of these, **11n**, was still less active than (±)-CP-99,994 (ED_{50} = 0.017 mg/kg, iv), the fairly good activities observed with oral administration of **11j** and **11n** stimulated further structural modification.

(c) Pyrido[3,4-*b*]pyridine Derivatives (30). From the SAR studies on the CP-96,345 series, a three-point binding model has been proposed and the importance of the bridgehead "basic nitrogen" in CP-96,345 for the NK_1 receptor recognition through ion-pair site interaction with the receptor has been indicated.[4c] Our series of compounds (**1**, **11**) lack the basic moiety, although they possess a diphenylmethane moiety linked to a phenyl ring *via* a spacer which seems essential for NK_1 receptor recognition. Taking these points into consideration, introduction of a basic nitrogen into the molecule was investigated in hopes of obtaining antagonists with improved activities. Satisfactory results were obtained by replacing the benzene ring in the isoquinolone nucleus with a pyridine ring. The biological data for the pyrido[3,4-*b*]pyridinecarboxamide derivatives (**30**) thus prepared are shown in Table 4. The SAR in

Table 4. Physicochemical and Biological Properties of 6-Pyrido[3,4-*b*]pyridinecarboxamide Derivatives (**30**)

compd no.	R^b	R^c	R	yield[a] (%)	mp (°C)	recrystn solvent[b]	formula	IC_{50}[c] (nM)	ED_{50} (mg/kg)[d] iv	ED_{50} (mg/kg)[d] po
30a	4-F	3,5-$(CF_3)_2$	Me	90	211–212	EA–EE	$C_{26}H_{18}F_7N_3O_2$	0.21 ± 0.03[e]	0.017 (0.013–0.024)[f]	0.068 (0.029–0.249)
30b	4-F	3,5-$(CF_3)_2$	H	68	210–212	M-DC–EA	$C_{25}H_{16}F_7N_3O_2$	1.1[g]	0.48 (0.37–0.60)	–[h]
30c	4-F	2-MeO	Me	34[i]	159–160	M–EE	$C_{25}H_{22}FN_3O_3$	2.5[g]	0.084 (0.032–0.177)	–
30d	4-F	3,5-Me_2	Me	66	178–180	M–EE	$C_{26}H_{24}FN_3O_2$	5.1[g]	–	–
30e	4-F	2-Cl	Me	69	243–245	M–A	$C_{24}H_{19}ClFN_3O_2{\cdot}0.3H_2O$	32	–	–
30f	H	3,5-$(CF_3)_2$	Me	51	191–192	M–EE	$C_{26}H_{19}F_6N_3O_2$	0.25 ± 0.07[e]	0.027 (0.016–0.041)	0.17 (0.12–0.25)
30g	4-Me	3,5-$(CF_3)_2$	Me	73	197–199	A–IPE	$C_{27}H_{21}F_6N_3O_2$	0.34 ± 0.07[e]	0.030 (0.018–0.054)	0.11 (0.076–0.178)
30g'[j]	4-Me	3,5-$(CF_3)_2$	Me	3.3	164–166	–	$C_{27}H_{21}F_6N_3O_2$	7.0	0.22 (0.13–2.16)	–
30h	4-Me	3,5-Me_2	Me	39	140–141	A–EE	$C_{27}H_{27}N_3O_2$	4.4[g]	–	–
30i	4-Me	3,5-Cl_2	Me	55	162–163	A–EE	$C_{25}H_{21}Cl_2N_3O_2$	3.4[g]	–	–
(±)-CP-99,994								0.20 ± 0.05[e]	0.017 (0.0079–0.027)	8.7 (6.0–21.2)

[a] Yield from **29** by amidation unless otherwise noted. [b–d] See corresponding footnotes of Table 1. [e] Mean ± SD value of three independent experiments run in duplicate. [f] 95% confidence limits are given in parentheses. [g] Mean value of two independent experiments run in duplicate. [h] –: not tested. [i] Yield *via* **30** (R = H) by alkylation. [j] *Cis* isomer about the amide bond.

this series (**30**) was similar to that in the isoquinolone-amide series (**11**). *N*-Methylation at the amide nitrogen increased the affinity (**30a** *vs* **30b**). Substitution on the 4-phenyl ring (R^b) showed minimal effects (**30f** *vs* **30a,g**). As for the R^c substituent on the phenyl ring in the side chain, substitution with trifluoromethyl groups at the 3,5-positions (**30a,f,g**) gave excellent results with IC_{50} values in the subnanomolar range which are comparable to that of (±)-CP-99,994; other substituents such as 2-methoxy (**30c**), 3,5-dimethyl (**30d,h**), and 3,5-dichloro (**30i**) also gave high affinities with IC_{50} values in the nanomolar range. Furthermore, the potencies of **30a** and **30f** are *ca.* 2–5-fold higher than those of their counterparts in the isoquinolone–amide series (**11n** and **11i**, respectively). These results indicate that the pyrido[3,4-*b*]pyridine nucleus is superior to the isoquinolone nucleus with regard to NK_1 receptor binding.

It is noteworthy that the *cis* rotamer (**30g'**) exhibited less potent activities than the *trans* rotamer (**30g**) both in *in vitro* and *in vivo* (iv). This again serves to emphasize the importance of the spatial orientation of the two phenyl rings for NK_1 receptor binding.[26]

Some of the compounds (**30a–c,f,g**) which showed potent binding affinity were examined for *in vivo* (iv) activity. These compounds showed fairly potent activity comparable to (±)-CP-99,994. Significantly, three potent compounds, *N*-[3,5-bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-8-oxo-5-(substituted phenyl)-6-pyrido[3,4-*b*]pyridinecarboxamides (**30a,f,g**), exhibited potent inhibitory effects upon *oral* administration with ED_{50} values of 0.068–0.17 mg/kg. From the above results, it is apparent that the basic nitrogen in **30** contributes not only to high affinity for the receptor but also to good oral availability.[27]

Compounds **30a**, **30f**, and **30g** inhibited SP-induced contraction in the guinea pig ileum preparation; the pA_2 values were determined to be 9.7–9.8, which are comparable to that of (±)-CP-99,994 (9.8). In all cases, increasing concentrations of these compounds produced parallel shifts of the log concentration–response curves of SP to the right, and the magnitude of the maximum responses to SP remained unchanged. Also, Schild plot regressions of **30a**, **30f**, and **30g** were linear with slopes of 1.03 ± 0.28, 1.11 ± 0.17, and 1.08 ± 0.29, respectively. These results indicate that the compounds behave as competitive antagonists of SP activity. Furthermore, compounds **30a**, **30f**, and **30g** exhibited *ca.* 1000-fold selectivity for the human NK_1 receptor (IM-9 cells) over the rat NK_1 receptor[28] (rat forebrain: IC_{50} values 0.43, 0.36, and 0.30 μM, respectively), and the affinities at the NK_2 (bovine psalterium)[29] and NK_3 (guinea pig cerebral cortex)[30] receptors were also weak with IC_{50} values greater than 1 μM for all of the compounds.[31]

To analyze the binding conformations of these potent non-peptide substance P antagonists, we compared low-energy conformers of **30g** (including the rotamer **30g'**) with those of CP-99,994. On the basis of the low-energy conformers of these antagonists obtained by systematic bond rotations, we predicted pharmacophores that describe the binding mode by Apex-3D.[32] From the resultant pharmacophore candidates, we selected two models using the criterion that the conformers have a large intersection volume when superimposed (Figure 4). The first model (Figure 4) has the largest intersection volume (191 Å^3), in which the conformer of **30g** is 17 kcal/mol less stable than the most stable one but has

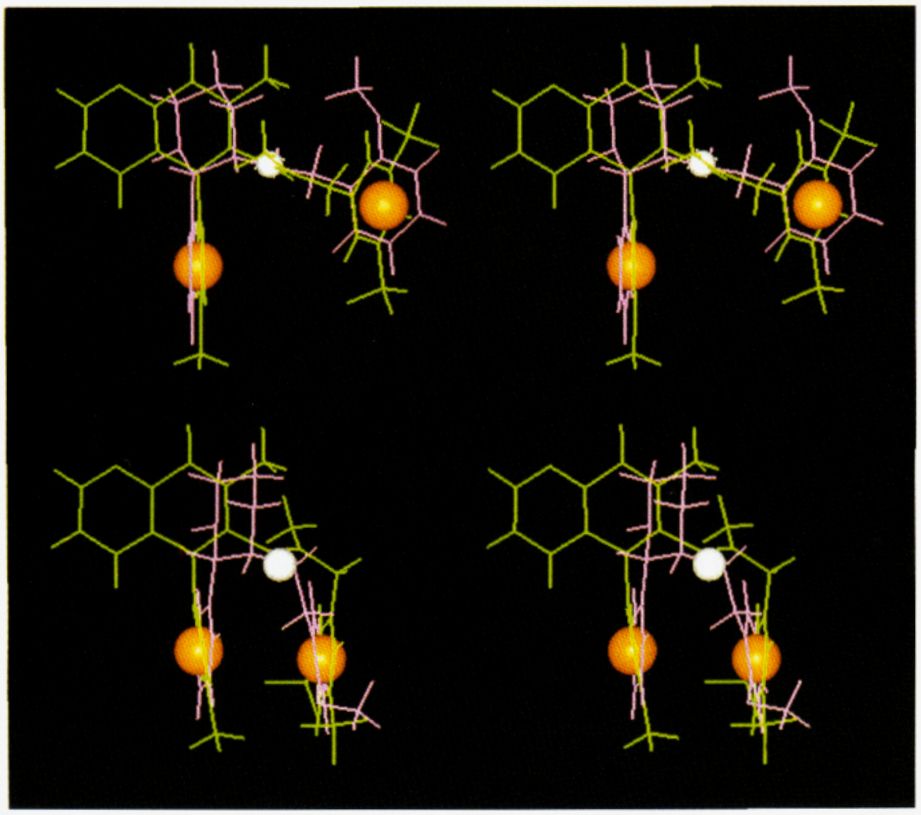


Figure 4. Stereoscopic view of the overlap between two stable conformers of **30g** (green) and those of CP-99,994 (pink) selected by the criterion that the conformers have a large intersection volume when superimposed: (a, top) the model with the largest intersection volume (191 Å^3); (b, bottom) the model with the next largest one (182 Å^3). The white sphere (an amide oxygen in **30g** and an exocyclic amine nitrogen in CP-99,994) and two yellow spheres (two phenyl rings) indicate plausible key sites for NK_1 receptor recognition.

a structure similar to that obtained from the X-ray analysis of **30g**.[33] In the second model with the next largest intersection volume (182 Å^3) (Figure 4), two phenyl rings in each compound adopt a stacking conformation, and **30g** is the most stable in this conformation. The stable conformers of CP-99,994 selected in the first and second models are on slightly higher energy levels than the most stable conformer (0.2 and 4.5 kcal/mol higher, respectively); the conformation of the latter is quite similar to the most stable one.[6a] Both of these pharmacophores indicate that two phenyl rings and a heteroatom (*i.e.*, the amide oxygen in **30g** and the exocyclic amine nitrogen in CP-99,994) are well superimposed in **30g** and CP-99,994,[34] suggesting that the suitable three-dimensional structure of these three points may be essential to the receptor binding, although it is difficult to conclude which of the above two possibilities is the more reasonable.

In addition, these modeling studies revealed that the basic nitrogen atoms in the pyrido[3,4-*b*]pyridine (**30g**) and CP-99,994 do not overlap at all. Concerning the receptor binding sites, the essential sites seem to be included also in the isoquinolone−amide series of SP antagonists (**11**), since some of the compounds (*e.g.*, **11i−n**) possess high affinity with IC_{50} values on the nano- to subnanomolar level. These results suggest that the ion-pair interaction with the receptor as proposed for CP-96,345[4c] is not as important for this new series of SP antagonists (**30**) and that the role of the basic nitrogen in **30** for the enhancement of the affinity may be an additional one such as an anchoring function in the phospholipid components of the membrane as discussed using *N*-alkyl derivatives of CP-96,345.[4g]

In summary, we have demonstrated the discovery of *N*-benzylcarboxamide derivatives of pyrido[3,4-*b*]pyridine (**30**) as a novel class of SP antagonists with highly potent activity upon oral administration, which might implicate potential therapeutic utility. These are apparently distinct from the previously reported SP antagonists[4−12] in that compounds **30** are derivatives of a conformationally rigid heterocycle. The conformational studies on **30g**, however, indicated that stable conformers of **30g** are quite similar to those of a representative antagonist, CP-99,994, suggesting that both antagonists bind to similar binding sites on the NK_1 receptor and that, as proposed for CP-99,994[6a] and its spirocyclic analogue,[6c] the relative spatial orientation of the two phenyl groups may be an important factor for binding. Pharmacological studies on these new SP antagonists and further studies on SAR of the compounds having related structures are in progress and will be reported in due course.

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. 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. IR spectra were obtained on a Hitachi IR-215 spectrometer. 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.

4-Phenyl-3-isocoumarincarboxylic Acid (3a). Com-

pound **3a** was prepared from 2-benzoylbenzoic acid (**2a**) by the procedure based on a protocol in the literature.[16]

4-(4-Fluorophenyl)-3-isocoumarincarboxylic Acid (3b). Compound **3b** was prepared from 2-(4-fluorobenzoyl)benzoic acid (**2b**) by the procedure based on a protocol in the literature.[17]

6,7-Dimethyl-4-phenyl-3-isocoumarincarboxylic Acid (3d). A mixture of 2-benzoyl-4,5-dimethylbenzoic acid (**2d**) (1.36 g, 5.35 mmol), acetone (35 mL), DMF (1 mL), K_2CO_3 (0.76 g, 5.50 mmol), and diethyl bromomalonate (1.43 g, 5.98 mmol) was stirred at room temperature for 60 h. After evaporation of the solvent, EtOAc was added to the residue. The mixture was washed with H_2O, dried, and concentrated. To the concentrate were added AcOH (25 mL) and concentrated HCl (25 mL), and the whole mixture was heated at 110 °C for 5 h. After evaporation of the solvent, the residue was diluted with H_2O and extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated to give **3d** as colorless crystals (1.39 g, 88%). Recrystallization from EtOAc–diisopropyl ether (IPE) gave colorless crystals: mp 265–268 °C; ^{1}H NMR 2.27 (3 H, s), 2.40 (3 H, s), 5.75 (1 H, bs, COOH), 6.85 (1 H, s), 7.18–7.30 (2 H, m), 7.40–7.55 (3 H, m), 8.18 (1 H, s). Anal. ($C_{18}H_{14}O_4$) C, H.

6-Chloro-4-phenyl-3-isocoumarincarboxylic Acid (3e). 2-Benzoyl-4-chlorobenzoic acid (**2e**) (16.0 g, 61.4 mmol) was treated according to the same procedure as described in the preparation of **3d** to afford **3e** as colorless crystals (13.3 g, 72%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 206–208 °C; ^{1}H NMR 7.07 (1 H, d, J = 2.0), 7.18–7.30 (2 H, m), 7.45–7.55 (3 H, m), 7.61 (1 H, dd, J = 8.6, 2.0), 8.35 (1 H, d, J = 8.6). Anal. ($C_{16}H_9ClO_4$) C, H.

1,2-Dihydro-2-methyl-1-oxo-4-phenyl-3-isoquinolinecarboxylic Acid (4a). Compound **4a** was prepared from **3a** by the procedure based on a protocol in the literature.[18]

4-(4-Fluorophenyl)-1,2-dihydro-2-methyl-1-oxo-3-isoquinolinecarboxylic Acid (4b). Compound **3b** (2.00 g, 7.04 mmol) was treated according to the same procedure as described in the preparation of **4d** to afford **4b** as colorless crystals (2.05 g, 98%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 196–197 °C; ^{1}H NMR 3.64 (3 H, s), 7.08–7.21 (3 H, m), 7.28–7.38 (2 H, m), 7.50–7.65 (2 H, m), 8.42–8.52 (1 H, m). Anal. ($C_{17}H_{12}FNO_3$) C, H, N.

1,2-Dihydro-2,6,7-trimethyl-1-oxo-4-phenyl-3-isoquinolinecarboxylic Acid (4d). To a solution of **3d** (3.75 g, 12.7 mmol) in MeOH (50 mL) was added 40% $MeNH_2$–MeOH solution (25 mL), and the mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was diluted with H_2O. The mixture was acidified with 1 N HCl, followed by extraction with EtOAc. The extract was washed with H_2O and dried. After evaporation of the solvent, 4 N HCl–EtOAc (50 mL) was added to the residue. The mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was diluted with H_2O. The resulting crystals were collected and washed successively with H_2O, acetone, and Et_2O to give **4d** as colorless crystals (3.51 g, 90%). Recrystallization from EtOH gave colorless crystals: mp >300 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 2.25 (3 H, s), 2.39 (3 H, s), 3.67 (3 H, s), 6.91 (1 H, s), 7.39–7.42 (5 H, m), 8.24 (1 H, s). Anal. ($C_{19}H_{17}NO_3$) C, H, N.

6-Chloro-1,2-dihydro-2-methyl-1-oxo-4-phenyl-3-isoquinolinecarboxylic Acid (4e). Compound **3e** (4.50 g, 15.0 mmol) was treated according to the same procedure as described in the preparation of **4d** to afford **4e** as colorless crystals (4.90 g, 100%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 248–250 °C; ^{1}H NMR 3.61 (3 H, s), 7.17 (1 H, d, J = 1.9), 7.30–7.40 (2 H, m), 7.40–7.55 (4 H, m), 8.36 (1H, d, J = 4.8). Anal. ($C_{17}H_{12}ClNO_3$) C, H, N.

***N*-[(Benzyloxycarbonyl)methyl]-*N*-methyl-2-(2-methylbenzoyl)benzamide (5).** To a solution of 2-(2-methylbenzoyl)benzoic acid (**2c**) (2.40 g, 9.99 mmol) in THF (40 mL) were added oxalyl chloride (1.12 mL, 12.8 mmol) and DMF (catalytic amount) at room temperature, and the mixture was stirred for 1 h. After evaporation of the solvent, the residue was dissolved in THF (50 mL). To the solution were added sarcosine benzyl ester hydrochloride (2.81 g, 13.0 mmol) and Et_3N (4.20 mL, 30.1 mmol), and the mixture was stirred at room temperature overnight. 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 to give **5** as a colorless oil (3.85 g, 96%): ^{1}H NMR 2.41 (3 H, s), 2.97 (3 H × $^3/_5$, s), 3.06 (3 H × $^2/_5$, s), 4.01 (2 H × $^2/_5$, s), 4.26 (2 H × $^3/_5$, s), 5.18 (2 H × $^2/_5$, s), 5.21 (2 H × $^3/_5$, s), 7.15–7.60 (13 H, m).

2-Methyl-4-(2-methylphenyl)-1(2*H*)-isoquinolinone (7). A mixture of **5** (3.85 g, 9.59 mmol), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (6.0 mL, 40.1 mmol), and toluene (200 mL) was refluxed for 3 h while water was azeotropically removed using a Dean–Stark apparatus. After being 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 using hexane–EtOAc (2:1) as eluant to give **7** as colorless crystals (1.55 g, 65%). Recrystallization from Et_2O–hexane gave colorless crystals: mp 127–129 °C; ^{1}H NMR 2.11 (3 H, s), 3.65 (3 H, s), 6.97 (1 H, s), 7.08 (1 H, m), 7.20–7.40 (4 H, m), 7.45–7.60 (2 H, m), 8.52 (1 H, m). Anal. ($C_{17}H_{15}NO$) C, H, N.

***N*-(Cyanomethyl)-*N*-methyl-2-(2-methylbenzoyl)benzamide (8).** To a solution of 2-(2-methylbenzoyl)benzoic acid (**2c**) (4.80 g, 20 mmol) in CH_2Cl_2 (100 mL) were added thionyl chloride (2.62 g, 22.0 mmol) and DMF (catalytic amount) at room temperature, and the mixture was stirred for 2 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (90 mL). To the solution were added (*N*-methylamino)acetonitrile hydrochloride (2.43 g, 22.8 mmol) and Et_3N (6.0 mL, 43.0 mmol), and the mixture was stirred at room temperature overnight. 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 to give **8** as a colorless oil (5.80 g, 99%): ^{1}H NMR 2.05 (3 H × $^1/_4$, s), 2.40 (3 H × $^3/_4$, s), 3.03 (3 H × $^3/_4$, s), 3.21 (3 H × $^1/_4$, s), 4.19 (2 H × $^1/_4$, s), 4.48 (2 H × $^3/_4$, s), 7.20–7.65 (8 H, m).

1,2-Dihydro-2-methyl-4-(2-methylphenyl)-1-oxo-3-isoquinolinecarbonitrile (9). A mixture of **8** (5.80 g, 19.8 mmol), DBU (3.0 mL, 20.1 mmol), and toluene (100 mL) was refluxed for 5 h, while water was azeotropically removed using a Dean–Stark apparatus. 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 to give **9** as colorless crystals (5.0 g, 92%). Recrystallization from EtOAc gave colorless crystals: mp 204–205 °C; ^{1}H NMR 2.12 (3 H, s), 3.85 (3 H, s), 7.06–7.14 (1 H, m), 7.20–7.50 (4 H, m), 7.56–7.72 (2 H, m), 8.51–8.58 (1 H, m). Anal. ($C_{18}H_{14}N_2O$) C, H, N.

1,2-Dihydro-2-methyl-4-(2-methylphenyl)-1-oxo-3-isoquinolinecarboxamide (10). A mixture of **9** (5.0 g, 18.2 mmol), EtOH (50 mL), and 1 N NaOH (25 mL) was refluxed for 1.5 h. After evaporation of the solvent, the residue was diluted with 1 N HCl. The crystals precipitated were collected by filtration and washed successively with H_2O, acetone, and Et_2O to give **10** as colorless crystals (4.30 g, 81%). Recrystallization from acetone–MeOH gave colorless crystals: mp 319–320 °C; ^{1}H NMR 2.12 (3 H, s), 3.69 (3 H, s), 5.48 (2 H, bs), 6.95–7.05 (1 H, m), 7.25–7.40 (4 H, m), 7.50–7.60 (2 H, m), 8.48–8.55 (1 H, m). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

1,2-Dihydro-2-methyl-4-(2-methylphenyl)-1-oxo-3-isoquinolinecarboxylic acid (4c). To a mixture of **10** (2.0 g, 6.84 mmol), AcOH (25 mL), and concentrated HCl (50 mL) was added $NaNO_2$ (9.0 g, 130 mmol) portionwise at room temperature, and the mixture was stirred overnight. After the mixture was diluted with H_2O, the crystals precipitated were collected by filtration and washed with H_2O and Et_2O to give **4c** as colorless crystals (0.97 g, 48%). Recrystallization from EtOAc–EtOH gave colorless crystals: mp 225–227 °C; ^{1}H NMR 2.09 (3 H, s), 3.61 (3 H, s), 4.16 (1 H, bs, COOH), 6.95–7.05 (1 H, m), 7.15–7.35 (4 H, m), 7.50–7.60 (2 H, m), 8.40–8.50 (1 H, m). Anal. ($C_{18}H_{15}NO_3 \cdot 0.2H_2O$) C, H, N.

Isoquinolone–Urea Derivatives (1, Table 1). As a typical example, the preparation of **1f** is described. To a stirred mixture of **4d** (307 mg, 1.0 mmol), DPPA (0.290 mL, 1.35 mmol), and benzene (20 mL) was added dropwise Et_3N (0.142 mL, 1.02 mmol). The mixture was stirred at room temperature for 1 h and then with heating under reflux for

30 min. *N*-Methylbenzylamine (0.154 mL, 1.19 mmol) was added to the mixture, and the whole mixture was refluxed for 30 min. The mixture was diluted with EtOAc and washed successively with H_2O, 1 N HCl, aqueous $NaHCO_3$, and H_2O. The organic layer was dried and concentrated to give **1f** as colorless crystals (250 mg, 59%). Similarly, **1a–e,g–l** were prepared from **4a–e** and (substituted)amines. The physicochemical properties of **1a–l** are listed in Table 1.

Isoquinolonecarboxamide Derivatives (11, Table 2): By Amidation. As a typical example, the preparation of **11k** is described. To a solution of **4c** (293 mg, 1.0 mmol) in THF (10 mL) were added oxalyl chloride (0.104 mL, 1.19 mmol) and DMF (catalytic amount) at room temperature, and the mixture was stirred for 1 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL). To the solution were added 3,5-bis(trifluoromethyl)benzylamine (340 mg, 1.40 mmol) and Et_3N (0.154 mL, 1.10 mmol), and the mixture was stirred at room temperature for 5 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 **11k** as colorless crystals (250 mg, 48%).

By Alkylation. As a typical example, the preparation of **11d** is described. A mixture of **11b** (206 mg, 0.5 mmol), NaH (60% dispersion in oil) (24 mg, 0.6 mmol), and DMF (5 mL) was stirred at room temperature for 30 min. After the mixture was cooled to 0 °C, iodomethane (0.5 mL, 8.0 mmol) was added to the mixture. The mixture was stirred at room temperature for 30 min, added to H_2O, and then extracted with EtOAc. The extract was washed successively with 1 N HCl, aqueous $NaHCO_3$, and H_2O, dried, and concentrated to give **11d** as colorless crystals (180 mg, 84%). Similarly, other isoquinolonecarboxamide derivatives (**11**) were prepared by amidation or alkylation. The physicochemical properties of **11a–n** are listed in Table 2.

3-(Hydroxymethyl)-2-methyl-4-phenyl-1(2*H*)-isoquinolinone (12a). To a solution of **4a** (10.0 g, 35.8 mmol) in THF (200 mL) were added oxalyl chloride (5.67 mL, 65.0 mmol) and DMF (catalytic amount) at room temperature, and the mixture was stirred for 30 min. After evaporation of the solvent, the residue was dissolved in THF (100 mL) and 1,2-dimethoxyethane (100 mL). The solution was added dropwise to the suspension of $NaBH_4$ (4.95 g, 131 mmol) in 1,2-dimethoxyethane (150 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min, poured into 2 N HCl, and extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$ and H_2O, dried, and concentrated to give **12a** as colorless crystals (8.80 g, 93%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 158–159 °C; ^{1}H NMR 1.88 (1 H, t, OH), 3.83 (3 H, s), 4.48 (2 H, d, J = 5.6), 7.0–7.5 (8 H, m), 8.43–8.50 (1 H, m). Anal. ($C_{17}H_{15}NO_2$) C, H, N.

3-(Hydroxymethyl)-2,6,7-trimethyl-4-phenyl-1(2*H*)-isoquinolinone (12b). Compound **4d** (10.0 g, 32.5 mmol) was treated according to the same procedure as described in the preparation of **12a** to afford **12b** as colorless crystals (8.7 g, 91%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 209–210 °C; ^{1}H NMR 2.09 (1 H, bt, J = 5.8), 2.20 (3 H, s), 2.34 (3 H, s), 3.81 (3 H, s), 4.43 (2 H, d, J = 5.8), 6.73 (1 H, s), 7.25–7.35 (2 H, m), 7.45–7.55 (3 H, m), 8.19 (1 H, s). Anal. ($C_{19}H_{19}NO_2 \cdot 0.2H_2O$) C, H, N.

3-[[(Methylsulfonyl)oxy]methyl]-2-methyl-4-phenyl-1(2*H*)-isoquinolinone (13a). To a stirred solution of **12a** (8.0 g, 30.2 mmol) in CH_2Cl_2 (200 mL) were added Et_3N (7.20 mL, 51.7 mmol) and methanesufonyl chloride (3.87 mL, 50.0 mmol) at 0 °C. The mixture was stirred for 30 min. After dilution with CH_2Cl_2, the mixture was washed with 0.1 N HCl and H_2O and dried. The organic layer was concentrated to give **13a** as colorless crystals (9.70 g, 94%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 149–150 °C; ^{1}H NMR 2.88 (3 H, s), 3.80 (3 H, s), 5.05 (2 H, s), 7.00–7.15 (1 H, m), 7.25–7.40 (2 H, m), 7.45–7.60 (5 H, m), 8.48–8.58 (1 H, m). Anal. ($C_{18}H_{17}NO_4S$) C, H, N.

3-[[(Methylsulfonyl)oxy]methyl]-2,6,7-trimethyl-4-phenyl-1(2*H*)-isoquinolinone (13b). Compound **12b** (3.0 g, 10.2 mmol) was treated according to the same procedure as described in the preparation of **13a** to afford **13b** as colorless crystals (2.98 g, 79%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 150–151 °C; ^{1}H NMR 2.25 (3 H, s), 2.40 (3 H, s), 2.86 (3 H, s), 3.77 (3 H, s), 5.01 (2 H, s), 6.82 (1 H, s), 7.25–7.35 (2 H, m), 7.45–7.60 (3 H, m), 8.27 (1 H, s). Anal. ($C_{20}H_{21}NO_4S$) C, H, N.

Isoquinolone–Amine Derivatives (14, Table 3). As a typical example, the preparation of **14c** is described. A mixture of **13b** (300 mg, 0.81 mmol), 2-methoxybenzylamine (0.51 mL, 3.91 mmol), and THF (5 mL) was heated in a stainless-steel tube at 130 °C for 2 h. The mixture was diluted with H_2O, followed by extraction with EtOAc. The extract was washed with aqueous K_2CO_3 and brine, dried, and concentrated. The concentrate was subjected to chromatography on silica gel using hexane–EtOAc (1:1) as eluant to give **14c** as colorless crystals (301 mg, 90%). Similarly, **14a,b,d,e** were prepared from **13a,b** and (substituted)benzylamines. The physicochemical properties of **14a–e** are listed in Table 3.

1,2-Dihydro-*N*,2-dimethyl-1-oxo-4-phenyl-3-isoquinolinemethylamine (14f). Compound **13a** (300 mg, 0.87 mmol) was treated according to a similar procedure as described in the preparation of **14c** using methylamine in place of 2-methoxybenzylamine to afford **14f** as colorless crystals (202 mg, 83%). Recrystallization from EtOAc–IPE gave colorless crystals: mp 198–200 °C; ^{1}H NMR 2.30 (3 H, s), 3.47 (2 H, s), 3.85 (3 H, s), 6.94–7.00 (1 H, m), 7.20–7.30 (2 H, m), 7.40–7.55 (5 H, m), 8.45–8.55 (1 H, m). Anal. ($C_{18}H_{18}N_2O$) C, H, N.

***N*-[3,5-Bis(trifluoromethyl)benzoyl]-1,2-dihydro-*N*,2-dimethyl-1-oxo-4-phenyl-3-isoquinolinemethylamine (15a).** Compound **14f** (150 mg, 0.54 mmol) was treated according to a similar procedure as described in the preparation of **11k** using 3,5-bis(trifluoromethyl)benzoic acid in place of **4c** to afford **15a** as colorless crystals (201 mg, 72%). The physicochemical properties of **15a** are listed in Table 3.

***N*-[3,5-Bis(trifluoromethyl)phenylacetyl]-1,2-dihydro-*N*,2-dimethyl-1-oxo-4-phenyl-3-isoquinolinemethylamine (15b).** Compound **14f** (150 mg, 0.54 mmol) was treated according to a similar procedure as described in the preparation of **11k** using 3,5-bis(trifluoromethyl)phenylacetic acid in place of **4c** to afford **15b** as colorless crystals (105 mg, 37%). The physicochemical properties of **15b** are listed in Table 3.

3-[[[3,5-Bis(trifluoromethyl)benzyl]oxy]methyl]-2-methyl-4-phenyl-1(2*H*)-isoquinolinone (16). A mixture of 3,5-bis(trifluoromethyl)benzyl alcohol (200 mg, 0.82 mmol), NaH (60% dispersion in oil) (50 mg, 1.25 mmol), and DMF (6 mL) was stirred at room temperature for 30 min. After the mixture was cooled to 0 °C, **13a** (200 mg, 0.58 mmol) was added to the mixture. The mixture was stirred at room temperature for 2 h, added to 2 N HCl, and then extracted with EtOAc. The extract was washed successively with aqueous K_2CO_3 and H_2O, dried, and concentrated. The concentrate was subjected to chromatography on silica gel using hexane–EtOAc (3:1) as eluant to give **16** as colorless crystals (50.3 mg, 18%). The physicochemical properties of **16** are listed in Table 3.

1,2-Dihydro-2-methyl-1-oxo-4-phenyl-3-isoquinolineacetonitrile (17). To a solution of **13a** (157 mg, 0.46 mmol) in DMSO (1 mL) was added sodium cyanide (100 mg, 2.04 mmol). The mixture was stirred at room temperature for 2 h and then diluted with H_2O. The crystals precipitated were collected by filtration and washed successively with H_2O, EtOAc, and Et_2O. Recrystallization from EtOAc–MeOH gave **17** as colorless crystals (125 mg, 100%): mp 253–255 °C; ^{1}H NMR 3.60 (2 H, s), 3.85 (3 H, s), 7.02–7.07 (1 H, m), 7.28–7.59 (7 H, m), 8.49–8.54 (1 H, m). Anal. ($C_{18}H_{14}N_2O$) C, H, N.

1,2-Dihydro-2-methyl-1-oxo-4-phenyl-3-isoquinolineacetic Acid (18). A mixture of **17** (2.19 g, 7.98 mmol), AcOH (50 mL), and concentrated HCl (50 mL) was refluxed for 8 h. After evaporation of the solvent, the residue was diluted with EtOAc. The mixture was washed with H_2O, dried, and concentrated to give **18** as colorless crystals (1.40 g, 60%). Recrystallization from EtOAc–MeOH gave colorless crystals: mp 200–201 °C; ^{1}H NMR 3.67 (2 H, s), 3.69 (3 H, s), 6.99–7.04 (1 H, m), 7.26–7.53 (7 H, m), 8.47–8.52 (1 H, m). Anal. ($C_{18}H_{15}NO_3$) C, H, N.

***N*-[3,5-Bis(trifluoromethyl)benzyl]-1,2-dihydro-*N*,2-dimethyl-1-oxo-4-phenyl-3-isoquinolineacetamide (19).** Compound **18** (250 mg, 0.85 mmol) was treated according to a

similar procedure described in the preparation of **11** using **18** in place of **4c** to afford **19** as colorless crystals (313 mg, 69%). The physicochemical properties of **19** are listed in Table 3.

3-Benzoyl-2-pyridinecarboxylic Acid (21a). Method A. To a stirred mixture of 2,3-pyridinedicarboxylic acid anhydride (**20**) (21.0 g, 141 mmol) and benzene (210 mL) was added $AlCl_3$ (30.0 g, 225 mmol) at room temperature. The mixture was refluxed for 4 h. After being cooled, the mixture was poured into concentrated HCl (25 mL)–ice water (200 mL) and stirred at room temperature for 1 h. The resulting crystals were collected and washed with H_2O and Et_2O to give the hydrochloride of **21a** as colorless crystals (23.7 g, 64%). Recrystallization from MeOH gave colorless crystals: mp 149–153 °C; ^{1}H NMR 7.44 (2H, t-like, J = 7.9), 7.59 (1 H, m), 7.78 (3 H, m), 7.88 (1 H, dd, J = 7.7, 1.5), 8.78 (1 H, dd, J = 4.7, 1.5). Anal. ($C_{13}H_{10}ClNO_3$) C, H, N.

Method B. To a stirred suspension of Mg (1.01 g, 41.5 mmol) in THF (8 mL) were added I_2 (catalytic amount) and a solution of bromobenzene (5.68 mL, 53.9 mmol) in THF (10 mL) dropwise and stirred for 30 min. The mixture was added dropwise to the stirred solution of anhydride **20** (4.5 g, 30.2 mmol) in THF (60 mL) at 0 °C and stirred for 30 min at room temperature. The mixture was poured into 1 N HCl (50 mL)–ice water (50 mL) and extracted with EtOAc. After evaporation of the solvent, the residue was dissolved in EtOAc. The aqueous layer was treated with concentrated HCl to adjust the pH to 2–3, and the mixture was extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated. The concentrate was subjected to chromatography on silica gel using EtOAc–AcOH (10:1) as eluant and treated with 4 N HCl–EtOAc to give hydrochloride of **21a** as colorless crystals (2.23 g, 28%). The physicochemical data were identical with those of **21a** prepared by method A.

3-(4-Fluorobenzoyl)-2-pyridinecarboxylic Acid (21b). Compound **20** (38.7 g, 260 mmol) was treated according to method A using fluorobenzene in place of benzene, and then the hydrochloride **21b** thus obtained was dissolved in H_2O. The solution was treated with aqueous $NaHCO_3$ to adjust the pH to 2–3, and the mixture was extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated to give **21b** as colorless crystals (21.0 g, 33%). Recrystallization from MeOH–EtOAc gave colorless crystals: mp 152–153 °C; ^{1}H NMR (DMSO-d_6) 7.35 (2 H, t-like, J = 8.8), 7.68–7.80 (3 H, m), 7.99 (1 H, dd, J = 7.6, 1.8), 8.84 (1 H, dd, J = 4.6, 1.8). Anal. ($C_{13}H_8FNO_3$) C, H, N.

3-(4-Methylbenzoyl)-2-pyridinecarboxylic Acid (21c). Compound **20** (50.0 g, 33.5 mmol) was treated according to the same procedure as described in the preparation of **21b** using toluene in place of fluorobenzene to afford **21c** as colorless crystals (50.6 g, 63%). Recrystallization from CH_2Cl_2–EtOAc gave colorless crystals: mp 168–170 °C; ^{1}H NMR 2.41 (3 H, s), 7.24 (2 H, d, J = 8.4), 7.62 (2 H, d, J = 8.4), 7.70 (1 H, dd, J = 8.0, 4.8), 7.85 (1 H, dd, J = 8.0, 1.5), 8.77 (1 H, dd, J = 4.8, 1.5). Anal. ($C_{14}H_{11}NO_3$) C, H, N.

3-Benzoyl-*N*-[(benzyloxycarbonyl)methyl]-*N*-methyl-2-pyridinecarboxamide (22a). To a solution of hydrochloride of **21a** (3.0 g, 11.4 mmol) in THF (60 mL) were added thionyl chloride (3.0 mL, 41.1 mmol) and DMF (catalytic amount) at room temperature, and the mixture was refluxed for 1 h. After evaporation of the solvent, the residue was dissolved in THF (75 mL). To the solution were added sarcosine benzyl ester hydrochloride (2.76 g, 12.8 mmol) and Et_3N (6.3 mL, 45.2 mmol), and the mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was diluted with EtOAc, washed with H_2O, dried, and concentrated to give **22a** as a colorless oil (3.57 g, 81%): ^{1}H NMR 3.12 (3 H × $^4/_9$, s), 3.18 (3 H × $^5/_9$, s), 4.24 (2 H × $^5/_9$, s), 4.26 (2 H × $^4/_9$, s), 5.19 (2 H × $^5/_9$, s), 5.26 (2 H × $^4/_9$, s), 7.23–7.85 (12 H, m), 8.40 (1 H × $^4/_9$, dd, J = 4.8, 1.4), 8.74 (1 H × $^5/_9$, dd, J = 4.8, 1.4).

***N*-[(Benzyloxycarbonyl)methyl]-3-(4-fluorobenzoyl)-*N*-methyl-2-pyridinecarboxamide (22b).** Hydrochloride of **21b** (2.0 g, 7.1 mmol) was treated according to the same procedure as described in the preparation of **22a** to afford **22b** (2.94 g, 100%): ^{1}H NMR 3.13, 3.19 (each 1.5 H, s), 4.20, 4.30 (each 1 H, s), 5.18, 5.25 (each 1 H, s), 7.12 (2 H, m), 7.22–7.50 (5 H, m), 7.22 (1 H, dd, J = 7.6, 1.8), 7.75–7.90 (2 H, m), 8.39 (1 H, dd, J = 4.8, 1.8), 8.74 (1 H, dd, J = 4.8, 1.8).

Benzyl 7,8-Dihydro-7-methyl-8-oxo-5-phenyl-6-pyrido[3,4-*b*]pyridinecarboxylate (25a). A mixture of **22a** (3.57 g, 9.19 mmol), DBU (2.0 mL, 13.4 mmol), and toluene (150 mL) was refluxed for 12 h, while water was azeotropically removed using a Dean–Stark apparatus. After evaporation of the solvent, the residue was diluted with EtOAc. The mixture was washed with H_2O, dried, and concentrated. The concentrate was subjected to chromatography on silica gel using EtOAc as eluant to give **25a** as colorless crystals (0.7 g, 21%). Recrystallization from CH_2Cl_2–EtOAc gave colorless crystals: mp 127–128 °C; ^{1}H NMR 3.63 (3 H, s), 4.99 (2 H, s), 7.03–7.08 (2 H, m), 7.23–7.55 (9 H, m), 7.62 (1 H, dd, J = 8.3, 1.4), 8.92 (1 H, dd, J = 4.2, 1.4). Anal. ($C_{23}H_{18}N_2O_3$) C, H, N.

Benzyl 5-(4-Fluorophenyl)-7,8-dihydro-7-methyl-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxylate (25b). Compound **22b** (2.94 g, 7.23 mmol) was treated according to the same procedure as described in the preparation of **25a** to afford **25b** as colorless crystals (0.63 g, 22%). Recrystallization from MeOH–EtOAc gave colorless crystals: mp 127–128 °C; ^{1}H NMR 3.63 (3 H, s), 5.06 (2 H, s), 7.02 (2 H, t-like, J = 8.8), 7.07–7.38 (7 H, m), 7.48 (1 H, dd, J = 8.4, 4.2), 7.55 (1 H, dd, J = 8.4, 1.8), 8.92 (1 H, dd, J = 4.2, 1.8). Anal. ($C_{23}H_{17}FN_2O_3$) C, H, N.

3-Benzoyl-*N*-(cyanomethyl)-*N*-methyl-2-pyridinecarboxamide (23a). To a suspension of hydrochloride of **21a** (10.0 g, 37.9 mmol) in THF (100 mL) were added thionyl chloride (13.8 mL, 189 mmol) and DMF (catalytic amount) at room temperature, and the mixture was refluxed for 3.5 h. After evaporation of the solvent, the residue was dissolved in THF (80 mL). To the solution were added (*N*-methylamino)-acetonitrile hydrochloride (4.85 g, 45.5 mmol) and Et_3N (26.4 mL, 189 mmol) in THF (40 mL), and the mixture was refluxed overnight. 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. The concentrate was subjected to chromatography on silica gel using EtOAc–hexane (1:1) as eluant to give **23a** as a brown oil (6.74 g, 64%): ^{1}H NMR 3.11 (3 H × $^1/_3$, s), 3.17 (3 H × $^2/_3$, s), 4.39 (2 H × $^2/_3$, s), 4.50 (2 H × $^1/_3$, s), 7.23–7.93 (6 H, m), 8.64–8.90 (2 H, m).

***N*-(Cyanomethyl)-3-(4-fluorobenzoyl)-*N*-methyl-2-pyridinecarboxamide (23b).** Compound **21b** (7.0 g, 28.5 mmol) was treated according to the same procedure as described in the preparation of **23a** to afford **23b** as a brown oil (4.9 g, 58%): ^{1}H NMR 3.16 (3 H × $^1/_3$, s), 3.21 (3 H × $^2/_3$, s), 4.44 (2 H × $^2/_3$, s), 4.55 (2 H × $^1/_3$, s), 7.17 (2 H, t, J = 8.4), 7.50 (1 H, m), 7.85 (3 H, m), 8.75 (1 H, dd, J = 4.8, 1.6).

***N*-(Cyanomethyl)-*N*-methyl-3-(4-methylbenzoyl)-2-pyridinecarboxamide (23c).** Compound **21c** (22.0 g, 91.2 mmol) was treated according to the same procedure as described in the preparation of **23a** to afford **23c** as a brown oil (24.9 g, 93%): ^{1}H NMR 2.43 (3 H, s), 3.13 (3 H × $^1/_3$, s), 3.18 (3 H × $^2/_3$, s), 4.42 (2 H × $^2/_3$, s), 4.49 (2 H × $^1/_3$, s), 7.28 (2 H, d, J = 8.4), 7.42–7.52 (1 H, m), 7.63–7.73 (2 H, m), 7.81–7.94 (1 H, m), 8.70–8.75 (1 H, m).

7,8-Dihydro-7-methyl-8-oxo-5-phenyl-6-pyrido[3,4-*b*]pyridinecarbonitrile (26a). A mixture of **23a** (6.4 g, 22.9 mmol), DBU (5.0 mL, 33.4 mmol), and toluene (100 mL) was refluxed for 4 h, while water was azeotropically removed using a Dean–Stark apparatus. After evaporation of the solvent, the resulting crystals were collected by filtration and washed with EtOH to give **26a** as colorless crystals (4.32 g, 72%). Recrystallization from MeOH–Et_2O gave colorless crystals: mp 274–276 °C; ^{1}H NMR 3.92 (3 H, s), 7.36 (2 H, m), 7.58 (4 H, m), 7.74 (1 H, dd, J = 7.3, 1.7), 9.03 (1 H, dd, J = 4.2, 1.7). Anal. ($C_{16}H_{11}N_3O \cdot {}^1/_4H_2O$) C, H, N.

5-(4-Fluorophenyl)-7,8-dihydro-7-methyl-8-oxo-6-pyrido[3,4-*b*]pyridinecarbonitrile (26b). Compound **23b** (4.9 g, 16.5 mmol) was treated according to the same procedure as described in the preparation of **26a** to afford **26b** as colorless crystals (2.66 g, 58%). Recrystallization from EtOH–CH_2Cl_2–Et_2O gave colorless crystals: mp 231–232 °C; ^{1}H NMR 3.92 (3 H, s), 7.29 (2 H, t-like, J = 8.8), 7.36–7.48 (2 H, m), 7.60 (1

H, dd, J = 8.4, 4.2), 7.71 (1 H, dd, J = 8.4, 1.8), 9.04 (1 H, dd, J = 4.2, 1.8). Anal. ($C_{16}H_{10}FN_3O\cdot0.1H_2O$) C, H, N.

7,8-Dihydro-7-methyl-5-(4-methylphenyl)-8-oxo-6-pyrido[3,4-*b*]pyridinecarbonitrile (26c). Compound **23c** (26.9 g, 91.7 mmol) was treated according to the same procedure as described in the preparation of **26a** to afford **26c** as colorless crystals (14.2 g, 56%). Recrystallization from EtOAc–Et_2O gave colorless crystals: mp 268–270 °C; ^{1}H NMR 2.47 (3 H, s), 3.92 (3 H, s), 7.28 (2 H, d, J = 8.0), 7.38 (2H, d, J = 8.0), 7.56 (1 H, dd, J = 8.0, 4.0), 7.75 (1 H, dd, J = 8.0, 2.0), 9.01 (1 H, dd, J = 4.0, 2.0). Anal. ($C_{17}H_{13}N_3O\cdot1/6H_2O$) C, H, N.

7,8-Dihydro-7-methyl-8-oxo-5-phenyl-6-pyrido[3,4-*b*]pyridinecarboxamide (27a). A mixture of **26a** (4.32 g, 16.5 mmol), EtOH (40 mL), and 1 N NaOH (40 mL) was refluxed for 40 min. After evaporation of the solvent, the resulting crystals were collected by filtration and washed with H_2O and EtOH to give **27a** as colorless crystals (4.49 g, 97%). Recrystallization from MeOH–Et_2O gave colorless crystals: mp >310 °C; ^{1}H NMR (DMSO-d_6) 3.57 (3 H, s), 7.28–7.55 (6 H, m), 7.65 (1 H, dd, J = 8.2, 4.2), 7.82 (1 H, bs), 8.09 (1 H, bs), 8.83 (1 H, dd, J = 4.2, 1.5). Anal. ($C_{16}H_{13}N_3O_2$) C, H, N.

5-(4-Fluorophenyl)-7,8-dihydro-7-methyl-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxamide (27b). Compound **26b** (2.55 g, 9.13 mmol) was treated according to the same procedure as described in the preparation of **27a** to afford **27b** as colorless crystals (2.49 g, 92%). Recrystallization from MeOH–CH_2Cl_2–Et_2O gave colorless crystals: mp >310 °C; ^{1}H NMR (DMSO-d_6) 3.56 (3 H, s), 7.25–7.55 (5 H, m), 7.66 (1 H, dd, J = 8.4, 4.2), 7.86 (1 H, bs), 8.11 (1 H, bs), 8.83 (1 H, dd, J = 4.2, 1.6). Anal. ($C_{16}H_{12}FN_3O_2$) C, H, N.

7,8-Dihydro-7-methyl-5-(4-methylphenyl)-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxamide (27c). Compound **26c** (14.2 g, 51.6 mmol) was treated according to the same procedure as described in the preparation of **27a** to afford **27c** as colorless crystals (14.5 g, 96%). Recrystallization from MeOH gave colorless crystals: mp >310 °C; ^{1}H NMR (DMSO-d_6) 2.43 (3 H, s), 3.66 (3 H, s), 6.08 (1 H, b), 6.92 (1 H, b), 7.2–7.3 (4 H, m), 7.40 (1 H, dd, J = 8.0, 4.0), 7.56 (1 H, dd, J = 8.0, 2.0), 8.82 (1 H, dd, J = 4.0, 2.0). Anal. ($C_{17}H_{15}N_3O_2\cdot1/4H_2O$) C, H, N.

3-Benzoyl-*N*-(formylmethyl)-*N*-methyl-2-pyridinecarboxamide (24a). To a solution of hydrochloride of **21a** (2.0 g, 7.58 mmol) in THF (30 mL) were added thionyl chloride (2.0 mL, 27.4 mmol) and DMF (catalytic amount) at room temperature, and the mixture was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL). To the solution was added a solution of (*N*-methylamino)acetaldehyde dimethyl acetal (1.5 g, 12.6 mmol) and Et_3N (3.5 mL, 25.1 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at room temperature for 15 h. After evaporation of the solvent, the residue was diluted with EtOAc, washed with H_2O, dried, and concentrated. To the concentrate were added THF (15 mL) and 6 N HCl (20 mL). The mixture was stirred for 30 min, poured into aqueous K_2CO_3, and extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated to give **24a** as a brown oil (1.13 g, 53%): ^{1}H NMR 3.15 (3 H × $^2/_5$, s), 3.19 (3 H × $^3/_5$, s), 4.15 (2 H, s), 7.35–7.90 (7 H, m), 8.61 (1 H × $^2/_5$, dd, J = 4.6, 1.4), 8.75 (1 H × $^3/_5$, dd, J = 4.6, 1.4), 9.49 (1 H × $^3/_5$, s), 9.87 (1 H × $^2/_5$, s).

3-(4-Fluorobenzoyl)-*N*-(formylmethyl)-*N*-methyl-2-pyridinecarboxamide (24b). Hydrochloride of **21b** (2.0 g, 7.10 mmol) was treated according to the same procedure as described in the preparation of **24a** to afford **24b** as a brown oil (1.12 g, 53%). This compound was used for the next step without further purification.

***N*-(Formylmethyl)-*N*-methyl-3-(4-methylbenzoyl)-2-pyridinecarboxamide (24c).** Compound **21c** (2.0 g, 8.29 mmol) was treated according to the same procedure as described in the preparation of **24a** to afford **24c** as a brown oil (1.46 g, 59%): ^{1}H NMR 2.43 (3 H, s), 3.16 (3 H × $^2/_5$, s), 3.17 (3 H × $^3/_5$, s), 4.14 (2 H, m), 7.28 (2 H, d, J = 8.0), 7.35–7.50 (1 H, m), 7.70 (2 H, d, J = 8.0), 7.79 (1 H × $^2/_5$, dd, J = 7.8, 1.6), 7.88 (1 H × $^3/_5$, dd, J = 7.8, 1.6), 8.61 (1 H × $^2/_5$, dd, J = 5.0, 1.6), 8.75 (1 H × $^3/_5$, dd, J = 5.0, 1.6), 9.52 (1 H × $^3/_5$, m), 9.88 (1 H × $^2/_5$, m).

7,8-Dihydro-7-methyl-8-oxo-5-phenyl-6-pyrido[3,4-*b*]pyridinecarboxaldehyde (28a). A mixture of **24a** (1.11 g, 3.93 mmol), DBU (0.2 mL, 1.34 mmol), and toluene (20 mL) was refluxed for 30 min, while water was azeotropically removed using a Dean–Stark apparatus. The mixture was cooled, and the resulting crystals were collected by filtration and washed with Et_2O to give **28a** as colorless crystals (0.82 g, 79%). Recrystallization from MeOH–THF–Et_2O gave colorless crystals: mp 212–215 °C; ^{1}H NMR (DMSO-d_6) 3.74 (3 H, s), 7.41–7.50 (2 H, m), 7.52–7.63 (4 H, m), 7.70 (1 H, dd, J = 8.2, 4.4), 8.96 (1 H, dd, J = 4.4, 1.6), 9.43 (1H, s). Anal. ($C_{16}H_{12}N_2O_2$) C, H, N.

5-(4-Fluorophenyl)-7,8-dihydro-7-methyl-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxaldehyde (28b). Compound **24b** (1.09 g, 3.63 mmol) was treated according to the same procedure as described in the preparation of **28a** to afford **28b** as colorless crystals (0.65 g, 63%). Recrystallization from MeOH–THF–Et_2O gave colorless crystals: mp 231–234 °C; ^{1}H NMR (DMSO-d_6) 3.73 (3 H, s), 7.35–7.65 (5 H, m), 7.74 (1 H, dd, J = 8.2, 4.4), 8.96 (1 H, dd, J = 4.4, 1.4), 9.45 (1H, s). Anal. ($C_{16}H_{11}FN_2O_2$) C, H, N.

7,8-Dihydro-7-methyl-5-(4-methylphenyl)-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxaldehyde (28c). Compound **24c** (1.46 g, 4.93 mmol) was treated according to the same procedure as described in the preparation of **28a** to afford **28c** as colorless crystals (1.07 g, 78%). Recrystallization from THF–IPE gave colorless crystals: mp 282–284 °C; ^{1}H NMR 2.48 (3 H, s), 3.95 (3 H, s), 7.24 (2 H, d, J = 8.0), 7.36 (2H, d, J = 8.0), 7.53 (1 H, dd, J = 8.2, 4.4), 7.68 (1H, dd, J = 8.2, 1.6), 9.01 (1 H, dd, J = 4.4, 1.6), 9.61 (1 H, s). Anal. ($C_{17}H_{14}N_2O_2$) C, H, N.

7,8-Dihydro-7-methyl-8-oxo-5-phenyl-6-pyrido[3,4-*b*]pyridinecarboxylic Acid (29a): From 25a. A mixture of **25a** (0.64 g, 1.73 mmol), 10% palladium–carbon (50% H_2O) (300 mg), and MeOH (30 mL) was stirred under hydrogen at room temperature for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated to give **29a** as colorless crystals (0.43 g, 89%). Recrystallization from MeOH–Et_2O gave colorless crystals: mp 230–233 °C dec; ^{1}H NMR (DMSO-d_6) 3.50 (3 H, s), 7.10–7.80 (7 H, m), 8.82 (1 H, m). Anal. ($C_{16}H_{12}N_2O_3\cdot1/4H_2O$) C, H, N. The compound **29a** was treated with 4 N HCl–EtOAc to give hydrochloride of **29a** as yellow crystals: mp 180–185 °C (turned to colorless crystals), 230–233 °C dec; ^{1}H NMR (DMSO-d_6) 3.57 (3 H, s), 7.30–7.40 (2 H, m), 7.45–7.55 (3 H, m), 7.60 (1 H, dd, J = 8.2, 1.6), 7.73 (1 H, dd, J = 8.2, 4.4), 8.88 (1 H, dd, J = 4.4, 1.6). Anal. ($C_{16}H_{13}ClN_2O_3\cdot0.2H_2O$) C, H, N.

From 27a. To a stirred mixture of **27a** (5.79 g, 20.7 mmol), AcOH (50 mL), and concentrated HCl (150 mL) was added $NaNO_2$ (50 g, 0.72 mol) portionwise at room temperature, and the mixture was stirred for 15 h. Salts were filtered off and washed with concentrated HCl and MeOH. The filtrate was concentrated, and the residue was dissolved in MeOH. Salts were removed by filtration, and the filtrate was concentrated to give hydrochloride of **29a** as yellow crystals (5.35 g, 82%). The physicochemical data were identical with those of **29a** prepared by the above method.

From 28a. To a stirred mixture of **28a** (1.0 g, 3.78 mmol), 0.3 N NaOH (6 mL), and ^{t}BuOH (20 mL) was added $KMnO_4$ (0.63 g, 3.99 mmol) portionwise at room temperature. After the mixture was stirred for 40 min, EtOH was added to the reaction mixture, which was stirred for 15 min. MnO_2 was removed by filtration, and the filtrate was concentrated. To the concentrate was added concentrated HCl, and the crystalline residue (a mixture of salts) was removed by filtration. The filtrate was concentrated to give hydrochloride of **29a** as yellow crystals (1.05 g, 91%). The physicochemical data were identical with those of **29a** prepared by the above method.

5-(4-Fluorophenyl)-7,8-dihydro-7-methyl-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxylic Acid (29b). Compound **29b** was prepared from **25b**, **27b**, and **28b** by the same procedure as described in the preparation of **29a** from **25a**, **27a**, and **28a**. The yields were 85% from **25b**, 88% from **27b**, and 95% from **28b**. Recrystallization from MeOH–EtOAc gave colorless crystals (free form): mp 238–239 °C; ^{1}H NMR (DMSO-d_6) 3.53

(3 H, s), 7.21 (2 H, t-like, J = 9.0), 7.39 (2 H, m), 7.45–7.61 (2 H, m), 8.68 (1 H, dd, J = 4.0, 1.8). Anal. ($C_{16}H_{11}FN_2O_3 \cdot {}^1/_8H_2O$) C, H, N.

7,8-Dihydro-7-methyl-5-(4-methylphenyl)-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxylic Acid (29c). Compound **29c** was prepared from **27c** and **28c** by the same procedure as described in the preparation of **29a** from **27a** and **28a**. The yields were 78% from **27c** and 93% from **28c**. Recrystallization from MeOH–THF gave yellow crystals (hydrochloride): mp 178–183 °C (turned to colorless crystals), 249–251 °C dec; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 2.43 (3 H, s), 3.77 (3 H, s), 7.29 (4 H, s), 7.88 (1 H, dd, J = 8.5, 4.8), 8.02 (1 H, dd, J = 8.5, 1.4), 9.04 (1 H, dd, J = 4.8, 1.4). Anal. ($C_{17}H_{15}ClN_2O_3 \cdot 0.2H_2O$) C, H, N.

6-Pyrido[3,4-*b*]pyridinecarboxamide Derivatives (30, Table 4). As a typical example, the preparation of **30a** is described. To a solution of hydrochloride of **29b** (8.90 g, 26.6 mmol) in THF (200 mL) were added thionyl chloride (9.8 mL, 134 mmol) and DMF (catalytic amount) at room temperature, and the mixture was refluxed for 3 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (200 mL). To the solution were added *N*-methyl-3,5-bis(trifluoromethyl)-benzylamine hydrochloride (8.8 g, 30.0 mmol) and Et_3N (10.7 mL, 76.8 mmol). The mixture was stirred at room temperature for 15 h. After evaporation of the solvent, the residue was diluted with EtOAc and washed successively with H_2O, 1 N HCl, aqueous $NaHCO_3$, and H_2O. The organic layer was dried and concentrated to give **30a** as colorless crystals (12.8 g, 90%). Similarly, **30b–i** were prepared from **29a–c** and (substituted)-benzylamines. The physicochemical properties of **30a–i**, all of which have *trans* conformation at the amide bond, are listed in Table 4. The detailed physicochemical data for **30g** (*trans* rotamer) and **30g′** (*cis* rotamer) are described below.

***N*-[3,5-Bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxamide (30g: *Trans* Rotamer at the Amide Bond).** Recrystallization from acetone–IPE gave colorless crystals: mp 197–199 °C; ^{1}H NMR 2.33 (3 H, s), 2.80 (3 H, s), 3.66 (3 H, s), 4.27 (1 H, d, J = 15), 4.79 (1 H, d, J = 15), 7.01–7.28 (4 H, m), 7.46 (1 H, dd, J = 8.0, 4.0), 7.57 (2 H, s), 7.60 (1 H, dd, J = 8.0, 2.0), 7.81 (1 H, s), 8.91 (1 H, dd, J = 4.0, 2.0); IR (Nujol, cm^{-1}) 1680, 1400, 1270, 1165; MS (electron impact) m/z 533 (M^+), 514, 442, 277, 250. Anal. ($C_{27}H_{21}F_6N_3O_2$) C, H, N.

***N*-[3,5-Bis(trifluoromethyl)benzyl]-7,8-dihydro-*N*,7-dimethyl-5-(4-methylphenyl)-8-oxo-6-pyrido[3,4-*b*]pyridinecarboxamide (30g′: *Cis* Rotamer at the Amide Bond).** The mother liquor obtained after crystallization of **30g** (*trans* rotamer) was concentrated, and the concentrate was subjected to silica gel column chromatography (MeOAc–CH_2Cl_2 = 4:1) to give **31g′** as colorless crystals, which were analyzed without recrystallization: mp 164–166 °C; ^{1}H NMR 2.46 (3 H, s), 2.73 (3 H, s), 3.69 (3 H, s), 4.21 (1 H, d, J = 16), 4.58 (1 H, d, J = 16), 7.03–7.80 (9 H, m), 8.92 (1 H, dd, J = 4.4, 1.6); IR (Nujol, cm^{-1}) 1670, 1640, 1420, 1400, 1280, 1170; MS (electron impact) m/z 533 (M^+), 514, 442, 277, 250. Anal. ($C_{27}H_{21}F_6N_3O_2$) C, H, N.

Single-Crystal X-ray Analysis of 30g. Crystals of **30g** were grown from ethanol/ethyl ether. Data were collected on a diffractometer, Rigaku AFC5R, and corrected for Lorentz and polarization factors. Absorption correction was not applied. The structure was determined by direct methods with the aid of TEXSAN[35] and refined by CRYLSQ[36] in the XTAL package. The parameters refined include the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included using a riding model in which the distances from the bonded carbon atoms were fixed at 1.09 Å. Thermal parameters of hydrogen atoms were taken from their bonded atoms as U_{iso} and fixed through the next several cycles of refinement. The final R factor was 0.096. It is presumed that this large R factor can be ascribed to the small size of the crystal. Crystal data and conditions of data collection are summarized in Table 5. Tables of atomic coordinates, thermal parameters, bond distances, bond angles, and torsion angles are available as supporting information.

Molecular Modeling Studies. A generation of low-energy conformers was carried out by Systematic Conformation Search of Search/Compare Module in Insight II (ver. 2.3.5, Biosym Technologies, Inc.). As for the azaisoquinolone (pyrido-[3,4-*b*]pyridine) ring of **30g** and **30g′**, the crystal structure, *i.e.*, a planar structure, was adopted in this procedure. Bond rotation increments for single bonds and an amide bond were set at 30° and 180°, respectively, and the energy threshold used was 20 kcal/mol from the most stable conformer. Relative energy of the conformers was estimated by single-point calculations using Discover CVFF force field (ver 2.96, Biosym Technologies, Inc.). The numbers of conformers obtained for **30g** (including **30g′**) and CP-99,994 are 85 and 50, respectively. Pharmacophore prediction was performed using Apex-3D (ver 1.4.3, Biosym Technologies, Inc. and DCL System International Ltd.) and molecular indices calculated by MOPAC (ver. 6.00, QCPE program). The plausible pharmacophores were chosen on the basis of the intersection volume of **30g** (including **30g′**) and CP-99,994 on Insight II. The calculated intersection volume is 191 Å^3 for the first pharmacophore (Figure 4) and 182 Å^3 for the second one (Figure 4). All these procedures were carried out on the INDIGO^2 workstation of Silicon Graphics, Inc.

Table 5. Summary of Crystal Data and Intensity Collections for **30g**

formula	$C_{27}H_{21}N_3O_2F_6$
formula weight	553.47
crystal color, habit	colorless, prism
crystal system	monoclinic
space group	$P2_1/n$
a (Å)	12.173(4)
b (Å)	12.462(5)
c (Å)	16.897(4)
β (deg)	106.38(2)
V (Å^3)	2452(1)
Z	4
calculated density (g/cm^3)	1.445
absorption coef (cm^{-1})	1.35
temperature (°C)	23
radiation	Mo Kα (0.710 73 Å)
2θ range of reflections for cell determination (deg)	11–22
scan mode	2θ-ω
scan speed (deg/min)	16
2θ range of data collection (deg)	3–50
no. of unique reflections	4549
no. of reflections used for refinement ($F \geq 3\sigma F$)	1672
R,[a] R_w[b]	0.096, 0.095

[a] $R = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $R_w = [\sum w||F_o| - |F_c||^2/w\sum|F_o|^2]^{1/2}$ where w = 1.0.

[^{125}I]Bolton–Hunter (BH) Substance P Binding in Human IM-9 Cells and in Rat Forebrain. (1) Preparation of Receptors. The receptors from human lymphoblast cells (IM-9) were prepared according to the protocol in the literature[21] with minor modification. IM-9 cells (2×10^5 cells/mL) were inoculated and incubated for 3 days (1 L) and then subjected to centrifugation for 5 min at 500g to obtain a cell pellet. The pellet was washed once with phosphate buffer (Flow Laboratories, cat. no. 28-103-05), crushed using a Polytron homogenizer (Kinematika, Germany) in 30 mL of 50 mM Tris-HCl buffer (pH 7.4) containing NaCl (120 mM), KCl (5 mM), chymostatin (2 μg/mL), bacitracin (40 μg/mL), phenylmethanesulfonyl fluoride (0.5 mM), and ethylenediaminetetraacetic acid (EDTA) (1 mM), and then centrifuged at 40000g for 20 min. The residue was washed twice with 30 mL of the above-mentioned buffer and then preserved frozen (−80 °C) as a receptor specimen. The receptors from the rat brain were prepared according to the protocol in the literature[28] with minor modification. The Wistar rats (male, 8 weeks old) (Charles-River) were sacrificed by decapitation, and the forebrain was homogenized in 30 mL/rat of 150 mM Tris-HCl buffer (pH 7.4) containing NaCl (120 mM) and KCl (5 mM) using a Polytron homogenizer and then centrifuged at 40000g for 20 min. The pellet was suspended in 30 mL of 50 mM Tris-HCl buffer (pH 7.4) containing KCl (300 mM) and EDTA (10 mM) and stirred gently with ice-cooling for 30 min. This suspension was centrifuged at 40000g for 20 min, and the

residue was washed with 30 mL of the above-mentioned buffer and then preserved frozen (−80 °C) as a receptor specimen.

(2) Radioligand Binding Assay. The above specimen was suspended in a reaction buffer [50 mM Tris-HCl buffer (pH 7.4), 0.02% bovine serum albumin, phenylmethanesulfonyl fluoride (1 mM), chymostatin (2 μg/mL), bacitracin (40 μg/mL) and $MnCl_2$ (3 mM)], and a 100 μL portion of the suspension (corresponding to 150 μg of rat brain or 75 μg of IM-9 protein) was used in the reaction. After addition of the sample and [^{125}I]BH-SP (0.46 kbq), the reaction was allowed to proceed in 0.2 mL of reaction mixture at 25 °C for 30min. The amount of nonspecific binding was determined by adding SP at a final concentration of 2×10^{-6} M. After the reaction, a cell harvester (290PHD, Cambridge Technology, Inc., Cambridge, England) was used, and the reaction was terminated by rapid filtration through a glass filter (GF/B) (Whatman, USA). After washing three times with 50 mM Tris-HCl buffer (pH 7.4) containing 0.02% bovine serum albumin, the radioactivity remaining on the filter was measured with a γ counter. Before use, the filter was immersed in 0.1% poly(ethylenimine) for 24 h and air-dried.

Ileum Contraction Assay. Experiments were performed on ilea taken from guinea pigs (Std Hartley, male, 250 g) fasted overnight. Animals were killed by stunning and exsanguination. Ileum segments of about 3 cm in length were suspended in 20 mL organ baths containing warm (37 °C) oxygenated (with a mixture of 95% O_2 and 5% CO_2) Tyrode's solution of the following composition in g/L: $MgCl_2 \cdot 6H_2O$, 0.214; NaH_2PO_4, 0.065; KCl, 0.2; $CaCl_2 \cdot 2H_2O$, 0.264; NaCl, 8; $NaHCO_3$, 1; glucose, 1. The tissues were stretched with 0.5 g of tension. Changes in tension were recorded on an Oscillograph model RECTUI-HORIZ-8K (Japan Electric Sanei Co. Ltd.) with an isotonic transducer (ME-4013) (Suruga Electric Co. Ltd.). The preparation was allowed to equilibrate for 60 min. Apparent affinity of samples (pA_2) was determined by measuring biological responses to SP on ileum in the absence or presence of the sample. The sample was added 5 min before the effect was measured. The inhibition with compounds **30a,f,g** was competitive in the concentration range of 1.0×10^{-8} M to 5.0×10^{-10} M. The pA_2 values of **30a,f,g** and (±)-CP-99,994 determined by Schild plotting[37] were 9.76 ± 0.17, 9.73 ± 0.13, 9.73 ± 0.17, and 9.81 ± 0.01, respectively (n = 3).

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[22] with minor modification. Guinea pigs (Std Hartley, male) (n = 6) were anesthetized with 35 mg/kg of pentobarbital injected intraperitoneally, and the test sample dissolved in DMSO was then administered intravenously (iv) (in the oral administration test, the sample was administered 45 min prior to the pentobarbital injection). Five minutes after administration, a solution of capsaicin (150 mg/kg) and Evans' blue dye (20 mg/kg) in ethanol−saline (3:7) was administered (iv) to cause the reaction. Ten minutes later, test animals were sacrificed by cutting the aorta and then were perfused through pulmonary artery 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 5 min, the concentration of Evans' blue dye in the supernatant was quantified by determining the absorbance at 620 nm. Plasma extravasation was expressed in terms of the amount of extracted Evans' blue dye (mg) relative to the weight of the trachea (g). The efficacy of the sample was evaluated by calculating the percent inhibition in accordance with the following formula: % inhibition = [1 − (A − B)/(C − B)] × 100, in which A, B, and C represent the amount of Evans' blue dye (mg/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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Supporting Information Available: Crystallographic data for **30g** and ^{1}H NMR data of **1, 11, 14, 15, 16, 19,** and **30** (12 pages). Ordering information is given on any current masthead page.

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(32) The conformations generated here are not minimized structures and a rather large threshold value (20 kcal/mol) was adopted, since the active conformation, which is not necessarily in a local minimum, might be missed by the energy minimization.

(33) The crystal structure might be stabilized to some extent by intermolecular interactions.

(34) The two models, in which the amide "nitrogen" in **30g** (instead of the amide "oxygen") are superimposed on the exocyclic amine nitrogen in CP-99,994, in place of Figure 4 were also shown possess large intersection volumes. However, we preferred the models depicted in Figure 4 since the amide "oxygen" in **30g** may be more likely as the key site for receptor recognition (presumably *via* hydrogen bonding) as recently reported for the tryptophan ester NK_1 antagonist L-732,138.[10d]

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