Discovery of a Novel Class of Selective Non-Peptide Antagonists for the Human Neurokinin-3 Receptor. 2. Identification of (*S*)-*N*-(1-Phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (SB 223412)†

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Optimization of the previously reported 2-phenyl-4-quinolinecarboxamide NK-3 receptor antagonist **14**, with regard to potential metabolic instability of the ester moiety and affinity and selectivity for the human neurokinin-3 (hNK-3) receptor, is described. The ester functionality could be successfully replaced by the ketone (**31**) or by lower alkyl groups (Et, **21**, or *n*-Pr, **24**). Investigation of the substitution pattern of the quinoline ring resulted in the identification of position 3 as a key position to enhance hNK-3 binding affinity and selectivity for the hNK-3 versus the hNK-2 receptor. All of the chemical groups introduced at this position, with the exception of halogens, increased the hNK-3 binding affinity, and compounds **53** (3-OH, SB 223412, hNK-3-CHO binding $K_i = 1.4$ nM) and **55** (3-NH_2, hNK-3-CHO binding $K_i = 1.2$ nM) were the most potent compounds of this series. Selectivity studies versus the other neurokinin receptors (hNK-2-CHO and hNK-1-CHO) revealed that **53** is about 100-fold selective for the hNK-3 versus hNK-2 receptor, with no affinity for the hNK-1 at concentrations up to 100 μM. In vitro studies demonstrated that **53** is a potent functional antagonist of the hNK-3 receptor (reversal of senktide-induced contractions in rabbit isolated iris sphincter muscles and reversal of NKB-induced Ca^{2+} mobilization in CHO cells stably expressing the hNK-3 receptor), while in vivo this compound showed oral and intravenous activity in NK-3 receptor-driven models (senktide-induced behavioral responses in mice and senktide-induced miosis in rabbits). Overall, the biological data indicate that (*S*)-*N*-(1-phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (**53**, SB 223412) may serve as a pharmacological tool in animal models of disease to assess the functional and pathophysiological role of the NK-3 receptor and to establish therapeutic indications for non-peptide NK-3 receptor antagonists.

Introduction

At least three distinct seven-transmembrane G protein-coupled receptors, named neurokinin-1 (NK-1), neurokinin-2 (NK-2), and neurokinin-3 (NK-3), mediate the pharmacological actions of tachykinins.[1] The main mammalian members of this family of small peptides are substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), and although they interact with all three neurokinin receptors, SP has higher affinity for NK-1, NKA for NK-2, and NKB for NK-3 receptors.[2] The initial focus of the research in this area was mainly on NK-1 and NK-2 receptors, for which potent and selective non-peptide antagonists became available in the early 1990s.[3] It was only from 1995 onward that reports on potent and selective non-peptide NK-3 receptor antagonists from diverse chemical classes[4−9] appeared in the literature. These compounds provided improved reagents to assist in the clarification of the physiological and pathophysiological roles of NK-3 receptors and the potential therapeutic utility of selective NK-3 receptor antagonists. Currently, evidence from pharmacological studies using selective peptide NK-3 receptor agonists indicates that the NK-3 receptor exerts a neuromodulatory role in the central nervous system (CNS) and in the periphery.[10,11] However, ultimate therapeutic indications for NK-3 receptor antagonists in both the CNS and the periphery have still to be defined, and it is anticipated that the testing of potent and selective compounds in animal models of disease will assist in addressing this key issue.

Our group recently described 2-phenyl-4-quinolinecarboxamides as potent and selective hNK-3 receptor antagonists and outlined the medicinal chemistry strategy followed to identify compound **14**.[8,9] A chemical program was then undertaken to (i) avoid potential metabolic instability problems associated with the presence of the ester functionality in compound **14** (Table 1) and (ii) optimize the hNK-3 binding affinity and selectivity. Regarding the latter, substitution at position 3 of the quinoline ring (Table 2) proved to be the best approach to optimize the hNK-3 receptor binding affinity.

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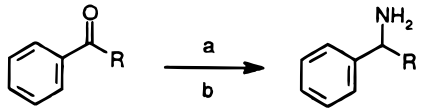
Scheme 1[a]

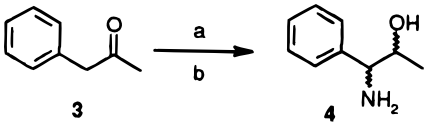


1a R=*n*-Pr
1b R=*i*-Pr
1c R=*n*-Bu
1d R=*n*-heptyl

2a R=*n*-Pr
2b R=*i*-Pr
2c R=*n*-Bu
2d R=*n*-heptyl

[a] Reagents: (a) $NH_2OH{\cdot}HCl$, NaOH, EtOH/H_2O, room temperature, 22 h; (b) H_2, 10% Pd/C, 96% EtOH, 60 psi, room temperature, 2.5−4 h, Parr apparatus.

Scheme 2[a]



3 **4**

[a] Reagents: (a) $NaNO_2$, AcOH/H_2O/1,4-dioxane, 15 °C to room temperature, overnight; (b) H_2, PtO_2, 96% EtOH, 35 psi, room temperature, 18 h, Parr apparatus.

In this paper, chemical synthesis, radioligand binding affinity for the cloned hNK-3 receptor stably expressed in Chinese hamster ovary cell lines (hNK-3-CHO), and structure−activity relationships (SARs) of the novel hNK-3 receptor antagonists **15**−**29**, **31**−**33**, **35**−**61**, and **64**−**72** (Tables 1 and 2) will be described. For some of the most potent compounds (**22**, **42**, **45**, **51**, **53**, **55**, **56**, **69**, and **72**), radioligand binding affinities for the cloned hNK-2 and hNK-1 receptors stably expressed in CHO cell lines (hNK-2-CHO and hNK-1-CHO) and functional activity in the rabbit isolated iris sphincter muscle preparation (antagonism of contractions induced by the selective NK-3 receptor agonist senktide) will also be presented in Table 3 and compared with the results obtained using the standard NK-3 receptor antagonist (*R*)-(+)-*N*-{{3-[1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]prop-1-yl}-4-phenylpiperidin-4-yl}-*N*-methylacetamide (SR 142801).[4,5] Furthermore, cellular functional NK-3 receptor antagonist activity of compounds **42** and **53** was determined in Ca^{2+} mobilization studies using hNK-3 receptors stably transfected into human embryonic kidney 293 cells (hNK-3-HEK 293). Finally, in vivo activity of compounds **42** and **53** in NK-3 receptor-driven models (senktide-induced behavioral effects in mice and senktide-induced miosis in conscious rabbits) will be discussed.

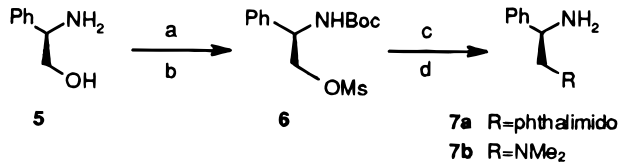
Chemistry

Syntheses of noncommercial amines, utilized in the coupling reaction with the appropriate carboxylic acids (**10**) to afford the desired 4-quinolinecarboxamides as shown in Scheme 4, are reported in Schemes 1−3.

α-Alkyl-substituted benzylamines **2a**−**d** (Scheme 1) were obtained by reacting the corresponding ketones **1a**−**d** with hydroxylamine hydrochloride and NaOH in a 1:3 mixture of H_2O/96% EtOH at room temperature and then reducing the formed oximes with hydrogen in the presence of 10% Pd/C in 96% EtOH at 60 psi.

The amino alcohol **4** (Scheme 2) was obtained via exhaustive catalytic hydrogenation (PtO_2, 96% EtOH, 35 psi) of the corresponding α-ketoxime, which was in turn synthesized from phenylacetone and $NaNO_2$ in a 4:9:6 mixture of AcOH/H_2O/1,4-dioxane, at room temperature.

Scheme 3[a]



5 **6**

7a R=phthalimido
7b R=NMe_2

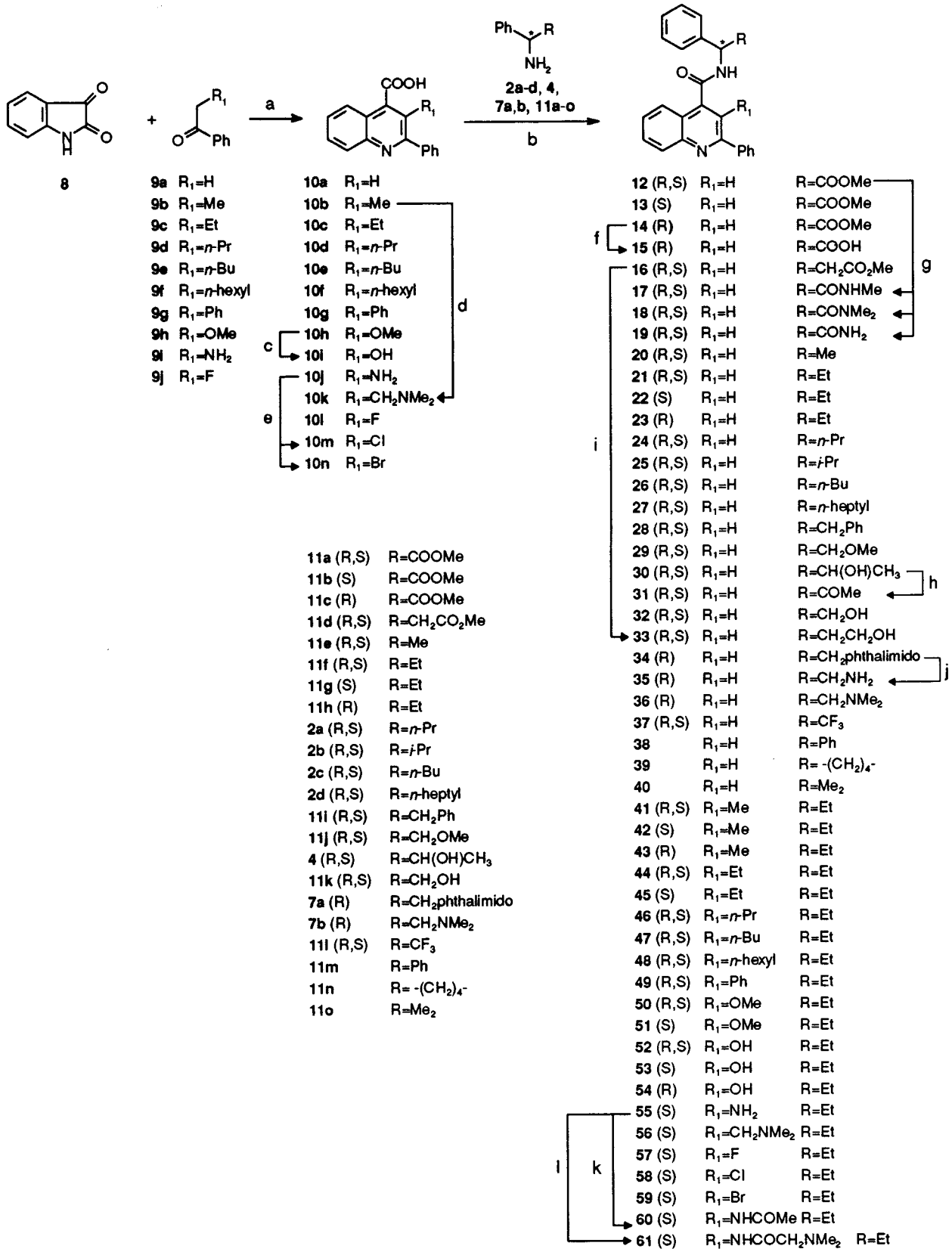
[a] Reagents: (a) $(Boc)_2O$, CH_2Cl_2, room temperature, 2 h; (b) MsCl, TEA, CH_2Cl_2, −10 to 0 °C, 1.5 h; (c) potassium phthalimide, DMF, 100 °C, 4 h (**7a**) or 28% Me_2NH in EtOH, 80 °C, 2 h, steel autoclave (**7b**); (d) 50% TFA in CH_2Cl_2, room temperature, 1.5 h.

Amines **7a**,**b** (Scheme 3) were synthesized starting from (*R*)-2-phenylglycinol (**5**). After Boc protection of the primary amine, the hydroxy group was activated via mesylate formation and displaced either with potassium phthalimide in DMF at 100 °C (**7a**) or with 28% Me_2NH in EtOH at 80 °C in a steel autoclave (**7b**). Cleavage of the Boc protecting group afforded the desired compounds **7a**,**b**.

Quinolinecarboxylic acids **10a**−**h**,**j**,**l** in Scheme 4 were obtained in high yields (typically greater than 80%) by the Pfitzinger reaction[12] of isatin (**8**) with the appropriate commercially available aryl ketones **9a**−**j** in 95−99% EtOH and 35−85% aqueous KOH at 80 °C for 1−3 days (occasionally, 10% NaOH was utilized). 3-Hydroxy-2-phenylquinoline-4-carboxylic acid (**10i**) was synthesized by demethylation of the corresponding methoxy derivative **10h** with 57% refluxing hydroiodic acid for 3 h. The amino acid **10k** was obtained from **10b** by bromination of the 3-methyl substituent with *N*-bromosuccinimide (NBS) in refluxing 1,2-dichloroethane in the presence of a catalytic amount of dibenzoyl peroxide and then displacing the bromine atom with 28% Me_2NH/EtOH in THF at room temperature. Whereas the 3-fluoro derivative **10l** was obtained directly from isatin and α-fluoroacetophenone, the corresponding 3-chloro and 3-bromo derivatives (**10m**,**n**) could not be synthesized by the Pfitzinger reaction due to the extreme reactivity of α-chloro- and α-bromoacetophenone in the presence of KOH.[13] They were obtained via Sandmeyer reaction from the 3-amino derivative **10j**, as described in the literature.[14]

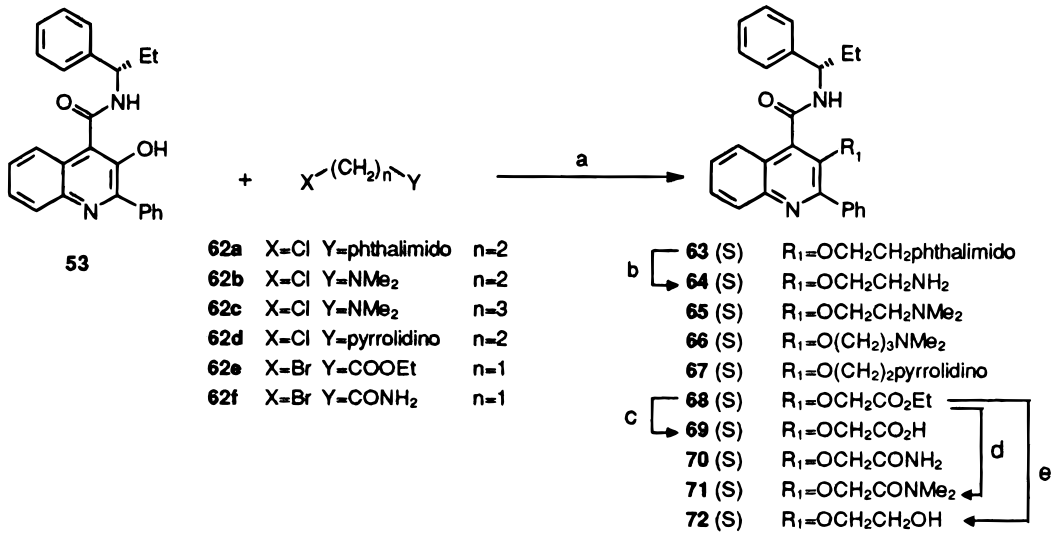
Secondary amides **12**−**14**, **16**, **20**−**30**, **32**, **34**, and **36**−**59** in Scheme 4 were synthesized starting from the corresponding 4-quinolinecarboxylic acids **10a**−**n** and the appropriate primary amines **2a**−**d**, **4**, **7a**,**b**, and **11a**−**o** of general formula $PhCHRNH_2$ (which are commercially available, synthesized according to literature procedures,[15−18] or described in Schemes 1−3). The amide linkage was obtained either in two steps, via preparation of the acyl chloride and subsequent reaction with the amine in the presence of K_2CO_3 in dry DMF or by directly coupling the carboxylic acid and the amine in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) in THF/MeCN (7:3). The carboxylic acid derivative **15** was obtained from the corresponding methyl ester **14** by refluxing in 10% HCl for 30 min. Amides **17**−**19** were synthesized by heating the methyl ester **12** in a steel autoclave in the presence of the appropriate amine dissolved in EtOH or MeOH; a catalytic amount of sodium cyanide was added to the

Scheme 4. Synthesis of Compounds **12**−**61**[a]



[a] Reagents: (a) 35−85% aq KOH, 95−99% EtOH, 80 °C, 1−3 days;[9,12] (b) 1. $(COCl)_2$, CH_2Cl_2, 5 °C to room temperature, 1−2 days, 2. $PhCH(R)NH_2$, DMF, K_2CO_3, room temperature, 24 h,[9] or $PhCH(R)NH_2$, DCC, HOBT, THF/MeCN (7:3), room temperature, 3 h;[9] (c) 57% HI, reflux, 3 h; (d) 1. NBS, dibenzoyl peroxide, 1,2-dichloroethane, reflux, 2 days, 2. 28% Me_2NH/EtOH, THF, room temperature, 18 h; (e) 1. 20% HCl (**10m**) or 25% HBr (**10n**), $NaNO_2$, 0 °C, 10 min, 2. CuCl/37% HCl (**10m**) or CuBr/48% HBr (**10n**), 0−80 °C, 1 h;[14] (f) 10% HCl, reflux, 30 min; (g) 33% $MeNH_2$/EtOH or 33% Me_2NH/EtOH or 16% NH_3/MeOH, NaCN (cat.), 70−120 °C, 1−6.5 h, steel autoclave; (h) 1. $(ClCO)_2$, DMSO, CH_2Cl_2, −55 °C, 30 min, 2. TEA, −55 °C to room temperature; (i) $NaBH_4$, *t*-BuOH/MeOH, reflux, 6 h; (j) 1. H_2NNH_2, 96% EtOH/1,2-dichloroethane, reflux, 7.5 h, 2. 37% HCl, reflux, 45 min; (k) Ac_2O, 70−100 °C, 4 h; (l) 1. $(ClCH_2CO)_2O$, toluene, reflux, 1 h, 2. 28% Me_2NH in EtOH, CH_2Cl_2, room temperature, overnight then 60 °C, 20 min, steel autoclave.

Scheme 5. Synthesis of Compounds **63**−**72**[a]



[a] Reagents: (a) X-(CH_2)-Y, K_2CO_3, KI (cat.), THF, reflux (room temperature in the case of **62e**,**f**), overnight; (b) 1. H_2NNH_2, 96% EtOH, reflux, 64 h, 2. 37% HCl, reflux, 1 h; (c) 37% HCl, reflux, 20 min; (d) 28% Me_2NH in EtOH, NaCN (cat.), 100−120 °C, 14 h, steel autoclave; (e) $NaBH_4$, *t*-BuOH/MeOH, reflux, 3 h.

reaction mixture to promote the aminolysis of the ester.[19] Swern oxidation[20] of the alcohol **30** with activated dimethyl sulfoxide afforded the ketone **31**, while the alcohol **33** was obtained by reducing the ester **16** with $NaBH_4$ in refluxing *t*-BuOH/MeOH.[21] The primary amine **35** was prepared by deprotection of phthalimide **34** with hydrazine monohydrate in a refluxing mixture of 96% EtOH/1,2-dichloroethane for 7.5 h. The 3-aminoquinoline derivative **55** was transformed into compound **60** by treatment with acetic anhydride at 100 °C for 4 h, while compound **61** was obtained in two steps by first reacting compound **55** with chloroacetic anhydride and then by replacing the chlorine with 28% Me_2NH in EtOH at 60 °C in a steel autoclave.

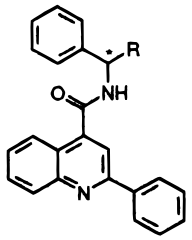
Compounds **63**, **65**−**68**, and **70** in Scheme 5 were obtained by alkylating 3-hydroxyquinoline **53** with chloro- or bromoalkyl derivatives **62a**−**f** in THF in the presence of K_2CO_3 and a catalytic amount of KI; normally, the reaction was refluxed overnight, except for the more reactive ethyl bromoacetate (**62e**) or bromoacetamide (**62f**), which were used at room temperature. Hydrazinolysis of the phthalimido derivative **63** with hydrazine monohydrate in 96% EtOH at reflux produced compound **64**. Compounds **69**, **71**, and **72** were all synthesized starting from the ester derivative **68**. Hydrolysis with refluxing 37% HCl for 20 min afforded the corresponding acid **69**; treatment of **68** with 28% Me_2NH in EtOH at 100−120 °C in a steel autoclave in the presence of a catalytic amount of NaCN[19] yielded the dimethylamide **71**, while the alcohol **72** was obtained via reduction of **68** with $NaBH_4$ in refluxing *t*-BuOH/MeOH.[21]

Pharmacology

Radioligand Binding Assays. Receptor binding assays were performed with crude membranes from CHO cells expressing the hNK-3, hNK-2, or hNK-1 receptors (hNK-3-CHO, hNK-2-CHO, and hNK-1-CHO, respectively) as detailed previously.[9,22] For NK-3 receptor competition binding studies, [^{125}I][MePhe^7]NKB binding to hNK-3-CHO membranes was performed using the procedure of Sadowski and co-workers[23] as described previously.[9] Concentration−response curves for compounds **15**−**29**, **31**−**33**, **35**−**61**, and **64**−**72** were run using duplicate samples; among them, compounds which gave an IC_{50} binding affinity lower than 1000 nM in the first experiment were run in three to five independent experiments (n = 3−5). Specific binding was determined by subtracting total binding from nonspecific binding, which was assessed as the binding in the presence of 0.5 μM cold [MePhe^7]NKB. Percent inhibition of specific binding was determined for each concentration of the compounds and the IC_{50}, defined as the concentration required to inhibit 50% of the specific binding, obtained from concentration−response curves. Values reported in Tables 1 and 2 are the apparent inhibition constant (K_i), which was calculated from the IC_{50} as described by Cheng and Prusoff.[24] For selectivity studies, compounds **22**, **42**, **45**, **51**, **53**, **55**, **56**, **69**, and **72** were also evaluated in hNK-2-CHO and hNK-1-CHO binding assays (Table 3). For NK-2 receptor competition binding studies, [^{125}I]NKA binding to hNK-2-CHO membranes was performed essentially as described by Aharony et al.[25] Nonspecific binding was determined in the presence of 0.5 μM cold NKA. The K_i was determined as described for the NK-3 binding assay. Competition binding studies for the NK-1 receptor were performed on hNK-1-CHO membranes essentially as described by Payan et al.[26] Nonspecific binding was determined in the presence of 1 μM cold substance P and K_i determined as for the NK-3 and NK-2 binding assays.

Senktide-Induced Contraction of Rabbit Isolated Iris Sphincter Muscle (RISM) Preparation. Since the rabbit isolated iris sphincter muscle preparation contains functional NK-3 receptors,[27,28] the effects of the most potent NK-3 receptor antagonists described in this paper (**22**, **42**, **45**, **51**, **53**, **55**, **56**, **69**, and **72**) were investigated in this tissue, assessing the inhibition of contractions induced by the selective NK-3 receptor agonist senktide (Table 3). Rabbit iris sphincter muscle strips were prepared and utilized as previously de-

Table 1. Physical Properties and Binding Affinity at Cloned hNK-3 Receptors Expressed in CHO Cells of Compounds **12**−**29**, **31**−**33**, and **35**−**40** of General Formula I



I

compd	R	*	formula	mp, °C	anal.	recryst solvent	$[\alpha]_D^{20}$ (c = 0.5, MeOH)	hNK-3-CHO binding,[a] K_i mean ± SEM (nM)[b]
12	COOMe	*(R,S)*	$C_{25}H_{20}N_2O_3$	170−172	C, H, N	*i*-PrOH		31 ± 4
13	COOMe	*(S)*	$C_{25}H_{20}N_2O_3$	180−181	C, H, N	*i*-PrOH	+42.0	926 ± 250
14	COOMe	*(R)*	$C_{25}H_{20}N_2O_3$	180−181	C, H, N	*i*-PrOH	−42.0	13 ± 3
15	COOH	*(R)*	$C_{24}H_{18}N_2O_3$·HCl	203−205	C, H, N, Cl	Me_2CO	−40.0	1653 ± 289
16	CH_2COOMe	*(R,S)*	$C_{26}H_{22}N_2O_3$	156−158	C, H, N	CH_2Cl_2		973 ± 220
17	CONHMe	*(R,S)*	$C_{25}H_{21}N_3O_2$	261−263	C, H, N	*i*-PrOH/EtOH		426 ± 215
18	$CONMe_2$	*(R,S)*	$C_{26}H_{23}N_3O_2$	219−221	C, H, N	*i*-PrOH/EtOH		488 ± 135
19	$CONH_2$	*(R,S)*	$C_{24}H_{19}N_3O_2$	237−238	C, H, N	*i*-PrOH/EtOH		983 (2)
20	Me	*(R,S)*	$C_{24}H_{20}N_2O$	156−157	C, H, N	EtOAc		264 ± 102
21	Et	*(R,S)*	$C_{25}H_{22}N_2O$	141−143	C, H, N	toluene		34 ± 2.6
22	Et	*(S)*	$C_{25}H_{22}N_2O$·1/2H_2O	140−141	C, H, N	*i*-PrOH	−26.7	13.8 ± 0.9
23	Et	*(R)*	$C_{25}H_{22}N_2O$	151−152	C, H, N	*i*-PrOH/*i*-Pr_2O	+26.6	840 ± 257
24	*n*-Pr	*(R,S)*	$C_{26}H_{24}N_2O$	149−150	C, H, N	toluene		47.2 ± 9.8
25	*i*-Pr	*(R,S)*	$C_{26}H_{24}N_2O$	165−166	C, H, N	*i*-PrOH		74.3 ± 13
26	*n*-Bu	*(R,S)*	$C_{27}H_{26}N_2O$	155−156	C, H, N	*i*-PrOH/*i*-Pr_2O		146 ± 16
27	*n*-heptyl	*(R,S)*	$C_{30}H_{32}N_2O$	121−128	C, H, N	*i*-PrOH/*i*-Pr_2O		4874 (2)
28	CH_2Ph	*(R,S)*	$C_{30}H_{24}N_2O$	194−196	C, H, N	EtOAc		3511 ± 1347
29	CH_2OMe	*(R,S)*	$C_{25}H_{22}N_2O_2$	144−145	C, H, N	toluene		314 ± 62
31	COMe	*(R,S)*	$C_{25}H_{20}N_2O_2$	160−161	C, H, N	*i*-PrOH/*i*-Pr_2O		27.4 ± 11.2
32	CH_2OH	*(R,S)*	$C_{24}H_{20}N_2O_2$	117−119	C, H, N	toluene		207 ± 75
33	CH_2CH_2OH	*(R,S)*	$C_{25}H_{22}N_2O_2$	167−169	C, H, N	*i*-PrOH/*i*-Pr_2O		382 ± 84
35	CH_2NH_2	*(R)*	$C_{24}H_{21}N_3O$	139−141	C, H, N	*i*-PrOH/*i*-Pr_2O	−6.9	1144 (2)
36	CH_2NMe_2	*(R)*	$C_{26}H_{25}N_3O$	133−135	C, H, N	*i*-PrOH/*i*-Pr_2O	−11.2	1068 (2)
37	CF_3	*(R,S)*	$C_{24}H_{17}F_3N_2O$	180−181	C, H, N	toluene		454 ± 48
38	Ph		$C_{29}H_{22}N_2O$	182−184	H, N; C[c]	toluene		134 ± 22
39	$-(CH_2)_4-$		$C_{27}H_{24}N_2O$	164−165	C, H, N	*i*-PrOH		129 ± 18
40	Me_2		$C_{25}H_{22}N_2O$	173−174	C, H, N	*i*-PrOH		295 ± 111

[a] Inhibition of [^{125}I][MePhe^7]NKB binding in hNK-3-CHO cell membranes. [b] Average of three to five independent determinations (n = 3−5), unless otherwise indicated in parentheses. [c] C: calcd, 84.03; found, 83.27.

scribed.[9] The dissociation constant, K_b, for the antagonist−NK-3 receptor complex was calculated from the equation: $K_b = [B]/CR - 1$, where CR is the concentration ratio of agonist used in the presence and absence of antagonist B.[29]

Calcium Mobilization Assay. Inhibition of NKB-induced Ca^{2+} mobilization in HEK 293 cells stably expressing the hNK-3 receptor (hNK-3-HEK 293) was utilized to confirm further the functional antagonist activity of compounds **42** and **53**.[22] Maximal intracellular Ca^{2+} levels after agonist stimulation were calculated as described by Grynkiewicz and co-workers.[30]

Senktide-Induced Behavioral Activity in Mice. The NK-3 receptor-selective ligand, senktide, induces a characteristic set of behaviors in rodents that appear to be mediated by serotonin release in brain and spinal cord.[31,32] A mouse model of this phenomenon was developed to investigate the in vivo oral activity of compounds **42** and **53**.

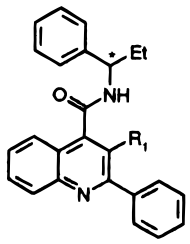
Senktide-Induced Miosis in Conscious Rabbits. An in vivo model was developed to mimic the NK-3 receptor-mediated contraction seen in the rabbit isolated iris sphincter muscle, which is a direct response involving stimulation of NK-3 receptors on smooth muscle rather than an indirect response through the release of other neurotransmitters.[34] The method developed for the study of miosis is less invasive than other previous studies investigating the effects of tachykinins in the eye. For example, intracameral injection during anesthesia is more likely to result in local inflammation, as well as pupillary constriction, since it is more invasive. NKB, the natural preferred ligand for NK-3 receptors, has been previously shown to induce miosis in the rabbit when injected intracamerally, but this could not be attributed to NK-3 receptor activation due to a lack of availability of selective antagonists.[33]

We observed intravenous administration of senktide-induced bilateral miosis in the conscious rabbit.[34] Behavioral responses induced by the agonist were negligible except that a high dose of senktide (100 μg) induced shivering. Interestingly, intraocular administration of senktide induced unilateral miosis only in the treated eye, and the miosis was not blocked by atropine, providing further evidence for a direct activation of NK-3 receptors in the iris sphincter muscle.[34] In the antagonist studies, compounds **42** and **53** were administered as 0.2-mL bolus injection (iv) 2.5 min before the administration of senktide.

Results and Discussion

1. Ester Functionality Replacement (Table 1). A chemical program, aimed at finding suitable replace-

Table 2. Physical Properties and Binding Affinity at Cloned hNK-3 Receptors Expressed in CHO Cells of Compounds **41**−**61** and **64**−**72** of General Formula II



II

compd	R_1	*	formula	mp, °C	anal.	recryst solvent	$[\alpha]_D^{20}$ (c = 0.5, MeOH)	hNK-3-CHO binding,[a] K_i mean ± SEM (nM)[b]
21	H	*(R,S)*	$C_{25}H_{22}N_2O$	141−143	C, H, N	toluene		34 ± 2.6
22	H	*(S)*	$C_{25}H_{22}N_2O\cdot 1/2H_2O$	140−141	C, H, N	*i*-PrOH	−26.7	13.8 ± 0.9
23	H	*(R)*	$C_{25}H_{22}N_2O$	151−152	C, H, N	*i*-PrOH/*i*-Pr_2O	+26.6	840 ± 257
41	Me	*(R,S)*	$C_{26}H_{24}N_2O$	156−158	C, H, N	toluene/hexane		10 ± 1.2
42	Me	*(S)*	$C_{26}H_{24}N_2O$	152−154	C, H, N	Et_2O	−36.4	5.5 ± 0.9
43	Me	*(R)*	$C_{26}H_{24}N_2O$	155−156	C, H, N	*i*-PrOH	+35.9	390 ± 120
44	Et	*(R,S)*	$C_{27}H_{26}N_2O$	158−159	C, H, N	Et_2O		7.1 ± 2.1
45	Et	*(S)*	$C_{27}H_{26}N_2O$	118−120	C, H, N	hexane	−42.0	5.4 ± 2.0
46	*n*-Pr	*(R,S)*	$C_{28}H_{28}N_2O$	149−151	C, H, N	toluene/hexane		13.7 ± 2.2
47	*n*-Bu	*(R,S)*	$C_{29}H_{30}N_2O$	147−150	C, H, N	hexane		15.2 ± 1.2
48	*n*-hexyl	*(R,S)*	$C_{31}H_{34}N_2O$	131−134	C, H, N	hexane/*i*-Pr_2O		55.4 ± 21.4
49	Ph	*(R,S)*	$C_{31}H_{26}N_2O\cdot 1/2H_2O$	198−200	C, H, N	hexane		45.3 ± 1.2
50	OMe	*(R,S)*	$C_{26}H_{24}N_2O_2$	163−165	C, H, N	*i*-PrOH/*i*-Pr_2O		5.8 ± 0.9
51	OMe	*(S)*	$C_{26}H_{24}N_2O_2$	132−134	C, H, N	Me_2CO	−45.0	1.8 ± 0.3
52	OH	*(R,S)*	$C_{25}H_{22}N_2O_2$	168−169	C, H, N	toluene		2.4 ± 0.1
53	OH	*(S)*	$C_{25}H_{22}N_2O_2$	122−125	C, H, N	*i*-Pr_2O	−28.4	1.4 ± 0.2
54	OH	*(R)*	$C_{25}H_{22}N_2O_2$	122−125	C, H, N	hexane/EtOAc	+27.2	254 ± 65
55	NH_2	*(S)*	$C_{25}H_{23}N_3O$	153−155	C, H, N	*i*-PrOH/*i*-Pr_2O	−68.0	1.2 ± 0.2
56	CH_2NMe_2	*(S)*	$C_{28}H_{29}N_3O\cdot HCl$	164−167	C, H, N, Cl	toluene/EtOH	+25.3	2.2 ± 0.3
57	F	*(S)*	$C_{25}H_{21}FN_2O\cdot 1/2H_2O$	67−68	C, H, N, F	toluene/hexane	−22.8	30.3 ± 4.5
58	Cl	*(S)*	$C_{25}H_{21}ClN_2O$	137−139	C, H, N, Cl,	toluene/hexane	−40.5	29.9 ± 8.7
59	Br	*(S)*	$C_{25}H_{21}BrN_2O$	119−122	C, H, N, Br	toluene/hexane	−41.4	37.2 ± 11.5
60	NHCOMe	*(S)*	$C_{27}H_{25}N_3O_2$	268−269	C, H, N	Me_2CO	−71.4	15.9 ± 5.2
61	$NHCOCH_2NMe_2$	*(S)*	$C_{29}H_{30}N_4O_2$	189−191	C, H, N	*i*-Pr_2O	−63.1	10.7 ± 4.3
64	$OCH_2CH_2NH_2$	*(S)*	$C_{27}H_{27}N_3O_2\cdot HCl$	119 dec	C, H, N, Cl,	EtOAc/Me_2CO	−19.4	4.7 ± 0.6
65	$OCH_2CH_2NMe_2$	*(S)*	$C_{29}H_{31}N_3O_2$	141−143	C, H, N	*i*-PrOH/*i*-Pr_2O	−48.6	5.7 ± 0.6
66	$OCH_2CH_2CH_2NMe_2$	*(S)*	$C_{30}H_{33}N_3O_2\cdot HCl$	108 dec	C, H, N, Cl,	EtOAc/Me_2CO	−16.0	8.6 ± 2.0
67	OCH_2CH_2pyrrolidino	*(S)*	$C_{31}H_{33}N_3O_2\cdot HCl$	110−115	H, N; C, Cl[c]	EtOAc/Me_2CO	+4.5	6.8 ± 2.3
68	OCH_2COOEt	*(S)*	$C_{29}H_{28}N_2O_4$	103−105	C, H, N	*i*-PrOH/*i*-Pr_2O	−42.5	2.0 ± 0.3
69	OCH_2COOH	*(S)*	$C_{27}H_{23}N_2O_4Na$	316−317	C, H, N, Na	CH_3CN	−7.2	2.2 ± 0.3
70	OCH_2CONH_2	*(S)*	$C_{27}H_{25}N_3O_3$	237−240	C, H, N	EtOH	−35.9	6.3 ± 2.7
71	OCH_2CONMe_2	*(S)*	$C_{29}H_{29}N_3O_3$	86−88	C, H, N	Et_2O	−41.2	2.4 ± 0.6
72	OCH_2CH_2OH	*(S)*	$C_{27}H_{26}N_2O_3$	129−130	C, H, N	*i*-Pr_2O	−41.2	1.5 ± 0.7

[a] Inhibition of [^{125}I][MePhe^7]NKB binding in hNK-3-CHO cell membranes. [b] Average of three to five independent determinations (n = 3−5), unless otherwise indicated in parentheses. [c] C: calcd, 72.15; found, 70.46. Cl: calcd, 6.87; found, 7.40.

ments of the methoxycarbonyl group to avoid potential metabolic instability problems associated with the presence of the ester functionality, was undertaken. In general, compounds were produced as racemates. Hydrolysis of the ester function of compound **14** to the corresponding acid derivative **15** resulted in a 130-fold reduction in hNK-3 binding affinity. Introduction of a methylene spacer between the stereogenic carbon atom and the ester functionality (compound **16**) produced a 30-fold decrease in binding affinity. Transformation of the ester into a primary (**19**), secondary (**17**), or tertiary (**18**) amide resulted again in a 14−30-fold loss of affinity. Incorporation of alkyl substituents (compounds **20**, **21**, and **24**−**27**) resulted in compounds with hNK-3 binding affinities fitting a bell-shape curve, the ethyl and *n*-propyl groups being the most potent and displaying affinities similar to that of the ester (compare **21**, K_i = 34 nM, and **24**, K_i = 47.2 nM, with **12**, K_i = 31 nM). Binding affinity for the hNK-3 receptor decreased substantially by increasing the length and the bulkiness of the alkyl (see compounds **26** and **27**) or arylalkyl (**28**) substituents. The ether (**29**) or primary alcohols (**32** and **33**) showed a 7−12-fold decrease in hNK-3 binding affinity, whereas the ketone was as potent as the original ester derivative (cf. **31**, K_i = 27.4 nM, with **12**, K_i = 31 nM). Incorporation of primary or tertiary amines (compounds **35** and **36**) resulted in a dramatic (about 85-fold) decrease in potency. The trifluoromethyl derivative **37** also showed a decrease in binding affinity similar to that displayed by the simple methyl analogue. Finally, achiral compounds **38**−**40** were from 4- to 10-fold less potent than the racemic ester **12**.

Taken together these data seem to indicate that the presence of hydrogen bond donor groups such as the acid (**15**), secondary and primary amides (**17** and **19**), or alcohols (**32** and **33**) results in a reduction of hNK-3 binding affinity of this family of quinolines, whereas compounds with a carbonyl function capable of behaving as a hydrogen bond acceptor moiety, such as the ester (**12**) or ketone (**31**), or indeed simple lipophilic lower

Table 3. Binding Affinity at Cloned hNK-1, hNK-2, and hNK-3 Receptors Expressed in CHO Cells and in Vitro Functional Activities (antagonism of senktide-induced contractions) in RISM Preparation for Compounds **22**, **42**, **45**, **51**, **53**, **55**, **56**, **69**, and **72** and the Standard Reference Compound SR 142801

	binding affinities, K_i mean ± SEM (nM)[a]			antagonism of senktide-induced contractions in RISM,[b]
compd	hNK-3[c]	hNK-2[d]	hNK-1[e]	K_b[f] mean ± SEM (nM)[a]
22	13.8 ± 0.9	237 ± 43	>100000	9.7 ± 1.7
42	5.5 ± 0.9	277 ± 57	>100000	7.7 ± 1.0
45	5.4 ± 2.0	316 ± 37	>100000	4.1 (2)
51	1.8 ± 0.3	329 ± 45	>100000	1.8 ± 0.86
53	1.4 ± 0.2	144 ± 22	>100000	5.4 ± 3.4
55	1.2 ± 0.2	111 ± 23	>100000	0.81 (2)
56	2.2 ± 0.3	172 ± 18	>100000	nd
69	2.2 ± 0.3	214 ± 14	>100000	5.9 (2)
72	1.5 ± 0.7	82 ± 19	>100000	nd
SR 142801[g]	1.2 ± 0.3	37 (2)	1300 (2)	2.0 ± 0.5

[a] Average of three to eight independent determinations ($n = 3-8$), unless otherwise indicated in parentheses. [b] Reference 28. [c] Inhibition of [^{125}I][MePhe^7]NKB binding in hNK-3-CHO cell membranes. [d] Inhibition of [^{125}I]NKA binding in hNK-2-CHO cell membranes. [e] Inhibition of [^{3}H]substance P binding in hNK-1-CHO cell membranes. [f] The equilibrium dissociation constant K_b for the antagonist−NK-3 receptor complex was calculated from the equation: $K_b = [B]/CR - 1$, where CR is the concentration ratio of agonist used in the presence and absence of antagonist B. [g] In-house data; nd, not determined.

alkyl groups (Et, **21**, or *n*-Pr, **22**) are optimal for binding affinity. Preparation of enantiomers **22** and **23** allowed us to establish that enantioselectivity exists also in the α-ethyl series (eudismic ratio = 61 (Et) compared to 71 (COOMe)). Accordingly, on the basis of the SAR data and synthetic accessibility, the ethyl group was considered as a suitable replacement of the methyl ester and maintained fixed in the subsequent molecules for optimization of hNK-3 binding affinity.

2. Optimization of hNK-3 Binding Affinity (Table 2). In a previous paper we described the chemical investigation and associated SARs with regard to the 2-phenyl substitution/replacement, substitution in the phenyl ring of the amide side chain, and replacement of the quinoline ring with other (hetero)aromatic moieties.[9] We therefore focused on the substitution of the quinoline system. Whereas introduction of various substituents (OMe, OH, Cl, F, Me) on the benzene-condensed portion resulted, in general, in a decreased hNK-3 binding affinity,[35] incorporation of a variety of groups at position 3 of the quinoline ring was beneficial. The most potent compounds (hNK-3-CHO binding affinities in the range 1.4−5.4 nM) were those featuring the Me (**42**), Et (**45**), and OMe (**51**) groups and also compounds containing protic polar groups (e.g., OH (**53**), NH_2 (**55**), OCH_2CH_2OH (**72**)). It is also interesting to note that amine-containing (e.g., CH_2NMe_2 (**56**), $OCH_2CH_2NMe_2$ (**65**)) or carboxylic acid-containing (OCH_2COOH (**69**)) compounds maintained high binding affinity.

A 2−3-fold reduction in binding affinity was observed after the introduction of halogen groups (cf. the F (**57**), Cl (**58**), or Br (**59**) derivatives, hNK-3-CHO binding affinity K_i = 29.9−37.2 nM, with unsubstituted **22**, hNK-3-CHO binding affinity K_i = 13.8 nM). The fact that the very small fluorine atom produced an effect similar to that of the larger bromine indicates that the reduction in binding affinity is likely to be due to the electron-withdrawing effect of the substituent rather than its steric hindrance.

Overall, we conclude that position 3 of the quinoline ring is rather tolerant toward substitution, irrespective of the basic or acidic nature and/or steric hindrance of the substituent. Whereas the enantioselectivity profile for the 3-H (**22**, eudismic ratio = 61) and 3-Me (**42**, eudismic ratio = 71) compounds is quite similar, an increase in enantioselectivity was observed with the 3-OH derivative (**53**, eudismic ratio = 180).

3. In Vitro Selectivity and Functional Activity (Table 3). Compounds incorporating a substituent at position 3 of the quinoline ring also showed an improvement in the selectivity for the hNK-3 versus the hNK-2 receptor (cf. in Table 3 the unsubstituted compound **22**, hNK-3-CHO binding affinity K_i = 13.8 nM, hNK-2-CHO binding affinity K_i = 237 nM, selectivity ratio = 17, with **53**, hNK-3-CHO binding affinity K_i = 1.4 nM, hNK-2-CHO binding affinity K_i = 144 nM, selectivity ratio = 100, or indeed with **55**, hNK-3-CHO binding affinity K_i = 1.2 nM, hNK-2-CHO binding affinity K_i = 111 nM, selectivity ratio = 93). The standard reference NK-3 receptor antagonist SR 142801 showed a hNK-2/hNK-3 selectivity ratio of 31 (Table 3). All quinoline NK-3 receptor antagonists described in Table 3 showed no hNK-1 binding affinity at concentrations up to 100 μM.

Senktide is a potent contractile agonist in the rabbit isolated iris sphincter muscle (RISM) preparation with a pD_2 value of 9.1 ± 0.1 (n = 4).[28] Representatives of the most potent compounds (**22**, **42**, **45**, **51**, **53**, **55**, and **69**, Table 3) surmountably antagonized the contractile responses to senktide with K_b values in the range from 0.81 (**55**) to 9.7 (**22**) nM.

Cellular functional NK-3 receptor antagonist activity of **42** and **53** was determined in Ca^{2+} mobilization studies using hNK-3-HEK 293 cells. Compound **42** inhibited NKB (1 nM)-induced Ca^{2+} mobilization with an IC_{50} of 18.4 ± 3.0 nM (n = 4), whereas compound **53** had an IC_{50} of 16.6 ± 1.6 nM (n = 7).[22] The cellular functional NK-3 receptor antagonist activity of **42** and **53** was not time-dependent (i.e., the inhibition of NKB-induced Ca^{2+} mobilization was identical with 10-s or 5-min pretreatment with antagonist). Furthermore, inhibition of the NKB-induced Ca^{2+} response was rapidly reversible, since treatment with varying concentrations of **42** and **53** for 5 min followed by rapid centrifugation and resuspension in original buffer or fresh buffer without antagonist resulted in significant loss of the inhibitory activity.

4. In Vivo Activity: Senktide-Induced Behavioral Activity in Mice. The NK-3-selective ligand senktide induces a characteristic set of behaviors in rodents.[31,32]

In mouse, oral administration of **42** and **53** (in 50% PEG-400/1% methylcellulose, 30-min pretreatment, 6 mice/group) produced a dose-related inhibition of senktide-induced (1 mg/kg, sc) behavioral effects (rapid head shakes and tail whips, counted for 10 min after senktide administration) with ED_{50}'s of 5.6 and 12.2 mg/kg, respectively. For comparison, SR 142801[4,5] administered orally in the same vehicle demonstrated dose-dependent inhibition with an ED_{50} of 14.7 mg/kg.

Although to our knowledge the ability of senktide to enter the CNS has not been assessed directly, this characteristic effect of NK-3 receptor agonists, including senktide, has been attributed, at least in part, to the release of 5-HT from the CNS.[31,32] Direct evidence for CNS penetration of **42** and **53** was provided by disposition studies in the rat. Following 6 h of continuous iv infusion at 1 mg/kg/h, brain tissue concentrations were 504 (**42**) and 356 (**53**) ng/g ($n = 3$), yielding brain tissue/plasma concentration ratios of approximately 1.3 and 0.20, respectively.[22]

4. In Vivo Activity: Senktide-Induced Miosis in Conscious Rabbits. Senktide induced bilateral miosis following iv administration in conscious rabbits.[33] Senktide (10 and 25 μg, iv) induced a significant pupillary constriction, whereas 1 μg of senktide was without significant effect. The mean maximum pupillary constriction observed with senktide (25 μg, iv) was 4.24 $\pm$ 0.25 mm ($n = 3$). A dose of 100 μg of senktide induced shivering and no further pupillary constriction and so was not studied further. Pupillary constriction generally occurred within 2−5 min postinjection and was partially reversed within 20 min.

Compounds **42** and **53** (0.5−2 mg/kg iv, 2-min pretreatment) produced a dose-related inhibition of senktide (25 μg, iv)-induced miosis with an ED_{50} of 0.99 and 0.44 mg/kg, respectively.[34] Also the standard NK-3 receptor antagonist SR 142801 at a dose of 1.5 mg/kg iv, but not 0.75 and 0.375 mg/kg iv, significantly blocked pupillary constriction induced by 25 μg of senktide (iv).

Conclusions

In this paper, optimization of the quinoline chemical structure with regard to binding affinity and selectivity for the hNK-3 receptor in comparison to the other neurokinin receptors has been described. The optimization process was conducted starting from compound **22**, featuring an ethyl group at the benzylic position of the amide side chain, identified as the best replacement for the potentially metabolically unstable ester functionality. Substitution with a variety of chemical groups at position 3 of the quinoline ring (identified as a key position for further optimization) increased hNK-3 binding affinity; optimal biological activity was found for compounds **53** ($R_1 = OH$) and **55** ($R_1 = NH_2$) in Table 2, hNK-3 binding affinity $K_i = 1.4$ and 1.2 nM, respectively. The fact that neutral, acidic, basic, protic, or aprotic substituents at position 3 increased hNK-3 binding affinity suggests that conformational properties of the resulting molecules (i.e., the relative spatial orientation of the amide side chain, the 3-substituent, and the 2-phenyl ring) forced by the presence of a substituent at position 3 are more important than any potential direct interaction between the 3-substituent and the receptor. Representatives of the most potent compounds (**22**, **42**, **45**, **51**, **53**, **55**, **56**, **69**, and **72**, Table 3) were investigated in selectivity studies among the tachykinin receptors, displayed a hNK-2/hNK-3 selectivity ratio in the range from 17 to 180 (compared to a hNK-2/hNK-3 selectivity ratio of 31 observed for the standard NK-3 receptor antagonist SR 142801), and showed potent and surmountable functional antagonism (reversal of senktide-induced contractions in rabbit isolated iris sphincter muscle). In cellular functional studies (reversal of NKB-induced Ca^{2+} mobilization), selected compounds **42** and **53** were confirmed to be competitive antagonists of the hNK-3 receptor stably transfected into HEK 293 cells.

Finally, we demonstrated potent in vivo oral and intravenous activity of compounds **42** and **53** in specific NK-3 receptor-driven models. Thus, in the senktide-induced behavioral responses in mice, **42** and **53** showed ED_{50} values of 5.6 and 12.2 mg/kg po, respectively, and in the senktide-induced miosis in rabbits they showed ED_{50} values of 0.99 and 0.44 mg/kg iv, respectively.

Taken collectively, the above biological data underline the potential for these compounds to serve as suitable pharmacological tools to investigate the biology of the NK-3 receptor. In particular, (*S*)-*N*-(1-phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (**53**, SB 223-412) appears to possess the appropriate pharmacological and pharmacokinetic profiles[22]—with regard to potency, selectivity, oral activity, and metabolic stability—to be a useful tool to assess the functional and pathophysiological role of NK-3 receptors and to establish ultimate therapeutic indications for non-peptide NK-3 receptor antagonists.

Experimental Section

Radioligand Binding Assays. The CHO cells expressing the hNK-1, hNK-2, and hNK-3 receptors were cultured at 37 °C in a humidifier incubator under 5% CO_2/95% air in 1017 SO_3 (in-house formulation) media containing nucleosides plus geneticin (400 mg/L). The cells were harvested by centrifugation at 600*g* for 10 min. The cell pellet was resuspended in hypotonic buffer (10 mM Tris, pH 7.4, 1.0 mM EDTA, 10 μg/mL soybean trypsin inhibitor, 100 μg/mL bacitracin, 100 μM benzamidine, and 10 μM phenylmethanesulfonyl fluoride), then rapidly frozen, and thawed (3 times) followed by Dounce homogenization for preparation of crude membranes. For NK-3 receptor competition binding studies,[23] membranes ($\sim$15 μg of protein) were incubated with 0.15 nM [^{125}I][MePhe^7]NKB in a total of 150 μL of 50 mM Tris, pH 7.4, 4 mM $MnCl_2$, 1 μM phosphoramidon, and 0.1% ovalbumin, with or without various concentrations of antagonist, for 90 min at 25 °C. Incubations were stopped by rapid filtration with a Brandell tissue harvestor (Gaithersburg, MD) through Whatman GF/C filters that were presoaked for 60 min in 0.5% bovine serum albumin (BSA). Membranes were washed with 10 mL of ice-cold 20 mM Tris, pH 7.4, containing 0.1% BSA, then placed in vials with 10 mL of Beckman Ready Safe, and counted in a Beckman LS 6000 (Fullerton, CA) liquid scintillation counter. For NK-2 competition binding studies,[25] cells were grown and membranes were prepared as described above for the hNK-3 binding assay. The assay buffer was the same as utilized for hNK-3 binding assay with a total volume of 150 μL, $\sim$10 μg of membrane protein and 0.15 nM [^{125}I]NKA, which was incubated for 90 min at 25 °C, with various concentrations of antagonist. Filtration was through Whatman GF/C filters soaked for 30 min in 0.1% poly(ethylenimine) (PEI), and membranes were washed as described above for the hNK-3 binding assay. For NK-1 competition binding studies,[26] the assay volume was 300 μL, and the assay buffer (25 mM Tris, pH 7.4, 2.0 mM $CaCl_2$, 2.0 mM $MgCl_2$, 1 μM phosphoramidon,

and 0.1% ovalbumin) contained various concentrations of antagonist and 1.0 nM [^{3}H]substance P. Membranes were incubated for 45 min at 25 °C; Whatman filters were presoaked with BSA and membranes washed as described for the hNK-3 binding assay.

Calcium Mobilization Assay. The HEK 293 cells expressing the hNK-3 receptor were grown to about 80% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were knocked loose from the flasks and suspended at 10^6 cells/mL in Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4, and 11 mM glucose) containing 50 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% BSA, and 2 μM Fura-2AM and incubated for 45 min at 37 °C. Cells were centrifuged at 200*g* for 3 min and resuspended in the same buffer without Fura-2AM, incubated for 15 min at 37 °C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (5×10^5 cells/mL) were resuspended in cold KRH with 50 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37 °C for 5 min in 3-mL plastic cuvettes, and fluoresence was measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA) with magnetic stirring and temperature maintained at 37 °C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added, and fluorescence was monitored for about 15 s to ensure that there was no change in baseline fluorescence, followed by the addition of 1 nM NKB. The percent of maximal NKB-induced Ca^{2+} mobilization was determined for each concentration of antagonists and the IC_{50}, defined as the concentration of test compound that inhibits 50% of the maximal 1 nM NKB response, obtained from the concentration−response curve (5−7 concentrations of antagonists). Values presented are the mean $IC_{50} \pm$ SEM of at least three individual experiments.

In Vivo Assays. All procedures were performed in accordance with protocols approved by the SmithKline Beecham Institutional Animal Care and Use Committee and met or exceeded the standards of the American Association for the Accreditation of Laboratory Animal Care (AAALAC), the United States Department of Health and Human Services, and all local and federal animal welfare laws.

The mean and SEM for each group of animals were determined, and Student's *t*-test was utilized to investigate statistical significance; a *p* value of 0.05 or lower was considered significant. The ED_{50} values for **42** and **53** were calculated from analysis of the dose−response curves by regression analysis software using BioStatistics P57 software.

Senktide-Induced Behavioral Activity in Mice.[22] Studies were conducted using male Balb/c inbred mice (6 mice/group, weight = 22−25 g), obtained from Charles River Breeding Laboratories (Raleigh, NC), which were maintained in a barrier-sustained facility. Animals were orally administered various concentrations of compounds **42** and **53** prepared in 50% PEG-400/1% methylcellulose, or vehicle alone. Thirty minutes later, the mice were challenged with senktide (1.0 mg/kg sc), and the head twitches and/or tail whips were counted over 10 min.

Senktide-Induced Miosis in Conscious Rabbits.[34] Male New Zealand white rabbits (2−4 kg; H.A.R.E. Rabbitry, Hewitt, NJ 07421) were utilized. The left pupil of each rabbit was measured under normal ambient fluorescent lighting with a comparator reticle (finescale comparator reticle scaled to 0.1 mm; Orange, CA). This value was recorded as the baseline in mm. The rabbit was then given an iv bolus of different doses of senktide in a volume of 0.2 mL in 50 μL of DMSO/950 μL of saline. The pupil measurements were then taken at times between 2.5 and 30 min after agonist administration. In the antagonist studies, compounds were administered as 0.2-mL bolus injection (iv) 2.5 min before the addition of senktide.

Determination of the extent of miosis was expressed as absolute pupillary constriction (mm), i.e., initial pupil diameter minus smallest pupil diameter recorded.

Chemistry. Melting points were determined with a Büchi 530 hot stage apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker ARX 300 spectrometer at 303 K unless otherwise indicated. Chemical shifts were recorded in parts per million (δ) downfield from tetramethylsilane (TMS); NMR spectral data are reported as a list. IR spectra were recorded in Nujol mull or neat on sodium chloride disks or in KBr with a Perkin-Elmer 1420 spectrophotometer; mass spectra were obtained on a Finnigan MAT TSQ-700 (or TSQ 70) spectrometer. Optical rotations were determined in MeOH solution at the indicated concentration with a Perkin-Elmer 341 polarimeter at the sodium D-line. Silica gel used for flash column chromatography was Kiesegel 60 (230−400 mesh) (E. Merck AG, Darmstadt, Germany). Evaporations were performed at reduced pressure, and all oily products were dried at 0.1 mbar for 16 h. Combustion elemental analyses were performed by Redox s.n.c., Milan, Italy, and found values were within 0.4% of the theoretical values (unless otherwise indicated).

Tetrahydrofuran (THF) was dried by distillation over $LiAlH_4$ and stored over 4-Å molecular sieves under nitrogen atmosphere; CH_2Cl_2 was dried over $CaCl_2$; MeCN and DMF were stored over 4-Å molecular sieves; triethylamine (TEA) was dried by distillation and stored over KOH. Ketones (**1a**−**d**, **3**, and **9a**−**j**), (*R*)-2-phenylglycinol (**5**), isatin (**8**), (*R*)- (**11h**), (*S*)- (**11g**), and (*R*,*S*)-1-phenylpropylamine (**11f**), (*R*,*S*)-1-phenylethylamine (**11e**), (*R*,*S*)-1,2-diphenylethylamine (**11i**), (*R*,*S*)-2-phenylglycinol (**11k**), benzhydrylamine (**11m**), cumylamine (**11o**), chloro- or bromoalkyl derivatives (**62a**−**f**), and all reagents utilized in Schemes 1−5 are commercially available compounds and were used without further purification.

3-Substituted 2-phenylquinoline-4-carboxylic acids **10a**−**h**,**j**, in Scheme 4, were synthesized utilizing the Pfitzinger reaction,[12] according to the general procedure described by Giardina et al.[9] 3-Halo-2-phenylquinoline-4-carboxylic acids **10m**,**n** were prepared according to Raveglia et al.[14] (*R*)- (**11c**), (*S*)- (**11b**), and (*R*,*S*)-methyl phenylglycinate hydrochloride (**11a**) and (*R*,*S*)-methyl 3-amino-3-phenylpropionate hydrochloride (**11d**) were prepared by refluxing the corresponding commercially available amino acid in MeOH in the presence of 1.7 equiv of $SOCl_2$. (*R*,*S*)-2-Methoxy-1-phenylethylamine (**11j**) was synthesized as described by Meyers et al.;[15] α-(trifluoromethyl)benzylamine (**11l**) was prepared starting from trifluoroacetophenone[16] according to the synthetic procedure reported by Barney et al.;[17] 1-phenylcyclopentylamine (**11n**) was obtained via a Curtius degradation as described by Kaiser and Weinstock.[18]

Synthesis of Intermediates. General Procedure for the Synthesis of Amines 2a−d in Scheme 1. The ketone **1a**−**d** (675 mmol) and hydroxylamine hydrochloride (64.6 g, 930 mmol) were dissolved in a mixture of 96% EtOH (300 mL) and H_2O (100 mL). After cooling at 10 °C, NaOH (37.2 g, 930 mmol) was added, and the reaction mixture was stirred at room temperature for 22 h. EtOH was then evaporated, and the mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness to yield the corresponding oximes, typically as a yellow solid. The crude oxime was dissolved in 96% EtOH (1000 mL), and 10% Pd/C (11 g) was added; the reaction mixture was hydrogenated in a Parr apparatus at 60 psi and room temperature for 4 h. After filtration on a Celite pad, the solvent was evaporated to dryness, and the amines were purified by distillation at reduced pressure. Typically, yields of this reaction were about 80%. As an example, spectroscopic data for **2b** are reported: IR (neat) 3378, 3306, 3063, 3027, 2960, 2870, 1603, 1492, 1468, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H), 3.60 (d, 1H), 1.88 (m, 1H), 1.55 (s br, 2H), 1.00 (d, 3H), 0.80 (d, 3H); ESI-MS (positive, solvent methanol, spray 4.5 keV, skimmer 60 eV, capillary 220 °C) *m*/*z* 150 (MH^+).

2-Hydroxy-1-phenylpropylamine (4). 1-Phenyl-2-propanone (19.7 mL, 149.1 mmol) was dissolved, under nitrogen atmosphere, in AcOH (40 mL). After cooling at 15 °C, a solution of $NaNO_2$ (12.0 g, 173.9 mmol) in H_2O (30 mL) was added

dropwise and the reaction mixture was maintained at 15 °C for 30 min and then allowed to reach room temperature. H_2O (60 mL) and dioxane (60 mL) were added, and stirring was continued overnight. The reaction mixture was evaporated to dryness to yield a crude product which was crystallized with a mixture of EtOH (40 mL) and H_2O (40 mL) to obtain the intermediate oxime (9.7 g, 59.5 mmol) as a white solid: IR (KBr) 3240, 3180, 3050, 3010, 1660, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (s br, 1H), 7.43 (m, 3H), 7.30 (m, 2H), 2.51 (s, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) *m*/*z* 163 ($M^{+\bullet}$). The oxime (9.7 g, 59.5 mmol) was dissolved in 96% EtOH (600 mL), and PtO_2 (0.97 g) was added; the reaction mixture was hydrogenated in a Parr apparatus at room temperature and 35 psi for 18 h. After filtration on a Celite pad, the solvent was evaporated to dryness to yield compound **4** (9.0 g, 59.3 mmol, 40%) as a yellow oil which crystallized on standing at 4 °C: IR (neat) 3680−3100, 3060, 3027, 2975, 2925, 1600 broad, 1495, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.22 (m, 5H), 3.95 (m, 2H), 1.65 (s br, 3H), 1.05 (d, 3H).

(*R*)-2-(*tert*-Butoxycarbonylamino)-2-phenylethyl Methanesulfonate (6). (*R*)-Phenylglycinol (5.0 g, 36.4 mmol) was suspended in CH_2Cl_2 (26 mL) under nitrogen atmosphere, and the mixture was cooled at 0 °C. Di-*tert*-butyl dicarbonate (10.0 mL, 43.7 mmol) was added; the reaction mixture was stirred at room temperature for 2 h and then evaporated to dryness. The residue was triturated with Et_2O and collected by suction filtration to yield the Boc-protected (R)-phenylglycinol (7.1 g, 30.0 mmol) which was used in the following reaction without further purification. (*R*)-*N*-(*tert*-Butoxycarbonyl)phenylglycinol (7.1 g, 30.0 mmol) and TEA (4.6 mL, 32.9 mmol) were dissolved in CH_2Cl_2 (71 mL), and the solution was cooled at −10 °C, under nitrogen atmosphere. Methanesulfonyl chloride (2.6 mL, 32.9 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 1.5 h and then quenched with ice and H_2O. The organic layer was separated, washed with 10% HCl, 10% Na_2CO_3, and brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was triturated with *i*-Pr_2O to yield the mesylate **6** (8.3 g, 26.4 mmol, 73% starting from (*R*)-phenylglycinol) as a solid: mp 117 °C; IR (KBr) 3359, 3013, 2982, 2939, 1692, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.18 (m, 5H), 5.62 (d, 1H), 4.93 (m, 1H), 4.33 (m, 2H), 2.82 (s, 3H), 1.35 (s, 9H); ESI-MS (positive, solvent methanol, spray 4.5 keV, skimmer 60 eV, capillary 220 °C) *m*/*z* 338 (MNa^+).

(*R*)-α-(Phthalimidomethyl)benzylamine (7a). Compound **6** (9.1 g, 29.0 mmol) was dissolved in DMF (60 mL); potassium phthalimide (5.8 g, 31.1 mmol) was added, and the reaction mixture was heated at 100 °C for 4 h. After cooling, CH_2Cl_2 (100 mL) and H_2O (200 mL) were added, and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were washed with 0.2 N NaOH and H_2O. The organic layer was evaporated to dryness, and the residue was triturated with *i*-Pr_2O; (*R*)-*N*-(*tert*-butoxycarbonyl)-α-(phthalimidomethyl)benzylamine (5.8 g, 15.8 mmol) was recovered by suction filtration as a white solid: mp 205−207 °C; ^1H NMR (DMSO-d_6) δ 7.85 (m, 4H), 7.51 (d br, 1H), 7.45−7.20 (m, 5H), 5.00 (m, 1H), 3.80 (m, 2H), 1.20 (s, 9H); EI-MS (source 180 °C, 70 eV, 200 mA) *m*/*z* 309, 250, 206, 150. (*R*)-*N*-(*tert*-Butoxycarbonyl)-α-(phthalimidomethyl)benzylamine (5.7 g, 15.5 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (30 mL) and stirred at room temperature, under nitrogen atmosphere, for 1.5 h. The reaction mixture was diluted with H_2O and basified with 10% Na_2CO_3; the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was triturated with *i*-Pr_2O and collected by suction filtration to yield **7a** (3.9 g, 14.5 mmol, 51% starting from **6**) as a white solid: mp 133−135 °C; IR (KBr) 3700−3120, 3060, 3025, 2930, 1780, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 2H), 7.40−7.20 (m, 7H), 4.38 (t, 1H), 3.89 (d, 2H), 1.85 (s br, 2H); FAB-MS (positive, matrix thioglycerol, gas Xe, 8 keV, source 50 °C) *m*/*z* 267 (MH^+).

(*R*)-α-(Dimethylaminomethyl)benzylamine (7b). Compound **6** (6.0 g, 19.0 mmol) was dissolved in 28% Me_2NH/EtOH (75 mL) and heated at 80 °C for 2 h in a steel autoclave. After evaporation to dryness, the crude product was dissolved in CH_2Cl_2 and washed with brine. The residue was purified by flash column chromatography on silica gel, eluting with a mixture of hexane/EtOAc/28% NH_4OH (50:50:0.5), to yield the Boc-protected (*R*)-α-(dimethylaminomethyl)benzylamine (3.5 g, 13.2 mmol): IR (KBr) 3370, 3060, 3038, 2980, 2810, 2760, 1680, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.30−7.20 (m, 6H), 4.60 (m, 1H), 2.50 (dd, 1H), 2.30 (dd, 1H), 2.20 (s, 6H), 1.35 (s, 9H); EI-MS (source 180 °C, 70 eV, 200 mA) *m*/*z* 264 ($M^{+\bullet}$). (*R*)-*N*-(*tert*-Butoxycarbonyl)-α-(dimethylaminomethyl)benzylamine (3.5 g, 13.2 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (18 mL) and stirred at room temperature, under nitrogen atmosphere, for 1.5 h. The reaction mixture was diluted with H_2O and basified with 10% Na_2CO_3; the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness to yield **7b** (2.1 g, 12.8 mmol, 67% starting from **6**) as an oil: IR (neat) 3360, 3270, 3060, 3038, 2970, 2940, 2855, 2810, 2770, 1690, 1495, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.20 (m, 5H), 4.09 (dd, 1H), 3.32 (s br, 2H), 2.61 (dd, 1H), 2.32 (s, 6H), 2.31 (dd, 1H).

3-Hydroxy-2-phenylquinoline-4-carboxylic Acid (10i). 3-Methoxy-2-phenylquinoline-4-carboxylic acid (**10h**; 2.0 g, 7.2 mmol) was dissolved in 57% HI (45 mL) and refluxed under stirring for 3 h. After evaporation to dryness, the residue was suspended in H_2O, basified with 40% NaOH to obtain a clear solution, and then cooled with ice and acidified with 37% HCl (the desired compound precipitates as free base) to obtain a yellow precipitate which was recovered by suction filtration and washed with H_2O. The title compound was dried in a ventilated oven at 80 °C (1.8 g, 6.8 mmol, 95%) and used without further purification: mp 202−204 °C; IR (KBr) 3459, 3122, 3061, 2566, 1937, 1632, 1600, 1529, 1497 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.78 (d, 1H), 8.02 (m, 3H), 7.67−7.50 (m, 5H); EI-MS (source 180 °C, 70 eV, 200 mA) *m*/*z* 265 ($M^{+\bullet}$).

3-(Dimethylaminomethyl)-2-phenylquinoline-4-carboxylic Acid (10k). 3-Methyl-2-phenylquinoline-4-carboxylic acid (**10b**; 5.6 g, 21.3 mmol), *N*-bromosuccinimide (7.6 g, 42.5 mmol), and dibenzoyl peroxide (0.48 g, 2.0 mmol) were refluxed in 1,2-dichloroethane (100 mL) for 24 h. The solvent was removed to dryness to obtain crude 3-(bromomethyl)-2-phenylquinoline-4-carboxylic acid, which was utilized in the following reaction without further purification. This crude material was dissolved in THF (100 mL), the solution was cooled with an ice bath, and 28% Me_2NH in EtOH (13.5 mL, 64.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. The solvent was removed to dryness; the residue was taken up with 10% K_2CO_3, stirred for 10 min, and then evaporated to dryness again. The residue was washed with Et_2O twice and dissolved in 20% HCl; the solvent was evaporated, and the residue was taken up with 28% NH_4OH. The solvent was removed to dryness, and the crude product so obtained was dissolved in a 1:1 mixture of MeOH/THF, filtering off insoluble material; the solvent was evaporated to dryness again, and the residue was purified by gradient flash column chromatography on silica gel, eluting with EtOAc/MeOH/28% NH_4OH, 80:20:0 to 60:40:3, to yield the title compound as a brown solid (3.7 g, 12.1 mmol, 57%): mp 173−175 °C; IR (KBr) 3406, 3120, 3060, 2520, 1632 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.18 (d, 1H), 8.14 (d, 1H), 7.96 (dd, 1H), 7.81 (dd, 1H), 7.75−7.70 (m, 2H), 7.61−7.56 (m, 3H), 4.38 (s, 2H), 2.20 (s, 6H); EI-MS (source 180 °C, 70 eV, 200 mA) *m*/*z* 306 ($M^{+\bullet}$).

Synthesis of Final Compounds. Final compounds **12**−**14**, **16**, **20**−**30**, **32**, **34**, and **36**−**59** were synthesized according to the general procedures to obtain 2-phenylquinoline-4-carboxamides described by Giardina et al.;[9] in particular, compounds **20**, **21**, **24**, **28**−**30**, **32**, **37**, **41**−**51**, and **57** were obtained by transforming the 2-phenylquinoline-4-carboxylic acids into the correspnding acyl chlorides and then coupling with the appropriate amine of general formula $PhCHRNH_2$ (method A of ref 9), whereas compounds **12**−**14**, **16**, **22**, **23**, **25**−**27**, **34**, **36**, **38**−**40**, **52**−**56**, **58**, and **59** were prepared by reacting the corresponding 2-phenylquinoline-4-carboxylic acids with the appropriate amine of general formula $PhCHRNH_2$

in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) (method B of ref 9).

As an example, spectroscopic data of compound **14** are reported: mp 180−181 °C (from *i*-PrOH); $[\alpha]_D^{20}$ (c = 0.5, MeOH) = − 42.0; IR (Nujol) 3300, 1750, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.72 (d, J = 6.9 Hz, 1H), 8.28 (dd, J = 8.3, 1.8 Hz, 2H), 8.20 (dd, J = 8.3, 0.8 Hz, 1H), 8.13 (dd, J = 8.5, 0.5 Hz,1H), 8.11 (s, 1H), 7.83 (ddd, J = 7, 7, 1.6 Hz, 1H), 7.66 (ddd, J = 7, 7, 1.2 Hz, 1H), 7.60−7.50 (m, 5H), 7.47−7.37 (m, 3H), 5.78 (d, J = 6.9 Hz, 1H), 3.72 (s, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 396 ($M^{+\bullet}$), 337, 232, 204. Anal. ($C_{25}H_{20}N_2O_3$) C, H, N.

(*R*)-*N*-(α-Carboxybenzyl)-2-phenylquinoline-4-carboxamide Hydrochloride (15). (*R*)-*N*-[α-(Methoxycarbonyl)-benzyl]-2-phenylquinoline-4-carboxamide (**14**; 0.20 g, 0.5 mmol), 10% HCl (10 mL), and 1,4-dioxane (3 mL) were refluxed under stirring for 30 min. The solvent was evaporated to dryness, and the residue was triturated with EtOAc/Et_2O 1:1 first and then with warm acetone to yield **15** as a white solid (0.17 g, 0.4 mmol, 86%): mp 203−205 °C; $[\alpha]_D^{20}$ (c = 0.5, MeOH) = −40.0; IR (KBr) 1740, 1670, 1635, 1610, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.64 (d, J = 7.6 Hz, 1H), 8.28 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 7.7 Hz, 1H), 8.16 (d, J = 7.7 Hz, 1H), 8.13 (s, 1H), 7.84 (dd, J = 7.7, 7.7 Hz, 1H), 7.66 (dd, J = 7.7, 7.7 Hz, 1H), 7.62−7.51 (m, 5 H), 7.46−7.34 (m, 3H), 5.70 (d, J = 7.6 Hz, 1H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 382 ($M^{+\bullet}$), 337, 204. Anal. ($C_{24}H_{18}N_2O_3$·HCl) C, H, N, Cl.

General Procedure for the Synthesis of Compounds 17−19 in Scheme 4. (*R,S*)-*N*-[α-(Methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide (**12**) (0.44 g, 1.1 mmol) was dissolved in 40 mL of 33% $MeNH_2$/EtOH (to obtain **17**) or 33% Me_2NH/EtOH (to obtain **18**) or 16% NH_3/MeOH (to obtain **19**); a catalytic amount of NaCN was added, and the reaction mixture was heated at 70−120 °C for 1−6.5 h in a Parr apparatus. The internal pressure rose to about 40 psi. The solution was evaporated to dryness, and the residue was triturated with water, filtered, dried, and recrystallized from a mixture of *i*-PrOH/EtOH (2:1) to yield the title compounds **17**−**19**. Typically, yields were in the range of 45−60%. As an example, spectroscopic data for compound **17** are reported: mp 261−263 °C (from *i*-PrOH/EtOH); IR (KBr) 3300, 3270, 1660, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.48 (d, J = 6.3 Hz, 1H), 8.33−8.25 (m, 3H), 8.18−8.10 (m, 3H), 7.8 (ddd, J = 7.9, 7.9, 1.1 Hz, 1H), 7.68−7.50 (m, 6H), 7.40−7.28 (m, 3H), 5.75 (d, J = 6.3 Hz, 1H), 2.63 (d, J = 7.6 Hz, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 395 ($M^{+\bullet}$), 337, 232, 204, 77. Anal. ($C_{25}H_{21}N_3O_2$) C, H, N.

(*R,S*)-*N*-(α-Acetylbenzyl)-2-phenylquinoline-4-carboxamide (31). Oxalyl chloride (0.27 mL, 3.1 mmol) was dissolved under nitrogen atmosphere in dry CH_2Cl_2 (2.3 mL). The solution was cooled to −55 °C, and DMSO (0.22 mL, 3.1 mmol), dissolved in dry CH_2Cl_2 (0.7 mL), was added dropwise while maintaining the temperature below −50 °C. The reaction was stirred at −55 °C for 7 min; then (*R,S*)-*N*-[α-(1-hydroxyethyl)-benzyl]-2-phenylquinoline-4-carboxamide (**30**; 0.96 g, 2.5 mmol), dissolved in dry CH_2Cl_2 (25 mL), was added keeping the temperature between −50 and −55 °C. After 30 min at −55 °C, TEA (1.9 mL) was added without exceeding −40 °C; then the reaction mixture was allowed to reach room temperature and stirred for an additional 15 min. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2; the organic layer was washed with H_2O, 20% citric acid, 5% $NaHCO_3$, and brine; the organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. The residual oil was flash chromatographed on 230−400 mesh silica gel, eluting with a mixture of hexane/EtOAc (7:3) containing 0.5% of 28% NH_4OH to afford a compound which was crystallized from *i*-PrOH/*i*-Pr_2O (1:2) to yield **31** (0.50 g, 1.3 mmol, 53%): mp 160−161 °C; IR (KBr) 3400, 3265, 1725, 1660, 1640, 1592 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.60 (d, J = 7.3 Hz, 1H), 8.29 (d, 2H), 8.17 (d, J = 7.5 Hz, 1H), 8.14 (d, 1H), 8.12 (s, 1H), 7.82 (dd, J = 7.5, 7.5 Hz, 1H), 7.65 (dd, J = 7.5, 7.5 Hz, 1H), 7.61−7.51 (m, 5H), 7.48−7.36 (m, 3H), 5.90 (d, J = 7.3 Hz, 1H), 2.19 (s, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 380 ($M^{+\bullet}$), 337, 232, 204. Anal. ($C_{25}H_{20}N_2O_2$) C, H, N.

(*R,S*)-*N*-[α-(2-Hydroxyethyl)benzyl]-2-phenylquinoline-4-carboxamide (33). (*R,S*)-*N*-[α-(Methoxycarbonylmethyl)-benzyl]-2-phenylquinoline-4-carboxamide (**16**; 0.70 g, 1.7 mmol) was dissolved under nitrogen atmosphere in *t*-BuOH (50 mL) and MeOH (2 mL). $NaBH_4$ (0.06 g, 1.6 mmol) was added in 15 min to the refluxing solution. The reaction mixture was refluxed for 6 h, quenched with a saturated solution of NH_4Cl (5 mL), and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed with brine; the organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. The crude product was flash chromatographed on 230−400 mesh silica gel, eluting with Et_2O containing 0.5% of 28% NH_4-OH, and then crystallized from *i*-PrOH/*i*-Pr_2O to yield **33** (0.19 g, 0.5 mmol, 29%): mp 167−169 °C; IR (KBr) 3360, 1650, 1592 cm^{-1};^1H NMR (DMSO-d_6) δ 9.30 (d, J = 6.1 Hz, 1H), 8.31 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.3 Hz, 1H), 8.10 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 8.4, 8.3 Hz, 1H), 7.64−7.51 (m, 4H), 7.46 (d, J = 8.5 Hz, 2H), 7.39 (dd, J = 8.5, 8.5 Hz, 2H), 7.29 (dd, J = 8.5, 8.5 Hz, 1H), 5.30 (dt, J = 6.1, 6.1 Hz, 1H), 4.61 (t, J = 4.5 Hz, 1H), 3.61−3.41 (m, 2H), 2.11−1.86 (m, 2H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 382 ($M^{+\bullet}$), 337, 232, 204. Anal. ($C_{25}H_{22}N_2O_2$) C, H, N.

(*R*)-*N*-[α-(Aminomethyl)benzyl]-2-phenylquinoline-4-carboxamide (35). (*R*)-*N*-[α-(Phthalimidomethyl)benzyl]-2-phenylquinoline-4-carboxamide (**34**; 1.0 g, 2.0 mmol) was suspended in 96% EtOH (100 mL) and heated to reflux. Hydrazine hydrate (0.15 g, 2.9 mmol) was added, and the reaction mixture was refluxed for 4 h. Additional hydrazine hydrate (0.41 g, 8.2 mmol) was added together with 1,2-dichloroethane (20 mL) to dissolve completely the reagents, and the reaction was refluxed for 3.5 h. The reaction mixture was then evaporated to dryness, dissolved in H_2O (20 mL), cooled, and acidified with 37% HCl (10 mL). The mixture was refluxed for 45 min and cooled; the phthalhydrazide was filtered off. The aqueous layer was made alkaline with 40% NaOH and extracted with CH_2Cl_2; the organic layer was washed with brine, separated, dried over Na_2SO_4, and evaporated to dryness. The residue was flash chromatographed on 230−400 mesh silica gel, eluting with CH_2Cl_2/MeOH (95:5) containing 0.5% of 28% NH_4OH to afford a purified product which was crystallized from *i*-Pr_2O/*i*-PrOH (95:5) to yield **35** as a white solid (0.29 g, 0.8 mmol, 40%): mp 139−141 °C; $[\alpha]_D^{20}$ (c = 0.5, MeOH) = −6.9; IR (KBr) 3300, 1635, 1590, 1530, 1495, 770 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.18 (d br, J = 7.2 Hz, 1H), 8.35 (d, J = 7.6 Hz, 2H), 8.20 (s, 1H), 8.13 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.81 (dd, J = 7.9, 7.9 Hz, 1H), 7.63−7.51 (m, 4H), 7.44 (d, J = 7.0 Hz, 2H), 7.38 (dd, J = 7.2, 7.2 Hz, 2H), 7.28 (dd, J = 7.2, 7.2 Hz, 1H), 5.08 (dt br, J = 7.2, 7.2 Hz, 1H), 2.89 (d, J = 7.2 Hz, 2H), 1.60 (s br, 2H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 338, 337, 255, 233, 232, 204. Anal. ($C_{24}H_{21}N_3O$) C, H, N.

(*S*)-*N*-(α-Ethylbenzyl)-3-acetamido-2-phenylquinoline-4-carboxamide (60). (*S*)-*N*-(α-Ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide (**55**; 0.38 g, 1.0 mmol) was heated in acetic anhydride (25 mL) at 70 °C for 1 h and then at 100 °C for an additional 3 h. The reaction mixture was then evaporated to dryness and the residue dissolved in EtOAc; the solution was washed with water, 5% $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated to dryness. The crude product was purified by silica gel flash column chromatography, eluting with a mixture of hexane/EtOAc/28% NH_4OH, 70:30:0.5, respectively, to afford a solid compound which was recrystallized from acetone to yield **60** (0.14 g, 0.33 mmol, 33%): mp 268−269 °C; $[\alpha]_D^{20}$ (c = 0.5, MeOH) = −71.4; IR (KBr) 3230, 1670, 1640, 1555, 1525 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.77 (s, 1H), 8.94 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.81 (dd, J = 8.5, 8.5 Hz, 1H), 7.71−7.59 (m, 4H), 7.50−7.25 (m, 8H), 5.02 (dt, J = 8.1, 8.1 Hz, 1H), 1.83−1.67 (m, 2H), 1.60 (s, 3H), 0.96 (t, J = 7.2 Hz, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 423 ($M^{+\bullet}$), 381, 334, 289, 261, 247, 218. Anal. ($C_{27}H_{25}N_3O_2$) C, H, N.

(*S*)-*N*-(α-Ethylbenzyl)-3-(dimethylaminoacetamido)-2-

phenylquinoline-4-carboxamide (61). (*S*)-*N*-(α-Ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide (**55**; 1.1 g, 2.8 mmol) was dissolved, under nitrogen atmosphere, in warm toluene (10 mL). Chloroacetic anhydride (0.96 g, 5.6 mmol), dissolved in toluene (5 mL), was added dropwise and the solution refluxed for 1 h. The reaction mixture was evaporated to dryness, suspended in CH_2Cl_2 (10 mL), and added dropwise into an ice-cooled solution of 28% Me_2NH/EtOH (5 mL). The solution was stirred at room temperature overnight, then 28% Me_2NH/EtOH (15 mL) was added, and the reaction mixture was heated at 60 °C in a Parr apparatus for 20 min. The mixture was evaporated to dryness, dissolved in 20% citric acid, and washed with EtOAc. The aqueous layer was basified with 2 N NaOH and extracted with EtOAc; the organic layer was washed with brine, separated, dried over Na_2SO_4, and evaporated to dryness to afford a crude product which was crystallized from *i*-Pr_2O to yield **61** (0.84 g, 1.8 mmol, 66%): mp 189−191 °C; $[\alpha]_D^{20}$ (*c* = 0.5, MeOH) = −63.1; IR (KBr) 3230, 3180, 1670, 1630, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.41 (s, 1H), 8.97 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.81 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.70−7.59 (m, 4H), 7.49−7.26 (m, 8H), 5.00 (dt, *J* = 8.2, 8.2 Hz, 1H), 2.55 (s, 2H), 1.97 (s, 6H), 1.90−1.65 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) *m*/*z* 466 ($M^{+\bullet}$), 331, 58. Anal. ($C_{29}H_{30}N_4O_2$) C, H, N.

General Procedure for the Synthesis of Compounds 63, 65−68, and 70 in Scheme 5. (*S*)-*N*-(α-Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (**53**; 1.9 g, 5.0 mmol) was dissolved in dry THF (20 mL). The alkylating agents **62a**−**f** (25.0 mmol), dissolved in THF (15 mL), K_2CO_3 (15.0 mmol), and KI (1.5 mmol), were added, and the reaction mixture was stirred at room temperature for 2.5 h and then refluxed for 10 h (only at room temperature in the case of **62e**,**f**). K_2CO_3 was filtered off, and the mixture was evaporated to dryness, dissolved in CH_2Cl_2, and washed with H_2O. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was flash chromatographed on 230−400 mesh silica gel to afford the title compounds which were crystallized from the appropriate solvents indicated in Table 2. Yields were around 90% for compounds **63**, **68**, and **70** and around 60% for compounds **65**−**67**. As an example, spectroscopic data for compound **63** are reported: mp 172−175 °C; $[\alpha]_D^{20}$ (*c* = 0.5, MeOH) = −16.3; IR (KBr) 3280, 3060, 2960, 1780, 1715, 1660, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.27 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.92−7.84 (m, 4H), 7.78−7.69 (m, 3H), 7.60−7.53 (m, 2H), 7.46−7.38 (m, 4H), 7.27 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.13−7.04 (m, 3H), 4.96 (dt, *J* = 8.1, 6.8 Hz, 1H), 3.92−3.78 (m, 2H), 3.72−3.55 (m, 2H), 1.78 (dq, *J* = 7.6, 6.8 Hz, 2H), 0.93 (t, *J* = 7.6 Hz, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) *m*/*z* 555 ($M^{+\bullet}$), 526, 421, 174.

(*S*)-*N*-(α-Ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide Hydrochloride (64). (*S*)-*N*-(α-Ethylbenzyl)-3-(2-phthalimidoethoxy)-2-phenylquinoline-4-carboxamide hydrochloride (**63**; 2.2 g, 3.9 mmol) was dissolved in 96% EtOH (150 mL), and hydrazine hydrate (0.39 g, 7.8 mmol) was added to the boiling solution, which was refluxed for 4 h. Additional 8.2-, 4.1-, 4.1-, 8.2-, and 8.2-mmol portions of hydrazine hydrate were added every 12 h, and the reaction mixture was maintained at reflux for a total of 64 h. The reaction mixture was then evaporated to dryness, dissolved in H_2O (20 mL), cooled, and acidified with 37% HCl (10 mL). The mixture was boiled for 1 h and cooled; the phthalhydrazide was filtered off. The aqueous layer was washed with EtOAc and then made alkaline with 2 N NaOH and extracted with EtOAc; the organic layer was washed with brine, separated, dried over Na_2SO_4, and evaporated to dryness. The residue was flash chromatographed on 230−400 mesh silica gel, eluting with EtOAc/MeOH (96:4) containing 1.2% of 28% NH_4OH to afford a purified product which was dissolved in EtOAc and treated with HCl/Et_2O to yield **64** (1.2 g, 2.6 mmol, 67%): mp 119 °C dec (EtOAc/Me_2CO); $[\alpha]_D^{20}$ (*c* = 0.5, MeOH) = −19.4; IR (KBr) 3400, 3080, 1640, 1545 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.45 (d, *J* = 6.9 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.00 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.94 (s br, 3H), 7.76 (ddd, *J* = 7.9, 5.6, 3.3 Hz, 1H), 7.65−7.51 (m, 4H), 7.48−7.40 (m, 3 H), 7.31 (dd, *J* = 6.6, 6.6 Hz, 1H), 5.09 (dt, *J* = 6.9, 6.9 Hz, 1H), 3.83 (t, *J* = 6.4 Hz, 2H), 2.72 (m, 2H), 1.93−1.80 (m, 2H), 0.99 (t, *J* = 6.9 Hz, 3H); FAB-MS (positive, matrix thioglycerol, gas Xe, 8 keV, source 50 °C) *m*/*z* 426 (MH^+). Anal. ($C_{27}H_{27}N_3O_2 \cdot HCl$) C, H, N, Cl.

(*S*)-*N*-(α-Ethylbenzyl)-3-(carboxymethoxy)-2-phenylquinoline-4-carboxamide (69). (*S*)-*N*-(α-Ethylbenzyl)-3-(ethoxycarbonylmethoxy)-2-phenylquinoline-4-carboxamide (**68**; 0.33 g, 0.7 mmol) was dissolved in 37% HCl (20 mL), and the reaction mixture was refluxed under stirring for 20 min. The solution was evaporated to dryness, and the crude product was triturated with warm EtOAc and recrystallized from EtOAc/*i*-PrOH to yield **69** hydrochloride as a white solid (0.22 g, 0.45 mmol, 64%): mp 203−204 °C; $[\alpha]_D^{20}$ (*c* = 0.5, MeOH) = −30.2; IR (Nujol) 3280−3120, 3100−3000, 1740, 1670, 1635, 1545 cm^{-1}. The acid hydrochloride was transformed into the corresponding sodium salt utilizing the following procedure. The compound was dissolved in 1% aqueous NaOH, and the solution was acidified to pH = 5 with 40% citric acid to precipitate **69** as free base. This precipitate was extracted several times with EtOAc, and the combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The solid obtained was dissolved in EtOH and the solution made alkaline with a stoichiometric amount of NaOH dissolved in EtOH. The solution so obtained was evaporated to dryness, the residue was dissolved in acetone, insoluble material filtered off, and the solution evaporated again to dryness. The residue was crystallized from CH_3CN to yield **69** as sodium salt. Yield of the conversion of hydrochloride to sodium salt was 75%: mp 316−317 °C; $[\alpha]_D^{20}$ (*c* = 0.5, MeOH) = −7.2; IR (KBr) 3420, 3275, 1673, 1616, 1419, 1298, 1193, 1141 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.95 (d, *J* = 7.0 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 8.2, 0.9 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.63 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.59−7.50 (m, 4H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.34 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.22 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.08 (dt, *J* = 7.4, 7.0 Hz, 1H), 3.99 and 3.95 (ABq, *J* = 16.0 Hz, 2H), 1.78 (dq, *J* = 7.4, 7.0 Hz, 2H), 0.97 (t, *J* = 7.0 Hz, 3H); ESI-MS (positive, solvent methanol, spray 4.5 keV, skimmer 60 eV, capillary 220 °C) *m*/*z* 463 (MNa^+). Anal. ($C_{27}H_{23}N_2O_4Na$) C, H, N, Na.

(*S*)-*N*-(α-Ethylbenzyl)-3-(dimethylaminocarbonylmethoxy)-2-phenylquinoline-4-carboxamide (71). (*S*)-*N*-(α-Ethylbenzyl)-3-(ethoxycarbonylmethoxy)-2-phenylquinoline-4-carboxamide (**68**; 0.61 g, 1.3 mmol) was dissolved in 28% Me_2NH/EtOH (30 mL); a small amount of NaCN was added, and the reaction mixture was heated in a Parr apparatus at 100 °C (external temperature) for 2 h and then at 120 °C for 12 h. The reaction mixture was evaporated to dryness; the residue was dissolved in EtOAc and washed with H_2O, 20% citric acid, 5% $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness to obtain a residue which was flash chromatographed on 230−400 mesh silica gel, eluting with a mixture of hexane/EtOAc (1:1) containing 0.5% of 28% NH_4OH. The purified compound was crystallized from Et_2O to yield **71** as a white solid (0.18 g, 0.39 mmol, 30%): mp 86−88 °C; $[\alpha]_D^{20}$ (*c* = 0.25, MeOH) = −41.2; IR (KBr) 3240, 3060, 2980−2820, 1685, 1625, 1550 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.40 (d, *J* = 7.2 Hz, 1H), 8.04 (m, 3H), 7.72 (ddd, *J* = 7.2, 7.2, 0.9 Hz, 1H), 7.65−7.47 (m, 5H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.26 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.28 (dd, *J* = 7.2, 7.2 Hz, 1H), 5.05 (dt, *J* = 7.2, 7.2 Hz, 1H), 4.46 and 4.42 (ABq, *J* = 13.0 Hz, 2H), 2.70 (s, 3H), 2.50 (s, 3H), 1.80 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) *m*/*z* 467 ($M^{+\bullet}$), 438, 333, 305, 262. Anal. ($C_{29}H_{29}N_3O_3$) C, H, N.

(*S*)-*N*-(α-Ethylbenzyl)-3-(2-hydroxyethoxy)-2-phenylquinoline-4-carboxamide (72). (*S*)-*N*-(α-Ethylbenzyl)-3-(ethoxycarbonylmethoxy)-2-phenylquinoline-4-carboxamide (**68**; 0.66 g, 1.4 mmol) was dissolved, under nitrogen atmosphere, in *t*-BuOH (50 mL); $NaBH_4$ (0.053 g, 1.4 mmol) was added, and the mixture was heated to reflux. MeOH (7 mL) was added dropwise; the reaction was refluxed for 3 h, then quenched with a saturated solution of NH_4Cl (5 mL), evaporated to dryness, dissolved in CH_2Cl_2, and washed with brine. The extracted organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness to yield a crude product which was purified by gradient flash column chromatography on 230−

400 mesh silica gel using a mixture of hexane/EtOAc (8:2) containing 0.5% of 28% NH_4OH as starting eluent and a mixture of hexane/EtOAc (1:1) containing 0.5% of 28% NH_4OH as final eluent. The purified product obtained was crystallized from *i*-Pr_2O to yield **72** as a white solid (0.30 g, 0.7 mmol, 50%): mp 129−130 °C; $[\alpha]_D^{20}$ (c = 0.5, MeOH) = −41.2; IR (KBr) 3240, 3060, 2980−2920, 1625, 1550 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.30 (d, J = 7.6 Hz, 1H), 8.07−7.90 (m, 3H), 7.76−7.67 (m, 1H), 7.60−7.49 (m, 5H), 7.45 (d, J = 7.6 Hz, 2H), 7.39 (dd, J = 7.6, 7.6 Hz, 2H), 7.29 (dd, J = 7.6, 7.6 Hz, 1H), 5.08 (dt, J = 7.6, 6.6 Hz, 1H), 4.57 (t, J = 5.1 Hz, 1H), 3.69 (m, 2H), 3.34 (dt, J = 5.1, 5.1 Hz, 2H), 1.82 (m, 2H), 0.99 (t, J = 6.9 Hz, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 426 ($M^{+\bullet}$), 397, 292, 264. Anal. ($C_{27}H_{26}N_2O_3$) C, H, N.

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Supporting Information Available: Detailed spectroscopic data (IR, MS, and ^1H NMR) for compounds **12**−**29**, **31**−**33**, **35**−**61**, and **64**−**72**. This material is available free of charge via the Internet at http://pubs.acs.org.

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