Discovery of a Novel Class of Selective Non-Peptide Antagonists for the Human Neurokinin-3 Receptor. 1. Identification of the 4-Quinolinecarboxamide Framework

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A novel class of potent and selective non-peptide neurokinin-3 (NK-3) receptor antagonists, featuring the 4-quinolinecarboxamide framework, has been designed based upon chemically diverse NK-1 receptor antagonists. The novel compounds **33**−**76**, prompted by chemical modifications of the prototype **4**, have been characterized by binding analysis using a membrane preparation of chinese hamster ovary (CHO) cells expressing the human neurokinin-3 receptors (hNK-3-CHO), and clear structure−activity relationships (SARs) have been established. From SARs, (*R*)-*N*-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide (**65**, SB 218795, hNK-3-CHO binding K_i = 13 nM) emerged as one of the most potent compounds of this novel class. Selectivity studies versus the other neurokinin receptors (hNK-2-CHO and hNK-1-CHO) revealed that **65** is about 90-fold selective for hNK-3 versus hNK-2 receptors (hNK-2-CHO binding K_i = 1221 nM) and over 7000-fold selective versus hNK-1 receptors (hNK-1-CHO binding K_i = >100 μM). *In vitro* functional studies in rabbit isolated iris sphincter muscle preparation demonstrated that **65** is a competitive antagonist of the contractile response induced by the potent and selective NK-3 receptor agonist senktide with a K_b = 43 nM. Overall, the data indicate that **65** is a potent and selective hNK-3 receptor antagonist and a useful lead for further chemical optimization.

Introduction

Since the discovery in 1991 of CP 96,345[1] (**1**; Figure 1), the first potent non-peptide human neurokinin-1 (NK-1) receptor antagonist from Pfizer, and of RP 67,580[2] (**2**), another potent NK-1 receptor antagonist identified from random screening by Rhône Poulenc in 1992, interest in the tachykinin area has dramatically increased. Almost all the major pharmaceutical companies dedicated efforts to the identification of non-peptide antagonists selective for the three neurokinin receptors (NK-1, NK-2, and NK-3). These receptors, widely distributed in both the central nervous system (CNS) and periphery,[3] belong to the seven transmembrane G-protein-coupled receptor superfamily (7TM-GPCR).[4] Their endogenous neurotransmitters, the tachykinins or neurokinins,[5] constitute a group of small peptides which are released from sensory nerves. The tachykinins are implicated in a wide range of pathophysiological conditions (including nociceptive, inflammatory, and immunoregulatory processes, airway obstruction and asthma, skin disorders, inflammatory bowel disease, emesis, and various CNS disorders).[4,6] The three main endogenous tachykinins identified to date, substance P, neurokinin A (NKA), and neurokinin B (NKB), show a preferred affinity for NK-1, NK-2, and NK-3 receptors, respectively, although all three tachykinins interact with the three neurokinin receptors.

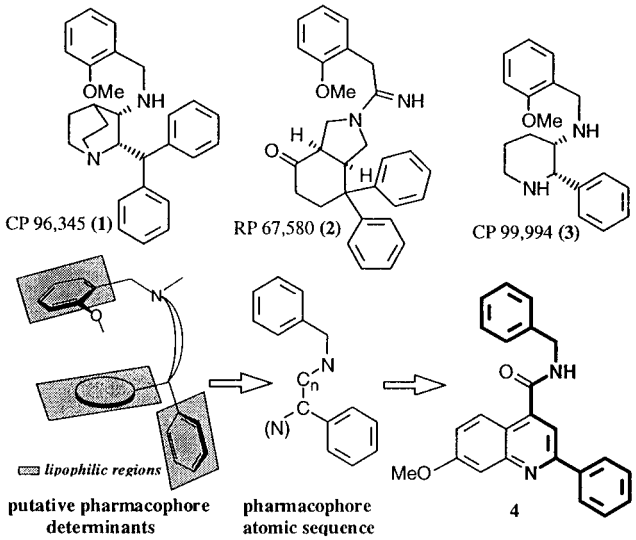

Figure 1. Identification of the 4-quinolinecarboxamide framework.

Initially, the focus of the research effort in the tachykinin area was on NK-1 and NK-2 receptor antagonists with much less research on NK-3 receptors;[7−9] this was due to the lack of availability, until recently, of potent and selective non-peptide NK-3 receptor antagonists. In 1995 novel NK-3 receptor antagonists from diverse chemical classes appeared in the literature.[10−14] Our research group published in this Journal in 1996 a Communication to the Editor in which a novel chemical class of potent and selective non-peptide competitive antagonists for the human NK-3 (hNK-3)

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receptor was disclosed.[15] In this paper we report in more detail the rational identification of the 2-phenyl-4-quinolinecarboxamide framework and part of our work aimed at optimizing the hNK-3 binding affinity of this novel chemical class.

As most of the other research groups, we started efforts in the tachykinin area in 1992 with focus on NK-1 receptor antagonists, utilizing compounds **1** and **2** as prototype models from which a putative neurokinin pharmacophore could be inferred. The identification from Pfizer of CP 99,994[16] (compound **3**, described to be much more selective than **1** in respect to Verapamil-sensitive L-type Ca^{2+} binding site; Figure 1)[17] suggested that one of the two phenyl groups of the benzhydryl moiety was not a key pharmacophore determinant for a potent NK-1 binding affinity. Possibly, the additional phenyl ring was responsible for the interaction with the L-type Ca^{2+} channel. Another piece of important information to help the clarification of key determinants of a putative neurokinin-1 pharmacophore was revealed by Merck researchers in 1993. They established that in both **1**- and **3**-like structures, the benzylamine group could be replaced by the benzyloxy moiety without affecting the binding affinity to NK-1 receptors.[18] This finding revealed that the role for the exocyclic nitrogen in compound **1** was just to be a hydrophilic, hydrogen bond acceptor center. Taking together all the features described above, we focused our efforts on the pharmacophore atomic sequence represented in Figure 1 and designed a number of chemical models which could offer, in principle, realistic opportunities to be potent NK-1 receptor antagonists.

During the screening efforts it was noted that the 2-phenyl-4-quinolinecarboxamide derivative **4** had no significant affinity for hNK-1 receptors ($K_i > 10\ \mu$M, for displacement of [^{3}H]substance P binding from hNK-1-CHO membranes) but possessed moderate affinity for the hNK-3 receptor ($K_i = 870$ nM, for displacement of [^{125}I]MePhe^7-NKB binding from hNK-3-CHO membranes).

The NK-3 receptor, present in both the CNS and periphery, is supposed to exert a neuromodulatory role, as suggested by pharmacological studies using selective peptide NK-3 receptor agonists. In particular, NK-3 receptor stimulation plays a key role in the modulation of neuronal input in airways,[19,20] skin,[21,22] spinal cord,[23,24] and nigrostriatal pathways.[25−29]

In contrast to the extensive investigation on the effects of NK-3 receptor agonists, no information is available on the activity of NK-3 receptor antagonists in disease models. Therefore, based on available evidence on NK-3 receptor distribution and agonist effects, potential therapeutic utility for NK-3 receptor antagonists in pulmonary diseases, renal and bladder disorders, skin disorders, neurogenic inflammation and pain, as well as CNS disorders, including anxiety, psychosis, movement, and convulsive disorders, can be envisiged.

Based on this information and on the moderate affinity of compound **4** for the hNK-3 receptor, a major effort was directed toward identifying more potent NK-3 receptor antagonists. 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 **33**−**76** will be described. For compounds **41**, **65**, and **66**, 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 *in vitro* 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.

Chemistry

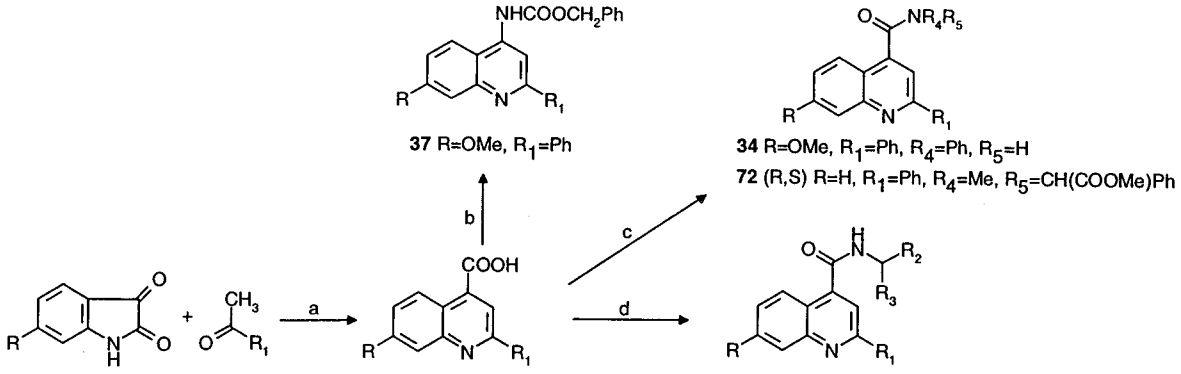
Intermediates **7a**−**x** in Scheme 1 were obtained in high yields (typically, greater than 80%) by the Pfitzinger reaction[30] of isatines **5** with the appropriate commercially available alkyl (**6b**−**d**)[31] and aryl (**6a**,**e**−**x**) ketones in 95−99% EtOH and 85% KOH pellets at 80 °C for 1−3 days (occasionally, 34% KOH was utilized). The benzyl carbamate derivative **37** was obtained by Curtius degradation of **7a′** in the presence of diphenyl phosphorazidate (DPPA), triethylamine (TEA), and benzyl alcohol, following a described procedure.[32] The anilide derivative **34** was prepared from **7a′** in two steps, *via* preparation of the corresponding acyl chloride and subsequent reaction with aniline in the presence of K_2CO_3 in dry DMF. For the preparation of the tertiary amide **72**, the carboxylic acid **7a** was treated with (*R*,*S*)-methyl *N*-(methylphenyl)glycinate·HCl,[33] dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBT), and *N*-methylmorpholine; for this reaction a solvent mixture consisting of THF/MeCN in a 7:3 ratio gave, in general, the best yields.

Secondary amides **4**, **33**, **38**, **40**−**69**, and **71** in Scheme 1 were synthesized from the corresponding 4-quinolinecarboxylic acids **7a**−**x** and the appropriate primary amines of general formula $R_2R_3CHNH_2$, following the procedures described above for compound **34** or **72** (occasionally, TEA was used instead of *N*-methylmorpholine). The carboxylic acid derivative **39** was obtained from the corresponding methyl ester **38** by treatment with 10% HCl in refluxing dioxane for 3 h. The (*p*-methoxyphenyl)glycine derivative **70** was obtained from the *p*-hydroxy derivative **69** by treatment with MeI in the presence of anhydrous K_2CO_3 in refluxing acetone containing traces of DMF (to facilitate the solution of the substrate).

Lithium aluminum hydride ($LiAlH_4$) reduction of the amide **33** to the corresponding secondary amine **35** was unsuccessful and resulted in the formation of several, nonidentified byproducts; thus, compound **35** was prepared as described in Scheme 2. The acyl chloride **8** was treated at −70 °C in THF with lithium tri-*tert*-butoxyaluminum hydride [Li(*t*-BuO)$_3$AlH, 1 M solution in THF]; attempts to stop the reaction at the aldehyde step were unsuccessful and resulted in a 1:1 mixture of the primary alcohol **9** and the aldehyde **10**; thus, an excess of the reducing agent was employed to obtain the primary alcohol **9** (62%) which was oxidized to the corresponding aldehyde (83%) by treatment with MnO_2 in CH_2Cl_2 at room temperature for 6 days. Reduction of the crude imine **11**, obtained by refluxing **10** and benzylamine in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid, was achieved with sodium triacetoxyborohydride [Na(AcO)$_3$BH], in AcOH at room temperature.

Since alkylation of 4-amino-7-methoxy-2-phenylquinoline (obtained by hydrolysis of the benzyl carbamate

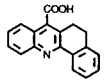
Scheme 1. Synthesis of Compounds **4**, **33**, **34**, and **37**−**72** of General Formulae I−IV in Tables 1−4[a]



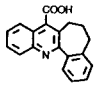
6a R_1=Ph
6b R_1=Me
6c R_1=CH_2Ph
6d R_1=cyclohexyl
6e R_1=3-thienyl
6f R_1=2-pyrryl
6g R_1=2-thienyl
6h R_1=2-furyl
6i R_1=3-pyrryl
6j R_1=2-benzofuryl
6k R_1=2-thiazolyl
6l R_1=4-pyridyl
6m R_1=2-F-Ph
6n R_1=2-Cl-Ph
6o R_1=2-Me-Ph
6p R_1=2-OMe-Ph
6q R_1=2-OH-Ph
6r R_1=3-Cl-Ph
6s R_1=4-Cl-Ph
6t R_1=4-Me-Ph
6u R_1=4-OMe-Ph
6v R_1=4-OH-Ph
6w =

6x =

7a R=H, R_1=Ph
7a' R=OMe, R_1=Ph
7b' R=OMe, R_1=Me
7c' R=OMe, R_1=CH_2Ph
7d R=H, R_1=cyclohexyl
7e R=H, R_1=3-thienyl
7f R=H, R_1=2-pyrryl
7g R=H, R_1=2-thienyl
7h R=H, R_1=2-furyl
7i R=H, R_1=3-pyrryl
7j R=H, R_1=2-benzofuryl
7k R=H, R_1=2-thiazolyl
7l R=H, R_1=4-pyridyl
7m R=H, R_1=2-F-Ph
7n R=H,R_1=2-Cl-Ph
7o R=H, R_1=2-Me-Ph
7p R=H, R_1=2-OMe-Ph
7q R=H, R_1=2-OH-Ph
7r R=H, R_1=3-Cl-Ph
7s R=H, R_1=4-Cl-Ph
7t R=H, R_1=4-Me-Ph
7u R=H, R_1=4-OMe-Ph
7v R=H, R_1=4-OH-Ph
7w =

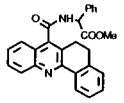


7x =

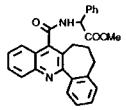


4 R=OMe, R_1=Ph, R_2=Ph, R_3=H
33 R=OMe, R_1=Ph, R_2=CH_2Ph, R_3=H
38 (R,S) R=OMe, R_1=Ph, R_2=Ph, R_3=COOMe
39 (R,S) R=OMe, R_1=Ph, R_2=Ph, R_3=COOH
40 R=H, R_1=Ph, R_2=Ph, R_3=H
41 (R,S) R=H, R_1=Ph, R_2=Ph, R_3=COOMe
42 R=OMe, R_1=Me, R_2=Ph, R_3=H
43 R=OMe, R_1=CH_2Ph, R_2=Ph, R_3=H
44 (R,S) R=H, R_1=cyclohexyl, R_2=Ph,R_3=COOMe
45 (R,S) R=H, R_1=3-thienyl, R_2=Ph, R_3=COOMe
46 (R,S) R=H, R_1=2-pyrryl, R_2=Ph, R_3=COOMe
47 (R,S) R=H, R_1=2-thienyl, R_2=Ph, R_3=COOMe
48 (R,S) R=H, R_1=2-furyl, R_2=Ph, R_3=COOMe
49 (R,S) R=H, R_1=3-pyrryl, R_2=Ph, R_3=COOMe
50 (R,S) R=H, R_1=2-benzofuryl, R_2=Ph, R_3=COOMe
51 (R,S) R=H, R_1=2-thiazolyl, R_2=Ph, R_3=COOMe
52 (R,S) R=H, R_1=4-pyridyl, R_2=Ph, R_3=COOMe
53 (R,S) R=H, R_1=2-F-Ph, R_2=Ph, R_3=COOMe
54 (R,S) R=H, R_1=2-Cl-Ph, R_2=Ph, R_3=COOMe
55 (R,S) R=H, R_1=2-Me-Ph, R_2=Ph, R_3=COOMe
56 (R,S) R=H, R_1=2-OMe-Ph, R_2=Ph, R_3=COOMe
57 (R,S) R=H, R_1=2-OH-Ph, R_2=Ph, R_3=COOMe
58 (R,S) R=H, R_1=3-Cl-Ph, R_2=Ph, R_3=COOMe
59 (R,S) R=H, R_1=4-Cl-Ph, R_2=Ph, R_3=COOMe
60 (R,S) R=H, R_1=4-Me-Ph, R_2=Ph, R_3=COOMe
61 (R,S) R=H, R_1=4-OMe-Ph, R_2=Ph, R_3=COOMe
62 (R,S) R=H, R_1=4-OH-Ph, R_2=Ph, R_3=COOMe
65 (R) R=H, R_1=Ph, R_2=Ph, R_3=COOMe
66 (S) R=H, R_1=Ph, R_2=Ph, R_3=COOMe
67 (R) R=H,R_1=Ph, R_2=$CH(Me)_2$, R_3=COOMe
68 (R,S) R=H, R_1=Ph,R_2=CH_2Ph, R_3=COOMe
69 (R) R=H, R_1=Ph, R_2=4-OH-Ph, R_3=COOMe
70 (R) R=H, R_1=Ph, R_2=4-OMe-Ph, R_3=COOMe
71 (R,S) R=H, R_1=Ph, R_2=2-thienyl, R_3=COOMe

63 (R,S) =

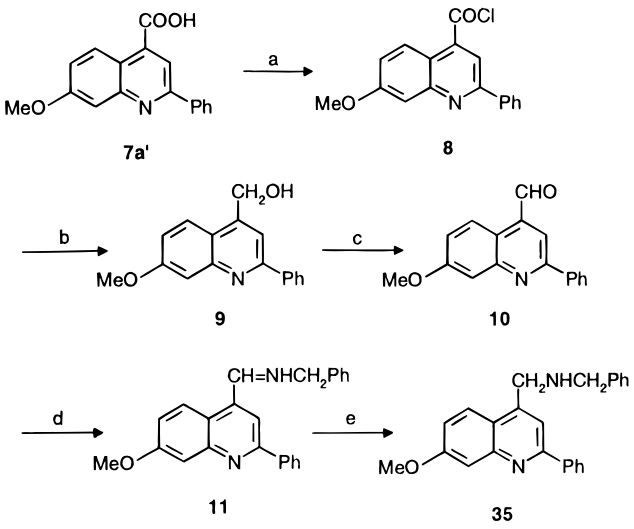


64 (R,S) =



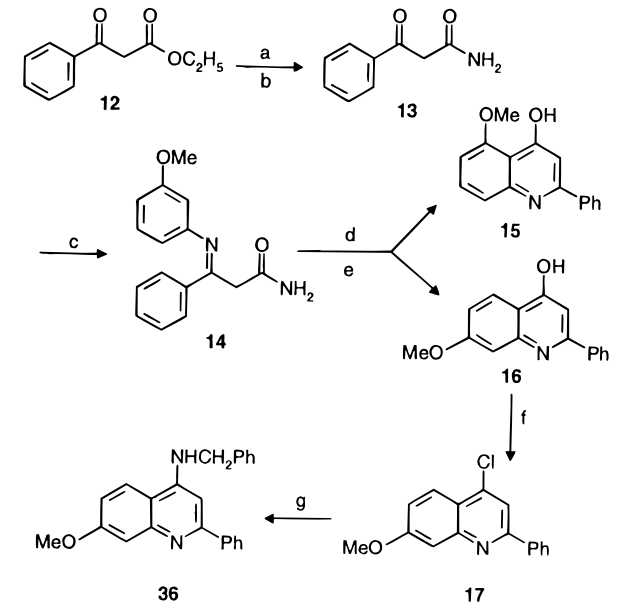
[a] Reagents: (a) 34−85% aq KOH, 95−99% EtOH, 80 °C, 1−3 days; (b) DPPA, TEA, $PhCH_2OH$, 80 °C, 20 h; (c) 1. $(COCl)_2$, CH_2Cl_2, 5 °C to room temperature, 2 days, 2. $PhNH_2$, DMF, K_2CO_3, room temperature, 24 h; or (*R*,*S*)-methyl *N*-(methylphenyl)glycinate·HCl, DCC, HOBT, *N*-methylmorpholine, THF/MeCN (7:3), 3 h, rt; (d) 1. $(COCl)_2$, CH_2Cl_2, 5 °C to room temperature, 2 days, 2. $R_2R_3CHNH_2$, DMF, K_2CO_3, room temperature, 24 h; or $R_2R_3CHNH_2$·HCl, DCC, HOBT, *N*-methylmorpholine, THF/MeCN (7:3), 3 h, room temperature; (e) 10% HCl, dioxane, reflux, 3 h; (f) K_2CO_3, MeI, Me_2CO/DMF, reflux.

Scheme 2[a]



[a] Reagents: (a) $(COCl)_2$, CH_2Cl_2, 5 °C to room temperature, 2 days; (b) Li(*t*-BuO)$_3$AlH, THF, −70 °C, 2 h, then room temperature, 16 h; (c) MnO_2, CH_2Cl_2, room temperature, 6 days; (d) $PhCH_2NH_2$, toluene, PTSA, reflux, 3 days; (e) Na(AcO)$_3$BH, AcOH, room temperature, 24 h.

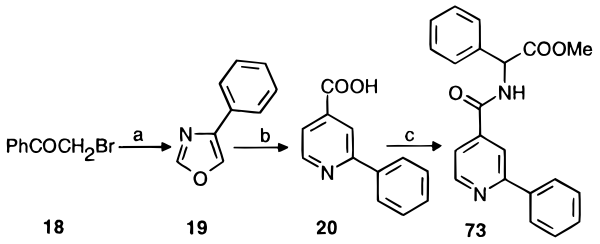
Scheme 3[a]



[a] Reagents: (a) 32% NH_4OH, 85 °C, 2 h, steel autoclave; (b) H_2O, 100 °C, 4 h; (c) *m*-anisidine, toluene, reflux, 8 h; (d) PPA, 135 °C, 20 min; (e) NaOH to pH 8, filtration and recrystallization of **16** from MeOH; (f) $POCl_3$, reflux, 2 h; (g) $PhCH_2NH_2$, phenol, 150 °C, 3 h.

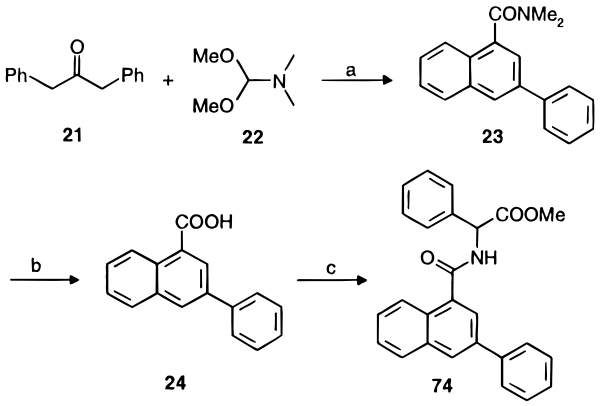
37) was not possible, due to the nonbasic nature of the 4-amino group, compound **36** was prepared by a multistep procedure (Scheme 3) starting from ethyl 3-oxo-3-phenylpropionate (**12**), which was converted to the corresponding primary amide by heating in a steel autoclave in the presence of concentrated NH_4OH and subsequent hydrolysis of the labile imine function. Polyphosphoric acid (PPA) cyclization of compound **14**, prepared from the ketone **13** and *m*-anisidine under standard conditions, was very effective and afforded a 2:3 mixture of 4-hydroxy-5-methoxy-2-phenylquinoline (**15**) and 4-hydroxy-7-methoxy-2-phenylquinoline (**16**), respectively. The 7-methoxy isomer **16** was obtained

Scheme 4[a]



[a] Reagents: (a) HCOOH (98%), $HCOONH_4$, reflux, 2.5 h; (b) maleic acid, 110 °C, 15 min; (c) (*R*,*S*)-methyl phenylglycinate·HCl, DCC, HOBT, *N*-methylmorpholine, THF/MeCN (7:3), 3 h, room temperature.

Scheme 5[a]



[a] Reagents: (a) 180 °C, 24 h, N_2, steel autoclave; (b) 85% KOH, ethylene glycol, 200 °C, 16 h; (c) (*R*,*S*)-methyl phenylglycinate·HCl, DCC, HOBT, *N*-methylmorpholine, THF/MeCN (7:3), 3 h, room temperature.

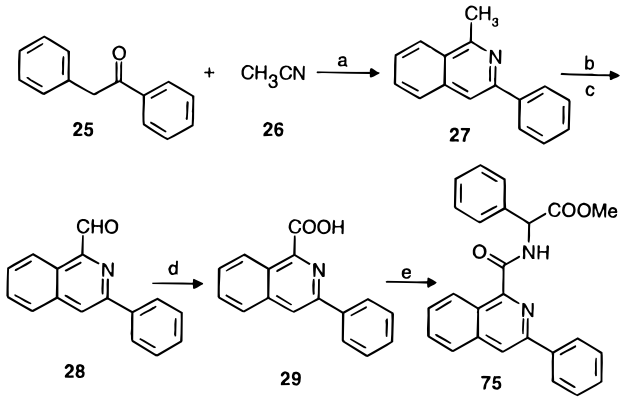
from the reaction mixture by adjusting to pH 8 with diluted NaOH, collecting the precipitate, and washing it with hot MeOH. Treatment of the 4-quinolinol derivative **16** in refluxing $POCl_3$ afforded the corresponding 4-chloro intermediate **17** in 68% yield. Finally, compound **17** was converted to the desired derivative **36** by refluxing with benzylamine in phenol for 3 h.

The 2-phenylpyridine-4-carboxamide derivative **73** was prepared as described in Scheme 4. Refluxing α-bromoacetophenone with ammonium formate in 98% HCOOH afforded 4-phenyloxazole (**19**).[34] Compound **19** was melted with maleic acid at 110 °C for 15 min following a reported procedure[35] and afforded 2-phenylpyridine-4-carboxylic acid (**20**) which was then coupled with (*R*,*S*)-methyl phenylglycinate, using the same conditions employed for compound **72**, to obtain the 4-pyridinecarboxamide derivative **73**.

The 2-phenylnaphthalene-4-carboxamide derivative **74** was synthesized according to Scheme 5. In this scheme, a mixture of 1,3-diphenylacetone (**21**) and *N*,*N*-dimethylformamide dimethyl acetal (**22**) was heated in a steel autoclave at 180 °C for 24 h according to the procedure described by R. F. Abdulla *et al*.[36] to give the dimethylamide **23**. Hydrolysis of compound **23** under strong conditions (KOH, ethylene glycol, 200 °C) afforded the desired 2-phenylnaphthalene-4-carboxylic acid **24**, which was transformed in high yield into the final secondary amide derivative **74** by the usual DCC coupling.

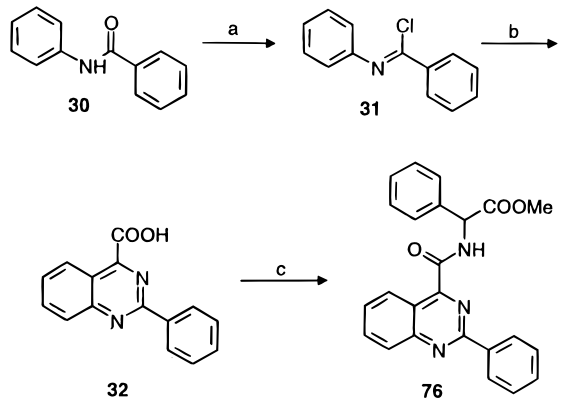
1-Methyl-3-phenylisoquinoline (**27**; Scheme 6) was prepared by refluxing a mixture of deoxybenzoin (**25**)

Scheme 6[a]



[a] Reagents: (a) $POCl_3$, reflux, 29 h; (b) NBS, dibenzoyl peroxide, CCl_4, reflux, 19 h; (c) $AgNO_3$, EtOH/H_2O/THF, reflux, 1 h; (d) $AgNO_3$, NaOH, EtOH/H_2O, 16 h; (e) (*R*,*S*)-methyl phenylglycinate·HCl, DCC, HOBT, *N*-methylmorpholine, THF/MeCN (7:3), 3 h, room temperature.

Scheme 7[a]



[a] Reagents: (a) $SOCl_2$, 90 °C, 3 h; (b) 1. NCCOOEt, $SnCl_4$, *o*-dichlorobenzene, 140 °C, 15 min, 2. 20% aq NaOH, dioxane (traces), reflux, 2 h; (c) 1. $(COCl)_2$, CH_2Cl_2/DMF (cat.), 5 °C to room temperature, 2 days, 2. (*R*,*S*)-methyl phenylglycinate·HCl, TEA, DMF/CH_2Cl_2, room temperature, 24 h.

and acetonitrile with $POCl_3$ for 29 h.[37] Subsequent oxidation of the aromatic methyl group to the corresponding carboxylic acid was achieved in three steps.[38] Firstly, the methyl was converted into the dibromomethyl group with *N*-bromosuccinimide (NBS); then, the aldehyde derivative **28** was obtained by neutral silver nitrate oxidation in refluxing EtOH/H_2O/THF, and finally, the oxidation was completed by stirring **28** at room temperature with an excess of silver nitrate under basic conditions. The carboxylic acid derivative **29** was coupled under the usual conditions to obtain the desired isoquinoline derivative **75**, in which the aromatic nitrogen occupies the ring position between the phenyl and the carboxamide substituents.

The 2-phenylquinazoline-4-carboxamide derivative **76** was obtained according to Scheme 7. Benzanilide imidoyl chloride (**31**), easily obtained in quantitative yield by refluxing benzanilide (**30**) and $SOCl_2$, was condensed with ethyl cyanoformate in the presence of stannic tetrachloride at 140 °C in *o*-dichlorobenzene.[39] The desired 2-phenylquinazoline-4-carboxylic acid (**32**) was recovered after basic hydrolysis of the corresponding ethyl ester. Finally, the secondary amide **76** was prepared in two steps from **32** *via* its corresponding acyl chloride.

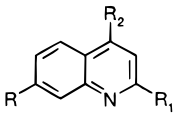
Pharmacology

Receptor Cloning and Expression. Human cDNAs for the NK-1, NK-2, and NK-3 tachykinin receptors, with sequences identical to those in published reports, were isolated from human placenta poly(A+) RNA using reverse transcriptase-polymerase chain reaction (PCR) technology and site-directed mutagenesis. Oligonucleotide primers for hNK-1 receptor cDNA,[40] hNK-2 receptor cDNA,[41] and hNK-3 receptor cDNA[42,43] were synthesized and used for PCR using the human placenta cDNA as template. The individual fragments were subcloned into the mammalian expression vector, pCDN,[44] and the resulting constructs were completely sequenced to confirm their identity and orientation. Stable CHO cell lines for the pCDN-NK-1, pCDN-NK-2, and pCDN-NK-3 expression vectors were obtained by electroporation followed by clonal selection using G418. The CHO stable cell lines were screened for high-level receptor expression by ligand binding assays on whole cells. From this screen, the clonal cell line producing the highest number of receptors per cell was chosen for each receptor.

Radioligand Binding Assays. Receptor binding assays were performed with crude membranes from CHO cells expressing the hNK-1, hNK-2, or hNK-3 receptors. 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.[45] Concentration−response curves for compounds **4** and **33**−**76** 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 1−4 are the apparent inhibition constants (K_i), which were calculated from the IC_{50} as described by Cheng and Prusoff.[46] For selectivity studies, compounds **41**, **65**, and **66** were also evaluated in hNK-2-CHO and hNK-1-CHO binding assays (Table 6). For NK-2 receptor competition binding studies, [^{125}I]NKA binding to membranes of CHO cells stably expressing the hNK-2 receptor (hNK-2-CHO) was performed essentially as described by Aharony *et al.*[47] Nonspecific binding was determined in the presence of 0.5 μM cold NKA. The K_i was determined as described for the NK-3 assay. Competition binding studies for the NK-1 receptor were performed on membranes of CHO cells stably expressing the hNK-1 receptor (hNK-1-CHO) essentially as described by Payan *et al.*[48] 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 assays.

Senktide-Induced Contraction in Rabbit Isolated Iris Sphincter (RIS) Muscle Preparation. Since the rabbit isolated iris sphincter muscle preparation contains functional NK-3 receptors,[49,50] the effects of one of the most potent racemic NK-3 receptor antagonists described in this paper (**41**) and of its enantiomers (**65** and **66**) were investigated in this tissue

Table 1. Physical Properties and Binding Affinity at Cloned Human Neurokinin-3 (hNK-3) Receptors Expressed in CHO Cells of Compounds **4** and **33**−**43** of General Formula I



I

compd	R	R_1	R_2	formula	mp, °C	anal.	recryst solvent	hNK-3-CHO binding[a] K_i, mean ± SEM (nM)[b]
4	OMe	2-Ph	$CONHCH_2Ph$	$C_{24}H_{20}N_2O_2$	167−169	C, H, N	*i*-PrOH/*i*-Pr_2O	870 ± 170
33	OMe	2-Ph	$CONHCH_2CH_2Ph$	$C_{25}H_{22}N_2O_2$	174−176	C, H, N	toluene	919 (2)
34	OMe	2-Ph	CONHPh	$C_{23}H_{18}N_2O_2$	222−224	C, H, N	toluene	1671 (1)
35	OMe	2-Ph	CH_2NHCH_2Ph	$C_{24}H_{22}N_2O{\cdot}2HCl$	216−218	H, N; C[c]	*i*-PrOH/*i*-Pr_2O	6203 (2)
36	OMe	2-Ph	$NHCH_2Ph$	$C_{23}H_{20}N_2O$	171−174	H, N; C[d]	Et_2O	10312 (2)
37	OMe	2-Ph	$NHCOOCH_2Ph$	$C_{24}H_{20}N_2O_3$	156−158	C, H, N	EtOAc	8133 (1)
38	OMe	2-Ph	CONHCH(COOMe)Ph	$C_{26}H_{22}N_2O_4$	187−190	C, H, N	*i*-PrOH/*i*-Pr_2O	57 ± 10
39	OMe	2-Ph	CONHCH(COOH)Ph	$C_{25}H_{20}N_2O_4{\cdot}HCl$	228−230	C, H, N	EtOH/EtOAc	5181 (1)
40	H	2-Ph	$CONHCH_2Ph$	$C_{23}H_{18}N_2O$	189−190	C, H, N	EtOAc	355 ± 63
41	H	2-Ph	CONHCH(COOMe)Ph	$C_{25}H_{20}N_2O_3$	170−172	C, H, N	*i*-PrOH/*i*-Pr_2O	31 ± 4
42	OMe	2-Me	$CONHCH_2Ph$	$C_{19}H_{18}N_2O_2{\cdot}HCl$	181−183	H, N; C[e]	EtOAc	>33000 (1)
43	OMe	2-CH_2Ph	$CONHCH_2Ph$	$C_{25}H_{22}N_2O_2$	149−152	C, H, N	EtOAc/*i*-Pr_2O	>33000 (1)

[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, 67.45; found, 66.80. [d] C: calcd, 81.15; found, 80.66. [e] C: calcd, 66.56; found, 65.18.

(Table 6). Iris sphincter muscle strips were prepared from male New Zealand White rabbits (2−3 kg, Charles River, U.K.). Tissues were placed in 50-mL organ baths containing Krebs-Henseleit solution for the isometric measurement of tension as previously described.[50] After a reference contractile response to 10 μM carbachol was obtained, experiments were conducted in the presence of 1 μM CP 99,994 and 1 μM atropine, to block NK-1 and muscarinic receptors, respectively. Tissues were then exposed to the NK-3 receptor antagonist under study (10 nM) or vehicle (DMSO) for 120 min before cumulative concentration−effect curves to senktide, the selective NK-3 receptor agonist, were constructed. Responses to senktide are expressed as a percentage of the carbachol-induced contraction. 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.[51]

Results and Discussion

Structure−Activity Relationships (Tables 1−5). 1. Lead Identification. After the identification of **4** as a possible prototype to design selective hNK-3 receptor ligands, three regions of the molecule were selected (Figure 2) to perform chemical modifications suitable to provide expedient and significant SAR information: (a) the carboxamide side chain, (b) the 7-OMe substituent, and (c) the 2-phenyl ring.

Either increasing or decreasing by one carbon atom the length of the carboxamide side chain did not affect significantly the hNK-3-CHO binding affinity (cf. compound **4** with **33** and **34**, Table 1). The benzylamide moiety (CONHBz) was therefore selected for further modifications. Carbonyl reduction (CH_2NHBz) or extrusion (NHBz) or, indeed, amide inversion (NHCOBz, data not shown) produced compounds with 7−12-fold lower affinity for the hNK-3 receptor (cf. **4** with **35** and **36**). Also the replacement of the benzylcarboxamide with the benzyl carbamate (NHCOOBz) moiety was detrimental (cf. **4** with **37**). Simple incorporation of an ester moiety (COOMe) at the benzylic position of **4** resulted in a 15-fold increase in affinity (cf. **38**, hNK-3-CHO binding K_i = 57 nM, with **4**). Hydrolysis to the corresponding carboxylic acid resulted in a 6-fold decreased affinity (cf. **4** with **39**), thus suggesting that an acidic functionality at this position is not tolerated. Removal of the 7-OMe substituent resulted in a 2.5-fold increase in binding affinity (cf. **4** with **40**). Replacement of the 2-phenyl ring by an aliphatic group (*e.g.*, Me, compound **42**) or benzylic group (compound **43**) produced inactive compounds (hNK-3-CHO binding K_i > 33 μM). Combination of both the introduction of the ester moiety and the removal of the 7-OMe substituent gave rise to compound **41** (hNK-3-CHO binding K_i = 31 nM), which had 28-fold higher affinity than **4** as a hNK-3 receptor ligand. Around this molecule, a chemical program was undertaken with the aim of optimizing hNK-3 binding affinity.

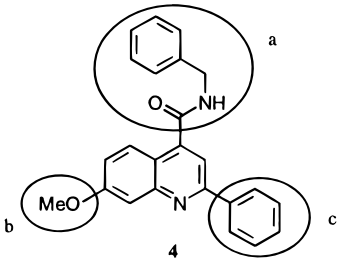
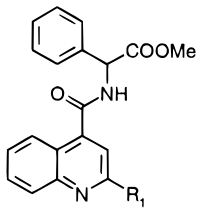


Figure 2. Regions of compound **4** selected to perform significant chemical modifications.

2. Lead Optimization. In addition to the 2-Me and 2-Bz substitutions (compounds **42** and **43**, Table 1), a further and exhaustive examination of the optimal steric, electronic, and lipophilic requirements of the substituent at position 2 of the quinoline system (Table 2) was undertaken.

Incorporation of the cyclohexyl moiety decreased the binding affinity by a factor of about 4 (cf. **41** with **44**), indicating that the aromaticity of the 2-substituent is important for optimal hNK-3 binding affinity. Within the (hetero)aromatic series, the sequence of potency was 3-thienyl = Ph ≥ 2-pyrryl ≥ 2-thienyl = 2-furyl > 3-pyrryl > 2-benzofuryl > 2-thiazolyl > 4-pyridyl (com-

Table 2. Physical Properties and Binding Affinity at Cloned Human Neurokinin-3 (hNK-3) Receptors Expressed in CHO Cells of Racemic Compounds **44**−**62** of General Formula II

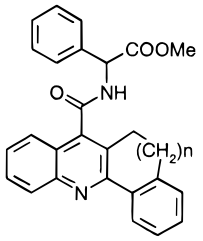


II

compd	R_1	formula	mp, °C	anal.	recryst solvent	hNK-3-CHO binding[a] K_i, mean ± SEM (nM)[b]
44	cyclohexyl	$C_{25}H_{26}N_2O_3$	151−153	C, H, N	EtOAc	132 ± 20
45	3-thienyl	$C_{23}H_{18}N_2O_3S$	169−171	C, H, N	*i*-PrOH	26 ± 3
46	2-pyrryl	$C_{23}H_{19}N_3O_3$	181−182	C, H, N	*i*-PrOH	49 ± 10
47	2-thienyl	$C_{23}H_{18}N_2O_3S$	188−189	C, H, N	EtOH	66 ± 5
48	2-furyl	$C_{23}H_{18}N_2O_4$	178−180	C, H, N	MeOH	77 ± 8
49	3-pyrryl	$C_{23}H_{19}N_3O_3$	202−203	C, H, N	*i*-Pr_2O	118 ± 11
50	2-benzofuryl	$C_{27}H_{20}N_2O_4$	240−241	C, H, N	EtOAc	377 ± 35
51	2-thiazolyl	$C_{22}H_{17}N_3O_3S$	209−211	C, H, N	*i*-PrOH	924 ± 330
52	4-pyridyl	$C_{24}H_{19}N_3O_3$	177−178	C, H, N	EtOAc	2226 (1)
53	Ph(2-F)	$C_{25}H_{19}FN_2O_3$	146−147	C, H, N	toluene	96 ± 12
54	Ph(2-Cl)	$C_{25}H_{19}ClN_2O_3$	175−178	C, H, N	toluene/hexane	2581 (1)
55	Ph(2-Me)	$C_{26}H_{22}N_2O_3$	180−182	C, H, N	*i*-PrOH	1235 (1)
56	Ph(2-OMe)	$C_{26}H_{22}N_2O_4$	124−125	C, H, N	toluene	786 (2)
57	Ph(2-OH)	$C_{25}H_{20}N_2O_4$	212−214	H, N; C[c]	*i*-PrOH	653 ± 274
58	Ph(3-Cl)	$C_{25}H_{19}ClN_2O_3$	161−163	C, H, N	toluene/hexane	629 ± 77
59	Ph(4-Cl)	$C_{25}H_{19}ClN_2O_3$	170−172	C, H, N	toluene/*i*-Pr_2O	820 ± 218
60	Ph(4-Me)	$C_{26}H_{22}N_2O_3$	172−174	C, H, N	*i*-PrOH	142 ± 33
61	Ph(4-OMe)	$C_{26}H_{22}N_2O_4$	182−183	C, H, N	*i*-PrOH	1853 (1)
62	Ph(4-OH)	$C_{25}H_{20}N_2O_4$	226−227	C, H, N	*i*-PrOH	493 ± 65

[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, 72.80; found, 71.65.

Table 3. Physical Properties and Binding Affinity at Cloned Human Neurokinin-3 (hNK-3) Receptors Expressed in CHO Cells of Racemic Compounds **63** and **64** of General Formula III



III

compd	n	formula	mp, °C	anal.	recryst solvent	hNK-3-CHO binding[a] K_i, mean ± SEM (nM)[b]
63	1	$C_{27}H_{22}N_2O_3$	217−219	C, H, N	EtOH	234 ± 13
64	2	$C_{28}H_{24}N_2O_3$	186−188	C, H, N	*i*-PrOH/*i*-Pr_2O	180 ± 8

[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.

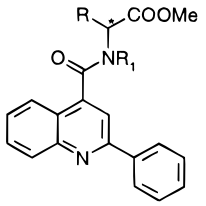
pounds **41** and **45**−**52**). The poor activity of the benzofuran system indicates that steric hindrance of the additional benzo-condensed ring is not tolerated (cf. **50** with **48**). Furthermore, incorporation of a basic nitrogen in the aromatic ring strongly reduced the hNK-3 binding affinity (cf. the pyridine derivative **52** with **41** and the thiazole **51** with the thiophenes **45** and **47** or pyrroles **46** and **48**). Introduction of substituents in any position of the 2-phenyl ring (irrespectively of their electronic and lipophilic nature) was, in general, not tolerated (see compounds **53**−**62**).

In addition, coplanarity of the 2-phenyl with the quinoline ring, obtained by cyclizing the *ortho* position of the phenyl with position 3 of the quinoline nucleus (compounds **63** and **64**, Table 3), appeared to be detrimental for activity; this suggests that the 2-phenyl substituent should be twisted out from the plane of the quinoline ring system.

The introduction of the methyl ester moiety in the benzylic position of the 4-amide chain (compound **41**) gave rise to a stereogenic center; preparation and testing of the two enantiomers revealed that the binding of this molecule to the hNK-3 receptor is enantioselective, the *R*-eutomer **65** (SB 218975; Table 4, hNK-3-CHO binding K_i = 13 nM) having 70-fold higher affinity than the *S*-distomer **66** (hNK-3-CHO binding K_i = 926 nM) and 2-fold higher affinity than the racemate **41**.

Within the lead optimization approach, the replacement/substitution of the phenyl ring of the amide side chain was also investigated (Table 4); the key role of

Table 4. Physical Properties and Binding Affinity at Cloned Human Neurokinin-3 (hNK-3) Receptors Expressed in CHO Cells of Compounds **41** and **65**−**72** of General Formula IV



IV

compd	*	R	R_1	formula	mp, °C	anal.	recryst solvent	$[\alpha]^{20}_D$ (c = 0.5, MeOH)	hNK-3-CHO binding[a] K_i, mean ± SEM (nM)[b]
41	*R*,*S*	Ph	H	$C_{25}H_{20}N_2O_3$	170−172	C, H, N	*i*-PrOH		31 ± 4
65	*R*	Ph	H	$C_{25}H_{20}N_2O_3$	180−181	C, H, N	*i*-PrOH	−42.0	13 ± 3
66	*S*	Ph	H	$C_{25}H_{20}N_2O_3$	180−181	C, H, N	*i*-PrOH	+42.0	926 ± 250
67	*R*	$CH(Me_2)$	H	$C_{22}H_{22}N_2O_3$	115−117	C, H, N	*i*-PrOH	+28.6	6208 (2)
68	*R*,*S*	CH_2Ph	H	$C_{26}H_{22}N_2O_3$	152−154	C, H, N	EtOAc		1154 (1)
69	*R*	Ph(4-OH)	H	$C_{25}H_{20}N_2O_4$	140 dec	C, H, N; Cl[c]	Me_2CO	−7.0	1926 (1)
70	*R*	Ph(4-OMe)	H	$C_{26}H_{22}N_2O_4$	160−162	C, H, N	Et_2O	nd	666 ± 165
71	*R*,*S*	2-thienyl	H	$C_{23}H_{18}N_2O_3S$	144−145	C, H, N	EtOAc		180 ± 49
72	*R*,*S*	Ph	Me	$C_{26}H_{22}N_2O_3$	128−129	C, H, N	*i*-PrOH		1078 ± 388

[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] Cl: calcd, 7.90; found, 7.48.

Table 5. Binding Affinity at Cloned Human Neurokinin-3 (hNK-3) Receptors Expressed in CHO Cells of Racemic Compounds **73**−**76** in Figure 3

compd	hNK-3-CHO binding[a] K_i, mean ± SEM (nM)[b]
73	>10000 (1)
74	1202 (2)
75	>10000 (1)
76	883 (2)

[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.

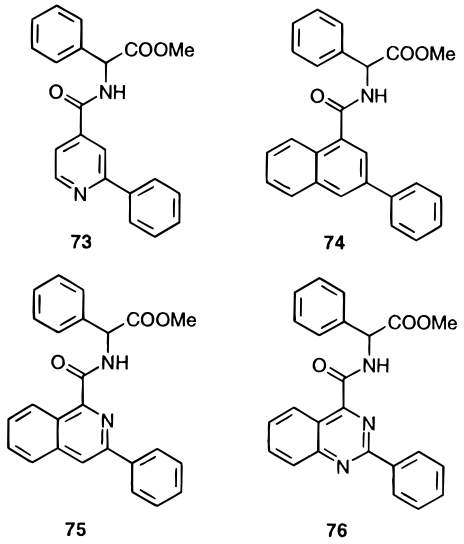


Figure 3. Chemical structures of compounds **73**−**76** in Table 5.

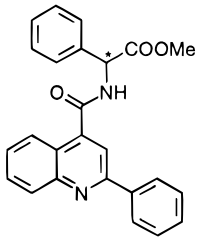
the aromatic ring and the precise distance between its centroid and the amidic nitrogen were assessed and confirmed by the replacement of the phenyl with the isopropyl moiety (cf. compound **67** with **65**) and by the incorporation of an additional methylene group (cf. **68** with **41**). The latter was suggested by the similar hNK-3 binding affinities obtained with compounds **4** and **33** (Table 1) in the unsubstituted series; in this case a 37-fold decrease in affinity was observed with the introduction of a methylene spacer. Also the incorporation into the phenyl ring of 4-OH (**69**) and 4-OMe (**70**) substituents was detrimental. The hNK-3 binding affinity decreased 6-fold when the phenyl ring was replaced by its bioisosteric thiophene (compound **71**).

The importance of the presence of an amidic hydrogen was assessed by the synthesis and evaluation of the corresponding NMe tertiary amide **72** (Table 4), which had a 35-fold lower affinity than the parent **41**. A possible explanation for this might be the capability of the secondary amidic hydrogen to interact with a hydrogen bond acceptor in the binding site of the NK-3 receptor, or in the case of the tertiary amide, the methyl group might determine an unfavorable steric interaction with the receptor.

Preliminary results of a medicinal chemistry approach aimed at replacing the quinoline ring with various (hetero)aromatic systems are reported in Table 5; all the compounds prepared (*i.e.*, the pyridine **73**, the naphthalene **74**, the isoquinoline **75**, and the quinazoline derivative **76**, Figure 3) showed a dramatically reduced hNK-3 binding affinity with respect to the parent quinoline **41**. These results suggest that both the benzene-condensed ring and the quinoline nitrogen are key determinants for optimal binding affinity to hNK-3 receptors. The inactivity of the isoquinoline derivative **75** and the poor activity of the quinazoline **76** could be due to the presence of the isoquinoline nitrogen, which may negatively interact with a charged site in the receptor or negatively affect the conformation of the 4-carboxamide side chain. Other modifications in this regard, including imidazopyridine, pyrazinopyridine, and indole derivatives, are in progress, and biological data will be presented in a future publication.

Selectivity and *in Vitro* Functional Activity (Table 6). The selectivity versus the other tachykinin receptors of one of the most potent hNK-3 receptor ligand identified in the SAR section, the *R*-enantiomer **65**, along with that of its *S*-enatiomer **66** and the racemate **41**, was assessed by competitive binding experiments using membranes prepared from CHO cells stably expressing the hNK-2 (hNK-2-CHO) and hNK-1

Table 6. Binding Affinities at Cloned Human Neurokinin Receptors (hNK-1, hNK-2, and hNK-3) Expressed in CHO Cells and *in Vitro* Functional Activities (Antagonism of senktide-induced contractions) in Rabbit Isolated Iris Sphincter (RIS) Muscle Preparation for Compounds **41**, **65**, and **66**



compd	*	binding affinities K_i, mean ± SEM (nM)[a] hNK-3[b]	hNK-2[c]	hNK-1[d]	antagonism of senktide-induced contractions in RIS muscle K_b,[e] mean ± SEM (nM)[a]
41	*R,S*	31 ± 4	2947 ± 585	>100000	42 ± 12
65 (SB 218795)	*R*	13 ± 3	1221 ± 189	>100000	43 ± 6.2
66	*S*	926 ± 250	8333 ± 926	>100000	3982 (2)

[a] Average of three to five independent determinations ($n = 3-5$), unless otherwise indicated in parentheses. [b] Inhibition of [^{125}I]MePhe^7-NKB binding in hNK-3-CHO cell membranes. [c] Inhibition of [^{125}I]NKA binding in hNK-2-CHO cell membranes. [d] Inhibition of [^{3}H]substance P binding in hNK-1-CHO cell membranes. [e] 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.

(hNK-1-CHO) and [^{125}I]NKA and [^{3}H]substance P, respectively. The results, summarized in Table 6, clearly demonstrate that the racemate **41** and the *R*-eutomer **65** have no affinity for the hNK-1 receptors (hNK-1-CHO binding K_i > 100 μM) and moderate affinity for the hNK-2 receptors (hNK-2-CHO binding K_is = 2947 and 1221 nM, respectively), thus resulting in a 90-fold selectivity for hNK-3 versus hNK-2 receptors.

Compounds **41** and **65** were demonstrated *in vitro* to be functional antagonists of senktide-induced contractions in the rabbit isolated iris sphincter muscle, a preparation rich in NK-3 receptors.[49] Senktide was a potent contractile agonist in this preparation with a pD_2 = 9.1 ± 0.1 (n = 4).[50] Compound **65** at a concentration of 10 nM surmountably antagonized the contractile responses to senktide with a K_b = 43 nM (Table 6). In addition, the enantioselectivity for the hNK-3 receptor, demonstrated in the binding studies for enantiomers **65** and **66**, was confirmed by the *in vitro* functional data; compound **65** was found to be 90-fold more potent than its poorly active counterpart **66** (K_b = 3982 nM).

Conclusions

In this study the design and synthesis of a novel class of potent and selective non-peptide NK-3 receptor antagonists are described in detail. The moderately potent hNK-3 receptor ligand **4** was identified starting from the potent NK-1 receptor antagonists CP 96,345, RP 67,580, and CP 99,994. From among the diverse chemical modifications performed on the 2-phenylquinoline-4-carboxamide skeleton of the prototype **4** (Tables 1−5), the following important features emerged as crucial determinants for optimal hNK-3 binding affinity: (i) the presence of the (benzylamino)carbonyl moiety (CONHBz, Table 1), (ii) the absence of the 7-OMe substituent (Table 1), (iii) the incorporation of COOMe at the benzylic position (Table 1), (iv) the presence of the unsubstituted phenyl ring in position 2 (Tables 1−3), (v) the stereogenic center of the 4-amide side chain in the *R* configuration (Table 4), (vi) the presence of the unsubstituted phenyl ring in the amide side chain (Table 4), (vii) the secondary amide at position 4 (Table 4), and (viii) the presence of the quinoline ring (Table 5).

Compounds **41**, **65**, and **66** were also evaluated for their selectivity for the three tachykinin receptors (NK-1, NK-2, and NK-3) and *in vitro* functional activity (Table 6). Binding results indicated that (*R*)-*N*-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide (**65**) is about 90-fold selective for the hNK-3 receptor (hNK-3-CHO binding K_i = 13 nM) versus the hNK-2 receptor (hNK-2-CHO binding K_i = 1221 nM) and over 7000-fold selective for the hNK-3 versus the hNK-1 receptor (hNK-1-CHO binding K_i = >100 μM). Functional studies in rabbit isolated iris sphincter muscle preparation revealed that compound **65** is a competitive antagonist of the contractile response induced by the potent and selective NK-3 receptor agonist senktide, with a K_b = 43 nM. Overall, the data indicate that **65** (SB 218795) is a potent and selective hNK-3 receptor antagonist and that compounds emanating from the 2-phenylquinoline-4-carboxamide series may represent suitable leads for further chemical optimization. Chemical modifications aimed at (a) replacing the methyl ester group (potentially metabolically unstable) and (b) optimizing the hNK-3 binding affinity, *in vitro* functional activity, and selectivity versus the hNK-2 receptor (based, essentially, on substitutions at the quinoline ring) are the subject of a publication in preparation.

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 humidified incubator under 5% CO_2−95% air in 1017 SO3 (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) and then rapidly frozen and thawed (three times) followed by Dounce homogenization for preparation of crude membranes.

For NK-3 receptor competition binding studies,[45] membranes (~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 What-

man 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 cocktail, and counted in a Beckman LS 6000 (Fullerton, CA) liquid scintillation counter.

For NK-2 competition binding studies,[47] cells were grown and membranes were prepared as described above for the hNK-3 binding assay. The assay buffer was the same as that utilized for the hNK-3 binding assay with a total volume of 150 μL, ~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,[48] 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.

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 are 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 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). Gas chromatographic (GC) analyses were run on a Hewlett Packard 5890 A gas chromatograph (column: Supelco 2-5315 SPB-1, 30 m × 0.53 mm, 0.50 μm film). 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).

Synthesis of Known Intermediates. 6-Methoxyisatin (**5a′**) was prepared according to Mangini and Passerini;[52] *N*-(methylphenyl)gycine was synthesized as described by O'Donnell *et al.*,[33] and all the α-amino acids were converted to the corresponding α-amino methyl esters·HCl by refluxing in MeOH in the presence of 1.7 equiv of $SOCl_2$. 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. Isatin (**5a**), ketones **6a**−**x**, 2-phenylquinoline-4-carboxylic acid (**7a**), aniline, 2-phenylethylamine, (*R*,*S*)-, (*R*)-, and (*S*)-phenylglycine, (*R*)-valine, (*R*)-(4-hydroxyphenyl)glycine, (*R*,*S*)-2-thienylglycine, ethyl 3-oxo-3-phenylpropionate (**12**), α-bromoacetophenone (**18**), 1,3-diphenylacetone (**21**), deoxybenzoin (**25**), benzanilide (**30**), and all reagents utilized in Schemes 1−7 are commercially available compounds and were used without further purification. Activated manganese(IV) oxide (MnO_2; <5 μm, ca. 85%) was supplied by Aldrich Chemical Co. and used without further activation.

General Procedure for the Pfitzinger Reaction[30] To Obtain 2-Phenylquinoline-4-carboxylic Acids 7a−x in Scheme 1. Isatins **5a**,**a′** (34.0 mmol), the appropriate ketone of formula **6a**−**x** (40.8 mmol), and 85% KOH pellets (102 mmol) were dissolved in EtOH (40 mL), and the reaction mixture was stirred at 80 °C for 24−72 h. Evaporation of the solvent afforded a residue which was dissolved in H_2O (50 mL), and the solution was washed twice with Et_2O (30 mL). The ice-cold aqueous phase was acidified to pH 1 with 37% HCl, and the precipitate was collected by suction filtration, washed with H_2O, and dried. Typically, yields of this reaction were about 90%, and compounds of formula **7a**−**x**[31] were triturated with *i*-Pr_2O and recrystallized from EtOH. As an example, spectroscopic data for **7a′** are reported: mp 226−228 °C; IR (KBr) 3440 br, 1630, 1600, 1240 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.59 (d, J = 9.1 Hz, 1H), 8.29 (s, 1H), 8.27 (dd, J = 7.5, 1.0 Hz, 2H), 7.61−7.50 (m, 3H), 7.55 (s, 1H), 7.36 (dd, J = 9.1, 2.8 Hz, 1H), 3.98 (s, 3H); FAB-MS (positive, matrix NBA, gas Xe, 8 keV, source 50 °C) *m*/*z* 280 (MH^+).

General Procedures To Obtain 2-Phenylquinoline-4-carboxamides 4, 33, 34, 38, 40−69, 71, and 72 of General Formulae I−IV in Tables 1−4. Method A: *Via* Acyl Chloride. 2-Phenylquinoline-4-carboxylic acids **7a**,**a′**−**c′**,**g**,**h**,**j**,**l**−**n**,**p**,**r** (7.9 mmol) were suspended in CH_2Cl_2 (30 mL), and oxalyl chloride (13.4 mmol) was added dropwise to the ice-cold reaction mixture; the stirring was continued at 0−5 °C for 1 h and then at room temperature overnight. Evaporation of the solvent afforded the crude acid chloride which was dissolved in dry DMF (40 mL) and added dropwise, at 0 °C, to a stirred suspension of the appropriate primary amine or α-amino ester·HCl (15.8 mmol) in dry DMF (15 mL), containing anhydrous K_2CO_3 (15.8 mmol). After 24 h the reaction mixture was filtered, the solvent evaporated, and the residue, taken up in water, extracted with EtOAc, and the organic layer was washed with H_2O, 5% citric acid, 5% $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated to dryness. The crude amide was triturated with toluene or *i*-Pr_2O and recrystallized from the appropriate solvent, affording the desired compounds in 68−85% yield. This method was always used in the case of primary amines and, occasionally, with α-amino esters·HCl to obtain the corresponding amides **4**, **33**, **34**, **38**, **40**, **42**, **43**, **47**, **48**, **50**, **52**, **53**, **54**, **56**, **58**, **68**, and **71**.

Method B: *Via* DCC/HOBT. 2-Phenylquinoline-4-carboxylic acids **7a**,**d**−**f**,**i**,**k**,**o**,**q**,**s**−**x** (8.0 mmol) were dissolved in a 7:3 mixture of THF/MeCN (200 mL), and the appropriate α-amino ester·HCl (9.8 mmol) was added along with *N*-methylmorpholine or triethylamine (TEA) (10.7 mmol) and 1-hydroxybenzotriazole (HOBT) (12.1 mmol); the reaction mixture was cooled to −5 °C, and dicyclohexylcarbodiimide (DCC) (12.1 mmol), dissolved in THF (10 mL), was added dropwise; the reaction mixture was kept at 0−5 °C for 1 h and then allowed to reach room temperature and left overnight. The precipitated dicyclohexylurea was filtered off and the filtrate evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O, 5% citric acid, 5% $NaHCO_3$, and brine. The separated organic layer was dried over Na_2SO_4 and evaporated to dryness; the residue was dissolved in CH_2Cl_2 (20 mL), and after overnight standing some more dicyclohexylurea precipitated and was filtered off. The solution was evaporated to dryness, and the crude product was triturated with *i*-Pr_2O and recrystallized from the appropriate solvent, affording the desired compounds in about 80% yield. This method was used with racemic α-amino esters to obtain the corresponding racemic amides **41**, **44**−**46**, **49**, **51**, **55**, **57**, **59**−**64**, **67**, **69**, and **72**; no significant difference in yields was found between methods A and B. Method B was also employed to prepare enantiomerically pure secondary amides **65** and **66** starting from compound **7a** and (*R*)- and (*S*)-methyl phenylglycinate, respectively. As an example, spectroscopic data for compound **65** are reported: mp 180−181 °C (from *i*-PrOH); $[\alpha]^{20}_D$ (c = 0.5, MeOH) = −42.0; IR (Nujol) 3300, 1750, 1640 cm^{-1}; ^{1}H 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, 6H), 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.

Enantiomeric excess of **65** and **66** was determined by chiral HPLC eluting the compounds on Daicel Chiralcel OC column (10 μm, 4.6 × 250 mm; 1.0 mL/min, UV 220) with a unique mobile phase consisting of 60% hexane, 40% EtOH, and 0.1% Et_3N; both enantiomers **65** and **66** had enantiomeric excess greater than 99%. Combustion elemental analyses of compounds **4**, **33**, **34**, **38**, **40**−**69**, **71**, and **72** of general formulae I−IV in Tables 1−4 agreed with calculated data within ±0.4%

unless otherwise indicated in footnotes to the tables. Detailed spectroscopic data for compounds **4**, **33**, **34**, and **38**−**72** are given in the Supporting Information.

4-(Hydroxymethyl)-7-methoxy-2-phenylquinoline (9). The acyl chloride **8** was prepared by method A, starting from **7a′** (50.4 mmol) and oxalyl chloride (85.7 mmol). Crude **8** was suspended, under nitrogen atmosphere, in THF (300 mL), the reaction mixture was cooled to −78 °C, and lithium tri-*tert*-butoxyaluminum hydride (1 M solution in THF, 80 mL) was added dropwise maintaining the temperature below −70 °C. After 2 h at −70 °C, the reaction mixture was stirred at room temperature overnight and ice-cooled and the reaction quenched with H_2O (150 mL). After evaporation of THF, CH_2Cl_2 (150 mL) was added, the mixture was filtered, and the organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. Compound **9** (31.3 mmol, 62%) was obtained as a white solid: mp 165−168 °C; IR (KBr) 3180 br, 1620, 1600, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.14 (dd, J = 6.6, 1.0 Hz, 2H), 7.85 (d, J = 9.0 Hz, 1H), 7.84 (s, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.52−7.42 (m, 3H), 7.20 (dd, J = 9.0, 2.5 Hz, 1H), 5.20 (s, 2H), 3.98 (s, 3H), 1.60 (s br, 1H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 265 ($M^{\bullet+}$), 264, 236.

7-Methoxy-2-phenylquinoline-4-carboxaldehyde (10). MnO_2 (92.0 mmol) was suspended in CH_2Cl_2 (300 mL); 4-(hydroxymethyl)-7-methoxy-2-phenylquinoline (**9**; 27.1 mmol), dissolved in CH_2Cl_2 (1000 mL), was added dropwise, and the reaction mixture was stirred at room temperature for 48 h. Additional MnO_2 (80.5 mmol) was added portionwise during a period of 4 days. The reaction mixture was filtered on a Celite pad, evaporated to dryness, and triturated with *i*-Pr_2O to yield **10** (22.4 mmol, 83%) as a pale yellow solid: mp 124−126 °C; IR (KBr) 2960, 1710, 1620, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.52 (s, 1H), 8.87 (d, J = 9.5 Hz, 1H), 8.21 (dd, J = 6.1, 1.1 Hz, 2H), 8.11 (s, 1H), 7.59 (d, J = 2.8 Hz, 1H), 7.58−7.48 (m, 3H), 7.34 (dd, J = 9.5, 2.8 Hz, 1H), 4.00 (s, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 263 ($M^{\bullet+}$), 248, 243, 235, 220.

4-[(Benzylamino)methyl]-7-methoxy-2-phenylquinoline Dihydrochloride (35). 7-Methoxy-2-phenylquinoline-4-carboxaldehyde (**10**; 3.8 mmol), benzylamine (4.1 mmol), and toluene (30 mL) were refluxed in a Dean−Stark apparatus with a catalytic amount of PTSA for 3 days. Formation of **11** was followed by GC. After removal of the solvent, **11** was obtained and used without further purification. Crude **11** was dissolved in AcOH (60 mL), and sodium triacetoxyborohydride (9.4 mmol) was added portionwise in 15 min, maintaining the temperature at 20 °C. The reaction mixture was maintained at room temperature for 24 h, then the solvent was evaporated to dryness, and the crude material was dissolved in CH_2Cl_2 and washed with 5% $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, evaporated to dryness, and purified by flash column chromatography on silica gel. The crude product was dissolved in Et_2O, acidified with HCl/Et_2O; the precipitate was collected and recrystallized from *i*-PrOH to yield **35** (1.4 mmol, 37% overall yield) as a pale yellow solid: mp 216−218 °C; IR (KBr) 3460 br, 2720 br, 1632, 1601, 1235 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.00 (s br, 2H), 8.35 (s, 1H), 8.30 (dd, 2H), 8.13 (d, 1H), 7.69−7.53 (m, 6H), 7.47−7.42 (m, 4H), 7.36 (dd, 1H), 4.79 (t, 2H), 4.39 (t, 2H), 4.00 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 354 ($M^{\bullet+}$), 249, 91. Anal. ($C_{24}H_{22}N_2O\cdot 2HCl$) H, N; C: calcd, 67.45; found, 66.80.

3-Oxo-3-phenylpropionamide (13). Ethyl 3-oxo-3-phenylpropionate (**12**; 0.17 mol) was heated with 32% NH_4OH in a steel autoclave at 85 °C for 2 h; the precipitated iminoamide was recovered by suction filtration and refluxed for 4 h in water; the precipitate was filtered and recrystallized from water, affording the pure amide **13** (0.14 mol, 81%): mp 110−111 °C (lit.[53] mp 111−113 °C).

4-Hydroxy-7-methoxy-2-phenylquinoline (16). Compound **13** (0.14 mol) was refluxed in a Dean−Stark apparatus with *m*-anisidine (0.14 mol) and *m*-anisidine·HCl (catalytic) in toluene (300 mL) for 8 h. Formation of imine **14** was followed by GC; the reaction mixture was concentrated to one-half volume, and **14** crystallized on standing; the crude imine intermediate was filtered, mixed with PPA (200 g), and heated to 135 °C for 20 min. The reaction mixture was poured into water and carefully adjusted to pH 8 with 20% NaOH; the precipitated mixture of compounds **15** and **16** was collected by suction filtration; pure **16** (47.5 mmol, overall 34%) was obtained by repeated washing with hot MeOH: mp >250 °C; ^1H NMR (DMSO-d_6) δ 8.00 (d, J = 8.0 Hz, 1H), 7.85−7.79 (m, 2H), 7.61−7.55 (m, 3H), 7.21 (d, J = 2.8 Hz, 1H), 6.92 (dd, J = 8.0, 2.8 Hz, 1H), 6.28 (s, 1H), 3.88 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 251 ($M^{\bullet+}$), 208.

From the concentrated methanolic mother liquor, the regioisomer **15** (32.0 mmol, 23%) crystallized on standing: mp 217−220 °C; ^1H NMR (DMSO-d_6) δ 7.84 (m, 2H), 7.60−7.50 (m, 5H), 7.33 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.33 (s br, 1H), 3.82 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 251 ($M^{\bullet+}$), 208.

4-Chloro-7-methoxy-2-phenylquinoline (17). 4-Hydroxy-7-methoxy-2-phenylquinoline (**16**; 43.6 mmol) was refluxed in $POCl_3$ (120 mL) for 2 h; the solvent was evaporated, and the residue was taken up with 10% NaOH and extracted with EtOAc; the organic layer was dried over Na_2SO_4 and the solvent evaporated to afford **17** (29.6 mmol, 68%): mp 99−100 °C; IR (Nujol) 1620, 1591, 1579, 1214 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.29 (m, 2H), 8.20 (s, 1H), 8.10 (d, J = 9.6 Hz, 1H), 7.59−7.50 (m, 4H), 7.39 (dd, J = 9.6, 2.5 Hz, 1H), 4.00 (s, 3H); ESI-MS (A positive, solvent methanol, spray 4.5 keV, skimmer 60 eV, capillary 220 °C) m/z 270 (MH^+); ESI-MS (B DAU$^+$ 270, collision gas Ar) m/z 227, 191, 165, 149, 114, 89.

4-(Benzylamino)-7-methoxy-2-phenylquinoline (36). A mixture of 4-chloro-7-methoxy-2-phenylquinoline (**17**; 3.7 mmol), benzylamine (3.7 mmol), and phenol (4.6 g) was heated at 150 °C for 3 h; after cooling, CH_2Cl_2 (20 mL) and 0.1 N NaOH (20 mL) were added to the reaction mixture; the organic layer was washed with 0.1 N NaOH until disappearance of phenol, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography, by eluting with CH_2Cl_2/MeOH/28% NH_4OH, 94:2:0.2, respectively. The resulting solid was crystallized from Et_2O, affording **36** (2.5 mmol, 67%): mp 171−174 °C; IR (KBr) 3260 br, 1620, 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.21 (d, J = 9.0 Hz, 1H), 8.02 (dd, J = 7.5, 0.9 Hz, 2H), 7.85 (t, J = 6.0 Hz, 1H), 7.48−7.40 (m, 5H), 7.35 (dd, J = 7.5, 7.5 Hz, 2H), 7.26 (d, J = 2.8 Hz, 1H), 7.22 (dd, J = 7.5, 7.5 Hz, 1H), 7.08 (dd, J = 9.0, 2.8 Hz, 1H), 6.80 (s, 1H), 4.67 (d, J = 6.0 Hz, 1H), 3.90 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 340 ($M^{\bullet+}$), 91. Anal. ($C_{23}H_{20}N_2O$) H, N; C: calcd, 81.15; found, 80.66.

***N*-(Benzyloxycarbonyl)-4-amino-7-methoxy-2-phenylquinoline (37).** 7-Methoxy-2-phenylquinoline-4-carboxylic acid (**7a′**; 59.1 mmol), DPPA (59.1 mmol), and TEA (59.1 mmol) were heated at 80 °C for 20 h in $PhCH_2OH$ (160 mL).[32] Evaporation of the solvent afforded a residue which was taken up in 5% $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/hexane (1:1), affording **37** (27.8 mmol, 47%) which was crystallized from EtOAc: mp 156−158 °C; IR (KBr) 3475, 1750, 1620, 1570, 1540, 1505, 1210 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.20 (s, 1H), 8.39 (s, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.13 (dd, J = 9.0, 1.7 Hz, 2H), 7.58−7.48 (m, 5H), 7.47−7.36 (m, 3H), 7.43 (s, 1H), 7.20 (dd, J = 9.0, 2.5 Hz, 1H), 5.28 (s, 2H), 3.92 (s, 3H); EI-MS (source 180 °C, 70 eV, 200 mA) m/z 384 ($M^{\bullet+}$), 276, 91, 77. Anal. ($C_{24}H_{20}N_2O_3$) C, H, N.

(*R,S*)-*N*-(α-Carboxybenzyl)-7-methoxy-2-phenylquinoline-4-carboxamide Hydrochloride (39). (*R,S*)-*N*-[α-(Methoxycarbonyl)benzyl]-7-methoxy-2-phenylquinoline-4-carboxamide (**38**; 0.40 mmol) was refluxed in 10 mL of 10% HCl and 5 mL of dioxane for 3 h; then the solvent was evaporated to dryness. Crystallization from EtOAc (containing a few drops of EtOH) afforded **39** (0.35 mmol, 89%): mp 228−230 °C; IR (KBr) 3180, 1735, 1655, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.6 (d, 1H), 8.26 (dd, 2H), 8.14 (d, 1H), 7.98 (s, 1H), 7.63−7.52 (m, 6H), 7.46−7.36 (m, 3H), 7.33 (dd, 1H), 5.66 (d, 1H), 3.98 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 412 ($M^{\bullet+}$), 368, 262, 234, 191, 77. Anal. ($C_{25}H_{20}N_2O_4\cdot HCl$) C, H, N.

(*R*)-*N*-[α-(Methoxycarbonyl)-4-methoxybenzyl]-2-phenylquinoline-4-carboxamide (70). (*R*)-*N*-[α-(Methoxycarbonyl)-4-hydroxybenzyl]-2-phenylquinoline-4-carboxamide (**69**; 1.5 mmol) was dissolved in 30 mL of dry acetone and 2 mL of dry DMF, and the solution was stirred for 30 min in

the presence of anhydrous K_2CO_3 (0.75 mmol); MeI (1.5 mmol) was added and the reaction mixture heated to 40 °C for 4 h; after cooling, anhydrous K_2CO_3 (0.75 mmol) and MeI (1.5 mmol) were added again, and the mixture was refluxed for an additional 6 h. The mixture was evaporated to dryness, dissolved in EtOAc, and washed with brine. The organic layer, dried over Na_2SO_4, was evaporated to dryness. The residue was crystallized from Et_2O affording **70** (1.06 mmol, 70%): mp 160−162 °C; IR (KBr) 3210, 1750, 1635, 1625, 1590, 1530, 1515 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.65 (d, 1H), 8.28 (d, 2H), 8.21 (d, 1H), 8.14 (d, 1H), 8.10 (s, 1H), 7.84 (dd, 1H), 7.67 (dd, 1H), 7.61−7.49 (m, 3H), 7.44 (d, 2H), 6.98 (d, 2H), 4.70 (d, 1H), 3.79 (s, 3H), 3.76 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) *m/z* 426 ($M^{\bullet+}$), 367, 232, 204. Anal. ($C_{26}H_{22}N_2O_4$) C, H, N.

4-Phenyloxazole (19).[34] A mixture of α-bromoacetophenone (**18**; 100.5 mmol), $HCOONH_4$ (348.8 mmol), and 98% HCOOH (106.5 mL) was refluxed under stirring for 2.5 h. The reaction mixture was poured into water, made alkaline with concentrated NaOH, and extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The crude product obtained was purified by flash column chromatography on silica gel, eluting with a mixture of EtOAc/hexane (3:7), to afford **19** (15.8 mmol, 16%) as a yellow oil: IR (neat) 3120, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (m, 2H), 7.75 (d, J = 7.5 Hz, 2H), 7.42 (dd, J = 7.5, 7.5 Hz, 2H), 7.33 (dd, J = 7.5, 7.5 Hz, 1H); EI-MS (source 200 °C, 70 eV, 200 mA) *m/z* 145 ($M^{\bullet+}$), 90, 41.

2-Phenylpyridine-4-carboxylic Acid (20).[35] A mixture of 4-phenyloxazole (**19**; 13.8 mmol) and maleic acid (14.2 mmol) was heated at 110 °C until melting for 15 min. The solid obtained after cooling was triturated with Et_2O, collected by suction filtration, suspended in a mixture of H_2O and MeOH, and acidified to pH 1 with 20% HCl. The solvent was removed by decantation, and the solid was stirred in EtOAc for 1 week and then recrystallized with 95% EtOH to yield **20** (2.5 mmol, 18%) as an off-white solid: mp 266−268 °C; IR (KBr) 3300, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.76 (dt, J = 4 Hz, 1H), 8.20 (s, 1H), 8.35−7.45 (m, 5H), 7.71 (dt, J = 4 Hz, 1H); FAB-MS (negative, matrix diethanolamine, gas Xe, 8 keV, source 50 °C) *m/z* 198 ($M - H^-$).

***(R,S)-N*-[α-(Methoxycarbonyl)benzyl]-2-phenylpyridine-4-carboxamide (73).** A mixture of 2-phenylpyridine-4-carboxylic acid (**20**; 2.4 mmol), (*R,S*)-methyl phenylglycinate·HCl (2.5 mmol), 1-hydroxybenzotriazole (4.8 mmol), *N*-methylmorpholine (5.4 mmol), THF (35 mL), and CH_3CN (15 mL) was cooled to 0 °C under nitrogen atmosphere; DCC (2.7 mmol), dissolved in THF (3 mL), was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The precipitate was filtered off, and the solvent was evaporated to dryness. The residue was dissolved in CH_2Cl_2, washed with H_2O, 20% citric acid, 5% $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel, eluting with a mixture of hexane/EtOAc/28% NH_4OH (60:40:0.5), respectively, and then washed with *i*-Pr_2O and recrystallized with *i*-PrOH to yield **73** (0.3 mmol, 12%) as a white solid: mp 139−141 °C; IR (KBr) 3290, 1750, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.60 (d, J = 6.8 Hz, 1H), 8.82 (d, J = 4.5 Hz, 1H), 8.37 (s, 1H), 8.14 (dd, J = 7.5, 0.8 Hz, 2H), 7.77 (dd, J = 4.5, 1.6 Hz, 1H), 7.57−7.37 (m, 8H), 5.73 (d, J = 6.8 Hz, 1H), 3.70 (s, 3H); TSP-MS (DAU^+ 347, −9 eV, collision gas Ar) *m/z* 347 (MH^+), 155. Anal. ($C_{26}H_{21}NO_3$) C, H, N.

***N*-(Dimethylamino)-2-phenyl-4-naphthalenecarboxamide (23).**[36] Diphenylacetone (**21**; 23.8 mmol) and *N,N*-dimethylformamide dimethyl acetal (**22**; 0.15 mol) were heated in a steel autoclave at 180 °C for 24 h under nitrogen atmosphere; the reaction mixture was then diluted with a mixture of Et_2O/hexane (1:5) and stirred for 1 h. The precipitate was filtered, washed with hexane, and dried to afford **23** (14.9 mmol, 63%) as white needles: 137−138 °C (lit.[36] mp 136−138 °C); IR (KBr) 1635, 1490, 1410, 890 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.29 (s, 1H), 8.07 (m, 1H), 7.85 (d, J = 7.4 Hz, 2H), 7.77 (d, J = 1.6 Hz, 1H), 7.73 (m, 1H), 7.63−7.56 (m, 2H), 7.52 (dd, J = 7.4, 7.4 Hz, 2H), 7.42 (dd, J = 7.4, 7.4 Hz, 1H), 3.13 (s, 3H), 2.80 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) *m/z* 275 ($M^{\bullet+}$), 231, 202.

2-Phenyl-4-naphthalenecarboxylic Acid (24). *N*-(Dimethylamino)-2-phenyl-4-naphthalenecarboxamide (**23**; 7.3 mmol) and 85% KOH pellets (21.4 mmol) were heated in ethylene glycol (20 mL) at 200 °C for 16 h; the mixture was then carefully diluted with a solution of 40% citric acid and extracted with EtOAc; the organic layer was washed with brine and dried over Na_2SO_4 and the solvent evaporated to dryness to afford **24** (7.2 mmol, 98%) as a white solid: mp 215−218 °C; IR (KBr) 2450, 1695, 1260, 765 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.05 (s br, 1H), 8.85 (m, 1H), 8.47 (d, J = 2.0 Hz, 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.11 (m, 1H), 7.84 (d, J = 7.0 Hz, 2H), 7.69−7.59 (m, 2H), 7.55 (dd, J = 7.0, 7.0 Hz, 2H), 7.45 (dd, J = 7.0, 7.0 Hz, 1H); EI-MS (source 200 °C, 70 eV, 200 mA) *m/z* 248 ($M^{\bullet+}$), 231, 202.

***N*-[α-(Methoxycarbonyl)benzyl]-2-phenylnaphthalene-4-carboxamide (74).** A mixture of **24** (6.8 mmol), (*R,S*)-methyl phenylglycinate·HCl (10.3 mmol), 1-hydroxybenzotriazole (10.3 mmol), TEA (17.0 mmol), THF (70 mL), and CH_3CN (30 mL) was cooled, under nitrogen atmosphere, to 0 °C. DCC (10.3 mmol), dissolved in THF (20 mL), was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight; 20% citric acid (20 mL) was added, and the reaction mixture was stirred for 2 h and filtered; the filtrate was evaporated to dryness, dissolved in Et_2O, and washed with 20% citric acid, 5% $NaHCO_3$, and brine; the organic layer was dried over Na_2SO_4 and the solvent evaporated to dryness. The crude product was crystallized from toluene to afford **74** (4.3 mmol, 63%) as white crystals: mp 141−143 °C; IR (KBr) 3310, 1755, 1640, 1600, 1520, 770 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.53 (d, J = 7.0 Hz, 1H), 8.33 (d, J = 1.6 Hz, 1H), 8.26 (m, 1H), 8.07 (m, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.86 (d, J = 7.0 Hz, 2H), 7.62−7.52 (m, 6H), 7.45−7.36 (m, 4H), 5.80 (d, J = 7.0 Hz, 1H), 3.75 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) *m/z* 395 ($M^{\bullet+}$), 336, 231, 202. Anal. ($C_{26}H_{21}NO_3$) C, H, N.

1-Methyl-3-phenylisoquinoline (27).[37] Deoxybenzoin (**25**; 25.5 mmol) was dissolved in CH_3CN (200 mL), and $POCl_3$ (15.6 mL) was added dropwise at room temperature. The reaction mixture was refluxed for 29 h and then evaporated to dryness. The crude product was dissolved in H_2O, made alkaline with 2 N NaOH, and extracted with CH_2Cl_2; the organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel eluting with a mixture of CH_2Cl_2/hexane (65:35) to afford **27** (5.9 mmol, 23%) as a pale yellow oil: IR (neat) 3050, 1620, 1590, 1570 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.26−8.21 (m, 4H), 8.01 (dd, J = 8.3, 1.2 Hz, 1H), 7.77 (ddd, J = 8.3, 8.3, 1.2 Hz, 1H), 7.65 (ddd, J = 8.3, 8.3, 1.2 Hz, 1H), 7.52 (dd, J = 7.5, 7.5 Hz, 2H), 7.41 (dd, J = 7.5, 7.5 Hz, 1H), 2.95 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) *m/z* 219 ($M^{\bullet+}$).

3-Phenylisoquinoline-1-carboxylic Acid (29).[38] A mixture of **27** (18.7 mmol), *N*-bromosuccinimide (NBS; 52.4 mmol), dibenzoyl peroxide (1.4 mmol), and CCl_4 (150 mL) was refluxed for 19 h. The insoluble material was filtered off, and the filtrate was washed with 5% $NaHCO_3$ and brine; the organic layer was dried over Na_2SO_4 and evaporated to dryness. 1-(Dibromomethyl)-3-phenylisoquinoline was obtained as an orange oil and utilized without further purification (TLC: eluent CH_2Cl_2, R_f(**27**) 0.38, R_f(dibromo derivative) 0.74).

The crude 1-(dibromomethyl)-3-phenylisoquinoline was dissolved in a mixture of 95% EtOH (120 mL) and THF (60 mL) and heated to reflux; $AgNO_3$ (73.6 mmol), dissolved in H_2O (15 mL), was added; the reaction mixture was refluxed for 1 h and filtered while still hot, washing with THF. The filtrate was evaporated to dryness to afford **28** which was used without further purification (TLC: eluent CH_2Cl_2, R_f(dibromo derivative) 0.74, R_f(**28**) 0.56).

The crude **28** was dissolved in EtOH and treated with $AgNO_3$ (45.9 mmol) dissolved in H_2O (8 mL). A solution of NaOH (158.8 mmol) in H_2O (98 mL) was added dropwise, and the reaction mixture was maintained under stirring overnight. Insoluble material was filtered on a Celite pad and washed with Et_2O, and the filtrate was acidified with concentrated HCl (5 mL), reduced to one-third of the volume, and ice-cooled. The formed precipitate was collected by suction filtration, washed with H_2O, dried, and triturated with Et_2O to yield **29** (8.8

mmol, 47% overall yield) as a yellow solid: mp 132−135 °C; IR (KBr) 1760 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.70 (s br, 1H), 8.63 (s, 1H), 8.51 (dd, J = 9.0, 1.2 Hz, 1H), 8.26 (d, J = 7.5 Hz, 2H), 8.14 (dd, J = 8.8, 1.0 Hz, 1H), 7.85 (ddd, J = 8.8, 8.8, 1.0 Hz, 1H), 7.74 (ddd, J = 9.0, 8.8, 1.0 Hz, 1H), 7.55 (dd, J = 7.5, 7.5 Hz, 2H), 7.46 (dd, J = 7.5, 7.5 Hz, 1H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 249 ($M^{\bullet+}$), 205, 204.

***(R,S)*-*N*-[α-(Methoxycarbonyl)benzyl]-3-phenylisoquinoline-1-carboxamide (75).** A mixture of **29** (6.0 mmol), (*R*,*S*)-methyl phenylglycinate·HCl (6.4 mmol), 1-hydroxybenzotriazole (11.8 mmol), *N*-methylmorpholine (7.3 mmol), THF (50 mL), and CH_3CN (20 mL) was cooled to 0 °C under nitrogen atmosphere. DCC (6.8 mmol), dissolved in THF (7 mL), was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The insoluble material was filtered off, and the solvent was evaporated to dryness. The crude product was dissolved in CH_2Cl_2, washed with H_2O, 20% citric acid, 5% $NaHCO_3$, and brine, and dried over Na_2SO_4 and the solvent evaporated. The residue was triturated with warm *i*-Pr_2O and recrystallized from 95% EtOH to yield **75** (4.1 mmol, 68%) as a white solid: mp 182−183 °C; IR (KBr) 3380, 1745, 1680, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.65 (d, J = 7.2 Hz, 1H), 8.80 (d, J = 9.0 Hz, 1H), 8.61 (s, 1H), 8.28 (d, J = 7.2 Hz, 2H), 8.12 (d, J = 9.0 Hz, 1H), 7.82 (dd, J = 9.0, 9.0 Hz, 1H), 7.71 (dd, J = 9.0, 9.0 Hz, 1H), 7.60−7.54 (m, 4H), 7.50−7.35 (m, 4H), 5.80 (d, J = 7.2 Hz, 1H), 3.75 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 396 ($M^{\bullet+}$), 337, 232, 204. Anal. ($C_{25}H_{20}N_2O_3$) C, H, N.

2-Phenylquinazoline-4-carboxylic Acid (32).[39] Benzanilide (**30**; 39.0 mmol) and $SOCl_2$ (10 mL) were refluxed for 3 h, and the solvent was evaporated to dryness to afford compound **31** as a yellow oil. $SnCl_4$ (39.0 mmol) was added dropwise to a solution of crude **31** and ethyl cyanoformate (39.0 mmol) in *o*-dichlorobenzene (30 mL); the reaction mixture was heated at 140 °C for 15 min, poured into water, made alkaline with 20% NaOH, and extracted with CH_2Cl_2; the organic layer was washed with brine and dried over Na_2SO_4. The dark oily residue was treated with warm *i*-Pr_2O and the insoluble material discarded by filtration; the filtrate was evaporated to dryness and the residue flash chromatographed on silica gel, eluting with hexane/EtOAc (98:2) to afford ethyl 2-phenylquinazoline-4-carboxylate as a yellow oil: IR (KBr) 1740, 1550, 1210, 770 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.55 (m, 2H), 8.35 (d, 1H), 8.15 (m, 2H), 7.80 (m, 1H), 7.60 (m, 3H), 4.60 (q, 2H), 1.40 (t, 3H).

The corresponding carboxylic acid **32** was obtained by refluxing the ethyl ester in a mixture of 20% NaOH (5 mL) and 95% EtOH (15 mL) for 2 h; the solvent was evaporated and the residue carefully treated with 20% citric acid. Compound **32** (12.0 mmol, 31%) precipitated from the acidic medium and was collected by suction filtration: mp 137−138 °C; IR (KBr) 3420, 1715, 1565, 1550 cm^{-1}; ^1H NMR (DMSO-d_6) δ 14.40 (s br, 1H), 8.61−8.55 (m, 2H), 8.41 (dd, J = 9.0, 1.5 Hz, 1H), 8.17 (dd, J = 9.0, 1.6 Hz, 1H), 8.10 (ddd, J = 9.0, 9.0, 1.5 Hz, 1H), 7.81 (ddd, J = 9.0, 9.0, 1.6 Hz, 1H), 7.63−7.56 (m, 3H); FAB-MS (negative, matrix diethanolamine, gas Xe, 8 keV, source 50 °C) m/z 249 ($M - H^-$), 205.

***N*-[α-(Methoxycarbonyl)benzyl]-2-phenyl-4-quinazolinecarboxamide (76).** Oxalyl chloride (10.2 mmol) was added to a stirred, ice-cold solution of 2-phenylquinazoline-4-carboxylic acid (**32**; 6.0 mmol) in CH_2Cl_2 (20 mL) containing 2 drops of DMF, and the reaction mixture was allowed to reach room temperature. After 2 h the solvent was evaporated to dryness, and the crude acyl chloride derivative was dissolved in CH_2Cl_2 (10 mL) and added dropwise to a stirred ice-cold solution of (*R*,*S*)-methyl phenylglycinate·HCl (7.9 mmol) and TEA (15.0 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred overnight and evaporated to dryness and the residue taken up in 10% K_2CO_3 and extracted with Et_2O; the organic layer was washed with brine and dried over Na_2SO_4 and the solvent evaporated. The crude product was crystallized from hexane/toluene (7:3) to afford **76** (4.3 mmol, 71%): mp 153−154 °C; IR (KBr) 3350, 1755, 1660, 1610, 1505 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.90 (d, J = 7.5 Hz, 1H), 8.59 (m, 2H), 8.53 (dd, J = 8.5, 1.1 Hz, 1H), 8.15 (dd, J = 8.5, 1.1 Hz, 1H), 8.08 (ddd, J = 8.5, 8.5, 1.1 Hz, 1H), 7.79 (ddd, J = 8.5, 8.5, 1.1 Hz, 1H), 7.64−7.53 (m, 5H), 7.47−7.37 (m, 3H), 5.85 (d, J = 7.5 Hz, 1H), 3.79 (s, 3H); EI-MS (source 200 °C, 70 eV, 200 mA) m/z 338, 205. Anal. ($C_{24}H_{19}N_3O_3$) C, H, N.

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Supporting Information Available: Detailed spectroscopic data (IR, MS, and ^1H NMR) for compounds **4**, **33**, **34**, and **38**−**72** (9 pages). Ordering information is given on any current masthead page.

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