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Synthesis and biological evaluation of novel fluoro and iodo quinoline carboxamides as potential ligands of NK-3 receptors for in vivo imaging studies

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Abstract—In order to develop radioligands of human NK-3 receptor (hNK-3r) for imaging studies by positron emission tomography (PET) or single photon emission computed tomography (SPECT), a new series of fluoro- and iodo-quinoline carboxamides were synthesized and evaluated in a target receptor binding assay. Compared to the unsubstituted parent compound SB 223 412 ($K_i = 27\,nM \pm 9$), affinity was not altered for the analogues **1c** and **2c** bearing a fluorine in position 8 ($K_i \sim 24$–$27\,nM$), and was only slightly reduced for compounds **1b**, **2b**, **1e** and **2e** fluorinated or iodinated at the position 7 ($K_i \sim 49$–$67\,nM$). A drastic reduction in binding ($K_i > 115\,nM$) was observed for all other halogenated compounds **1a**, **2a**, **1d**, **2d**, **1f** and **2f**.

1. Introduction

The three main mammalian tachykinins, substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) belong to the family of neuropeptides sharing the common COOH-terminal pentapeptide sequence of Phe-X-Gly-Leu-Met-NH_2. As neurotransmitters, these peptides exert their biological activity via three distinct neurokinin (NK) receptors termed as NK-1, NK-2 and NK-3. SP binds preferentially to the NK-1 receptor, NKA to the NK-2r and NKB to the NK-3r.[1–4] These receptors have been characterized by pharmacological studies and binding assays, cloned and expressed in stably transfected cells.[5–7] Their distribution has been studied by autoradiography, and by in situ hybridization and immunocytochemistry.[8–11] The NK-1 receptor is widely distributed in central (CNS) and peripheral (PNS) nervous system whilst the NK-2 receptor is primarily confined in PNS. The NK-3 receptor is characterized by a predominant expression in CNS and its involvement in the modulation of central monoaminergic system has been shown. These properties make the NK-3 receptor a potential target for central nervous system disorders such as anxiety, psychosis, depression.[12–16]

Positron emission tomography (PET) and single photon emission computed tomography (SPECT), are fundamental in vivo imaging techniques for the study of brain receptors. These methods allow their visualization during both physiological and pathophysiological conditions by the interactions of the biological target with a specific radioligand. As of present, no radioligand for the NK-3 receptor has been described. The discovery of SR 142801 (Osanetant)[17] and SB 223412 (Talnetant)[18–20] as lead compounds given that they are potent and selective non-peptidergic NK-3r antagonists, promises much for future in vivo biological investigations (Scheme 1).

SR 142801, has been tritiated and used in ex vivo imaging studies.[8,9] However, it displays a lower selectivity than SB 223412. This latter seemed to us particularly attractive as it was found to be metabolically

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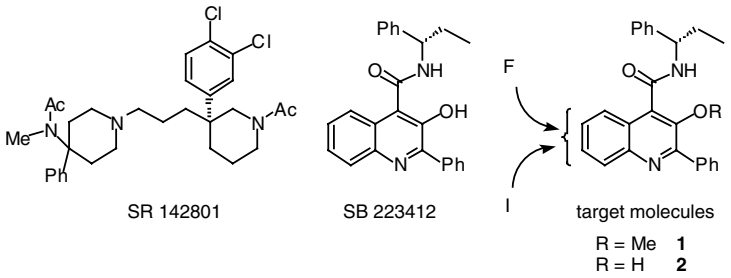


Scheme 1. h-NK3r antagonists and target molecules.

stable and able to cross the blood–brain barrier. Moreover, SAR studies on the quinoline carboxamide structures showed that chemical modifications on the quinoline ring could be envisaged without loss of affinity at NK-3r.[19,21] In order to develop ligands for in vivo imaging studies by PET or SPECT, we aimed to design fluoro- and iodoanalogues of SB 223412 that retain the biological activity of the parent compound. Herein, we describe the synthesis of new halogenated methoxy- or hydroxyquinoline carboxamides **1**–**2** and their in vitro evaluation (Scheme 1).

2. Results and discussion

2.1. Chemistry

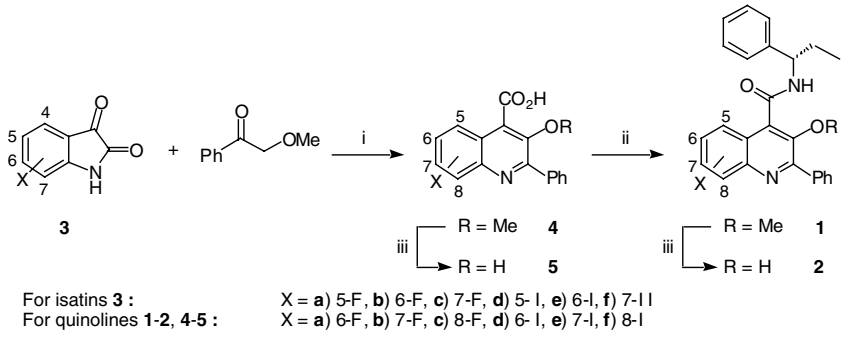
Synthesis of the target compounds was based on the Pfitzinger reaction converting isatin into quinolinic acid.[19,21,22] The previously described isatins **3a**–**f**, bearing a fluorine or an iodine atom in position 5, 6 or 7 were used as starting materials.[23,24] The treatment of these latter with 2-methoxyacetophenone under basic conditions led to the corresponding 3-methoxyquinolinic acids **4a**–**f** in 53–100% yields (Scheme 2). The same reaction from 5-fluoroisatin **3a** and 2-hydroxyacetophenone afforded the corresponding hydroxyacid **5a** in poor yields (34%).

Access to hydroxyacids **5a**–**f** was envisaged by demethylation of methoxyacids **4a**–**f**. In preliminary experiments carried out with HI,[18,19] yields did not exceed 50%. Then, we turned towards the use of BBr_3; under these conditions, fluorohydroxyacids **5a**–**c** were obtained in high yields (75–93%). In the iodinated series, only the hydroxyacid **5d** substituted in the position 6 was formed in satisfactory yield (70%). Hydroxyacids **5e**,**f** bearing an iodine in the positions 7 and 8, respectively, could not be isolated.

Methoxy- and hydroxyacids **4**–**5** were converted into quinoline carboxamides **1**–**2** by amidation with (*S*)-phenylpropylamine either in the presence of HOBt (1-hydroxybenzotriazole) and EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) in CH_2Cl_2, or via an activation with *N*-hydrosuccinimide in the presence of EDCI in DMF. This step afforded methoxyquinoline carboxamides **1a**–**f** in yields ranging from 67% to 98%, and the hydroxy analogues **2a**–**f** in only 10–30% yields. Finally, demethylation of methoxycarboxamides **1a**–**f** using BBr_3 was found to be the method of choice to prepare hydroxyacids **2a**–**f**. In both fluoro- and iodo series, yields in **2a**–**f** were in the 64–81% range. Finally, 12 quinoline carboxamides **1a**–**f** and **2a**–**f**, bearing either a methoxy or a hydroxy group in the position 3, and either a fluorine or an iodine atom in the positions 6, 7 or 8, were prepared.

2.2. Affinity and selectivity of the synthesized ligands

Affinities of the novel quinoline carboxamides **1**–**2** at the NK-3 receptor, were evaluated by analyzing the specific displacement of [^{3}H]-senktide binding on CHO cells stably expressing the human recombinant NK-3 receptor (hNK-3r). In each experiment, the results were



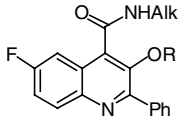
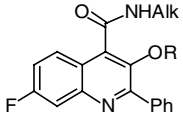
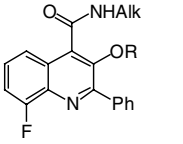
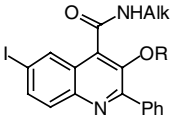
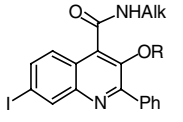
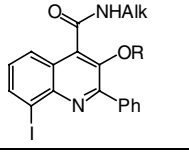
Scheme 2. Synthesis of target quinoline carboxamides. Reagents and conditions: (i) KOH, EtOH, 70 °C, 72 h; (ii) EDCI, HCl, Et_3N, HOBt, (*S*)-phenylpropylamine, CH_2Cl_2, −5 °C for 1 h then rt for 18 h, or (1) EDCI, NHS, DMF, −5 °C for 1 h then rt for 6 h; (2) (*S*)-phenylpropylamine, CH_2Cl_2, Δ, 4 h; (ii) BBr_3, CH_2Cl_2, −78 °C for 1.5 h then rt for 3 h; (2) EtOH, −78 °C.

compared with those obtained on the same in vitro model with endogenous NKB, the senktide itself, the known potent synthetic antagonists SB 223412 and SB 222200[25] and finally with endogenous NKA, which exhibits preferential binding to the NK-2 receptors (Table 1).

As described for the SB 223412 reference compound,[20] the replacement of the hydroxyl function by a methoxy group in position 3 in the novel halogenated series, did not modify affinities. However, the position and the nature of the halogen atom, was crucial for affinity. The quinolines **1c** and **2c** possessing a fluorine atom in position 8, displayed similar affinities compared to SB 223412, senktide and NKB, whereas the corresponding iodoanalogues **1f** and **2f** were devoid of significant hNK-3r binding affinity. Compounds **1b**,**e** and **2b**,**e** fluorinated or iodinated in position 7, exhibited an approximately 2-fold lower affinity than those of the references. Halogenation, and especially iodination, in position 6 led to a reduction or loss of the binding properties (compounds **1a**,**d** and **2a**,**d**).

The haloquinolines **1b**,**c**,**e** and **2b**,**c**,**e**, which showed the most significant affinities for NK-3r, exhibited no affinity for NK-1r ($K_i > 10\,000$), determined by specific

Table 1. Binding affinities of the novel quinoline carboxamides compared to NKB, senktide and the parent SB 223412 and SB 222200 compounds at cloned hNK-3 and hNK-1 receptors

Compd		Binding affinities (K_i, nM; mean ± SEM)[a]			
		hNK-3[b]		hNK-1[c]	
References					
NKB		28 (±3)		450 (±40)	
Senktide		22 (±1)[d]		—[e]	
SB 223412		27 (±9)		>10,000	
SB 222200		31 (±5)		>10,000	
NKA		>1000		—[e]	
SP		—[e]		4.7 (±1.6)	
Quinolines		1 (*R* = *Me*)	2 (*R* = *H*)	1 (*R* = *Me*)	2 (*R* = *H*)
	a	162 ± 78	115 ± 15	—[e]	—[e]
	b	62 ± 12	49 ± 3	>10,000	>10,000
	c	27 ± 11	24 ± 13	>10,000	>10,000
	d	410 ± 172	>1000	—[e]	—[e]
	e	57 ± 11	67 ± 26	>10,000	>10,000
	f	625 ± 35	>1000	—[e]	—[e]

[a] Average of two to nine independent determinations ($n = 2$–9).
[b] Inhibition of [^{3}H]-senktide binding on hNK-3r-CHO cell membranes.[26,27]
[c] Inhibition of [^{125}I]-Bolton-Hunter SP binding on hNK-3r-CHO cells.
[d] K_d 12 ± 2 nM, determined by three independent saturation experiments.
[e] Not determined.

displacement of [^{125}I]-BH-SP (Bolton-Hunter Substance P) binding (Table 1). Thus, the selectivity for hNK-3r over hNK-1r was retained after substitution by a fluorine atom in position 7 or 8 or by an iodine in position 7.

3. Conclusion

A new series of halogenated 2-phenylquinoline-4-carboxamides **1**–**2** was prepared from the corresponding isatins **3**. These compounds were evaluated as novel NK-3 ligands. Their binding properties were found strongly dependent on the nature and position of the halogen atom. The fluoro compounds **1b**,**c** and **2b**,**c** and the iodo compounds **1e** and **2e** displayed a similar or close affinity compared to that of unsubstituted SB 223412 as reference. In view of the in vivo potential use of these quinolines, work is in progress for their labelling with fluorine-18 or iodine-123 for NK-3 receptor imaging studies by PET or SPECT.

4. Experimental

4.1. Chemistry

4.1.1. General considerations. All reagents were used as supplied from commercial sources (Aldrich, Acros or Fluka). Solvents were purchased from Carlo Erba. *N*,*N*-Dimethylformamide (DMF) and dichloromethane (CH_2Cl_2) were freshly distilled from calcium hydride under nitrogen prior to use. Pentane, methanol (MeOH), ethanol (EtOH), diethyl ether (Et_2O), tetrahydrofuran (THF) and ethyl acetate (AcOEt) were used as received. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz (^{1}H) or 100.6 MHz (^{13}C) or on a Bruker DPX 250 at 250 MHz (^{1}H) or 62.9 MHz (^{13}C), and were calibrated according to the chemical shift of tetramethylsilane. ^{19}F nuclear magnetic resonance spectra were recorded on a Bruker DPX 400 (376.5 MHz) or Bruker DPX 250 (235 MHz) spectrometer, and were calibrated according to the chemical shift of trifluorotoluene. Chemical shift (δ) are quoted in ppm and coupling constants (J) in Hz. The following abbreviations are used to denote multiplicities: s, singlet; d, doublet; dd, double-doublet; ddd: double-double-doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra were recorded on a Perkin–Elmer 16 PC FT IR spectrophotometer in KBr and peaks are given in cm^{-1}. Low (EI) and high resolution (HRMS, EI) mass spectra were recorded on a JEOL JMS GCMate instrument at 70 eV. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm, concentrations (c) are quoted in g/100 mL. Elemental analyses were performed on a ThermoQuest analyzer CHNS–O, and were within ±0.4% of the calculated values. Melting points (mp) were measured on a Kofler hot-block apparatus. Thin layer chromatography (TLC) was carried out on aluminium or plastic sheets coated with 60 F-254 silica from Merck (0.1 mm). Plates were revealed with UV detection or by ninhydrine (10% in ethanol) treatment followed by heating. Flash chromatography was carried out using Si 60 (40–63 μm) silica from Merck.

4.1.2. General procedure for the synthesis of 3-methoxy-4-quinolinic acid hydrochlorides 4. A mixture of haloisatin **3** (1 equiv), 2-methoxyacetophenone (1.2 equiv) and KOH pellets (85%, 3 equiv) in ethanol (5–50 mL) was refluxed for 72 h. After concentration under vacuum, the residue was dissolved in H_2O and washed twice with Et_2O. The ice cold aqueous layer was acidified to pH 1 with HCl 37%. The precipitate formed was filtrated, washed with H_2O and dried at 65 °C in an oven to give the expected acid hydrochloride **4**.

4.1.2.1. 6-Fluoro-3-methoxy-2-phenylquinoline-4-carboxylic acid hydrochloride 4a. Acid hydrochloride **4a** was obtained from 5-fluoroisatin **3a** (3.0 g, 18.1 mmol), 2-methoxyacetophenone (3.27 g, 21.8 mmol) and KOH (3.0 g, 53.6 mmol) in EtOH (25 mL): brown solid, mp 214–216 °C; 87% (5.26 g). ^{1}H NMR (DMSO-d_6) δ 3.60 (s, 3H), 7.35–7.62 (m, 4H), 7.67–7.72 (m, 1H), 7.93–7.97 (m, 2H), 8.13–8.18 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 62.5, 108.4 (d, $^2J_{CF} = 23.5$ Hz), 120.0 (d, $^2J_{CF} = 25.4$ Hz), 125.6 (d, $^3J_{CF} = 10.4$ Hz), 129.3, 129.8, 130.3, 136.7 (d, $^5J_{CF} = 5.6$ Hz), 133.1 (d, $^4J_{CF} = 9.8$ Hz), 137.6, 142.1, 149.1, 154.4, 161.5 (d, $^1J_{CF} = 246.0$ Hz), 167.4. ^{19}F NMR (DMSO-d_6) δ −(111.5–111.6) (m). IR (KBr) 1724, 1614, 1504 and 1246. m/z 297 ($M^{+\cdot}$, $C_{17}H_{12}FNO_3$,100), 296 (99), 222 (43). HRMS ($M^{+\cdot}$, $C_{17}H_{12}FNO_3$) calcd 297.08010, found 297.08123.

4.1.2.2. 7-Fluoro-3-methoxy-2-phenylquinoline-4-carboxylic acid hydrochloride 4b. Acid hydrochloride **4b** was obtained from 6-fluoroisatin **3b** (5.41 g, 32.9 mmol), 2-methoxyacetophenone (5.93 g, 39.5 mmol) and KOH (5.5 g, 98.2 mmol) in EtOH (40 mL): brown solid, mp 218–222 °C; 90% (9.87 g). ^{1}H NMR (DMSO-d_6) δ 3.58 (s, 3H), 7.52–7.59 (m, 4H), 7.76 (dd, $^4J_{H5F} = 2.7$ Hz, $^3J_{H5H6} = 9.9$ Hz, 1H), 8.01–8.03 (m, 2H), 8.77 (dd, $^4J_{H8H6} = 6.2$ Hz, $^3J_{H8F} = 9.4$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 62.1, 113.7 (d, $^2J_{CF} = 20.3$ Hz), 119.1 (d, $^2J_{CF} = 25.4$ Hz), 121.8, 127.6 (d, $^3J_{CF} = 10.3$ Hz), 129.3, 129.4, 129.8, 129.9, 130.4, 133.7, 137.6, 145.7 (d, $^3J_{CF} = 12.6$ Hz), 147.8 (d, $^4J_{CF} = 2.8$ Hz), 156.0, 158.8 (d, $^1J_{CF} = 248$ Hz), 167.5. ^{18}F NMR (DMSO-d_6) δ −(111.1–111.2) (m). IR (KBr) 3422, 1720, 1626, 1232, 1060 and 704. m/z 297 ($M^{+\cdot}$, $C_{17}H_{12}FNO_3$, 91), 296 (90), 222 (36), 122 (37), 105 (57), 73 (100). HRMS ($M^{+\cdot}$, $C_{17}H_{12}FNO_3$) calcd 297.08010, found 297.08029.

4.1.2.3. 8-Fluoro-3-methoxy-2-phenylquinoline-4-carboxylic acid hydrochloride 4c. Acid hydrochloride **4c** was obtained from 7-fluoroisatin **3c** (1.35 g, 8.2 mmol), 2-methoxyacetophenone (1.49 g, 9.9 mmol) and KOH (1.50 g, 26.8 mmol) in EtOH (12 mL): brown solid, mp 254 °C (decomposition); 53% (1.45 g). ^{1}H NMR (DMSO-d_6) δ 3.47 (s, 3H), 7.41–7.54 (m, 6H), 7.83–7.88 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 62.0, 113.7 (d,

$^2J_{CF} = 19.1$ Hz), 120.4 (d, $^3J_{CF} = 4.3$ Hz), 126.1 (d, $^4J_{CF} = 2.0$ Hz), 128.0, 128.8, 129.4, 130.0, 132.8 (d, $^3J_{CF} = 2.8$ Hz), 134.4 (d, $^2J_{CF} = 12.0$ Hz), 137.2, 148.4, 154.6, 156.7 (d, $^1J_{CF} = 256$ Hz), 166.9. ^{19}F NMR (DMSO-d_6) δ −123.4 (dd, $^4J_{FH6} = 3.8$ Hz, $^3J_{FH7} = 7.5$ Hz). IR (KBr) 2536, 1732, 1468, 1244, 1230, 762 and 702. m/z 297 ($M^{+\cdot}$, $C_{17}H_{12}FNO_3$, 91), 296 (100), 223 (35), 222 (44). HRMS ($M^{+\cdot}$, $C_{17}H_{12}FNO_3$) calcd 297.08010, found 297.08036.

4.1.2.4. 6-Iodo-3-methoxy-2-phenylquinoline-4-carboxylic acid hydrochloride 4d. Acid hydrochloride **4d** was obtained from 5-iodoisatin (2.24 g, 8.22 mmol), 2-methoxyacetophenone (1.48 g, 9.9 mmol) and KOH (1.4 g, 25.0 mmol) in EtOH (12 mL): brown solid, mp 202 °C; 100% (3.62 g). ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 3H), 7.43–7.54 (m, 3H), 7.83 (d, $^3J_{H7H8} = 8.8$ Hz, 1H), 7.93–8.01 (m, 3H), 8.10–8.12 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 62.5, 95.6, 126.4, 129.3, 129.4, 129.8, 130.1, 130.4, 131.8, 132.0, 133.0, 137.6, 138.3, 143.7, 148.6, 155.5, 167.4. IR (KBr) 3504, 1702, 1448 and 1348. m/z 405 ($M^{+\cdot}$, $C_{17}H_{12}INO_3$, 70), 404 (100). HRMS ($M^{+\cdot}$, $C_{17}H_{12}INO_3$) calcd 404.98680, found 404.98511.

4.1.2.5. 7-Iodo-3-methoxy-2-phenylquinoline-4-carboxylic acid hydrochloride 4e. Acid hydrochloride **4e** was obtained from 6-iodoisatin **3e** (2.24 g, 8.20 mmol), 2-methoxyacetophenone (1.48 g, 9.9 mmol) and KOH (1.4 g, 25.0 mmol) in EtOH (12 mL): light brown solid, mp 230 °C (decomposition); 72% (2.61 g). ^{1}H NMR (DMSO-d_6) δ 3.59 (s, 3H), 7.55–7.58 (m, 4H), 7.92–7.97 (m, 3H), 8.48 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 62.4, 96.3, 124.0, 126.7, 129.3, 129.9, 130.4, 133.9, 136.9, 137.8, 138.3, 145.6, 148.3, 155.6, 167.5. IR (KBr) 3058, 2936, 1716, 1624, 1594, 1350, 1324, 1286, 1234, 1144, 1008, 724 and 698. m/z 405 ($M^{+\cdot}$, $C_{17}H_{12}INO_3$, 100), 404 (69), 97 (21), 84 (23). HRMS ($M^{+\cdot}$, $C_{17}H_{12}INO_3$) calcd 404.98680, found 404.98466.

4.1.2.6. 8-Iodo-3-methoxy-2-phenylquinoline-4-carboxylic acid hydrochloride 4f. Acid hydrochloride **4f** was obtained from 7-iodoisatin **3f** (1.44 g, 5.29 mmol), 2-methoxyacetophenone (0.95 g, 6.35 mmol) and KOH (1.19 g, 21.2 mmol) in EtOH (20 mL), after extraction of the aqueous layer with CH_2Cl_2 (five times), drying over Na_2SO_4, filtration and concentration under vacuum: brown solid, mp 74 °C; 90% (2.09 g). ^{1}H NMR (DMSO-d_6) δ 3.71 (s, 3H), 7.35–7.42 (m, 1H), 7.52–7.61 (m, 3H), 7.96 (dd, $^4J_{H5H7} = 1.2$ Hz, $^3J_{H5H6} = 9.5$ Hz, 1H), 8.25–8.28 (m, 2H), 8.32 (dd, $^4J_{H7H5} = 1.2$ Hz, $^3J_{H6H7} = 7.4$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 62.1, 104.8, 124.4, 125.3, 128.9, 129.5, 130.1, 133.1, 133.5, 137.0, 139.7, 148.5, 154.4, 166.9, 177.2. IR (KBr) 2936, 1718, 1342, 1196 and 760. m/z 405 ($M^{+\cdot}$, $C_{17}H_{12}INO_3$, 36), 404 (47), 204 (19), 190 (19), 73 (100). HRMS ($M^{+\cdot}$, $C_{17}H_{12}INO_3$) calcd 404.98680, found 404.98622.

4.1.3. General procedure for demethylation of 3-methoxy-4-quinolinic acid hydrochlorides 4. BBr_3 in CH_2Cl_2 (0.7 M, 3.6 equiv) was added dropwise in 1 h to a solution of acid **4** (0.2 M, 1 equiv) in CH_2Cl_2 at −78 °C. After stirring for 1.5 h at −78 °C, then for 3 h at room temperature, the mixture was cooled to −78 °C and ethanol 96% was added. The mixture was concentrated under vacuum and the residue was dissolved in ethanol 96%, then concentrated under vacuum and finally dissolved in a mixture of THF/NaOH aqueous (2 N) 1:1. After stirring for 1 h at 60 °C, HCl 37% was added until pH 1 and a precipitate was formed. The precipitate was filtered off, washed with water and dried in an oven at 65 °C to afford hydroxyacids **5**.

4.1.3.1. 6-Fluoro-3-hydroxy-2-phenylquinoline-4-carboxylic acid hydrochloride 5a. Acid hydrochloride **5a** was obtained from methoxyacid **4a** (4.0 g, 12.0 mmol) in CH_2Cl_2 (60 mL) and BBr_3 (10.9 g, 43.3 mmol) in CH_2Cl_2 (60 mL): yellow solid, mp 224 °C; 93% (3.55 g). ^{1}H NMR (DMSO-d_6) δ 7.52–7.60 (m, 4H), 7.77 (dd, $^4J_{H8F} = 2.7$ Hz, $^3J_{H8H7} = 9.9$ Hz, 1H), 8.00–8.02 (m, 2H), 8.77 (dd, $^4J_{H5H7} = 6.2$ Hz, $^3J_{H5F} = 9.5$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 109.1 (d, $^2J_{CF} = 26$ Hz), 116.0 (d, $^2J_{CF} = 26$ Hz), 126.0 (d, $^3J_{CF} = 12$ Hz), 128.3, 129.8, 130.0, 130.1, 131.6 (d, $^3J_{CF} = 10$ Hz), 136.2, 137.6, 151.5 (d, $^4J_{CF} = 3$ Hz), 156.4, 161.7 (d, $^1J_{CF} = 245$ Hz), 171.9. ^{19}F NMR (DMSO-d_6) δ −111.0 (s). IR (KBr) 1918, 1630, 1600, 1526, 1450, 1406, 1374, 1322, 1292 and 1246. m/z 283 ($M^{+\cdot}$, $C_{16}H_{10}FNO_3$, 29), 265 (32), 238 (100), 237 (72), 208 (22), 183 (18). HRMS ($M^{+\cdot}$, $C_{16}H_{10}FNO_3$) calcd 283.06445, found 283.06437.

4.1.3.2. 7-Fluoro-3-hydroxy-2-phenylquinoline-4-carboxylic acid hydrochloride 5b. Acid hydrochloride **5b** was obtained from methoxyacid **4b** (5.1 g, 15.9 mmol) in CH_2Cl_2 (75 mL) and BBr_3 (13.8 g, 55.0 mmol) in CH_2Cl_2 (75 mL): orange solid, mp 228 °C; 92% (4.67 g). ^{1}H NMR (DMSO-d_6) δ 7.52–7.59 (m, 4H), 7.77 (dd, $^4J_{H5F} = 2.7$ Hz, $^3J_{H5H6} = 9.9$ Hz, 1H), 8.00–8.03 (m, 2H), 8.76 (dd, $^4J_{H8H6} = 6.2$ Hz, $^3J_{H8F} = 9.4$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 113.4 (d, $^2J_{CF} = 20.8$ Hz), 116.2, 118.6 (d, $^2J_{CF} = 24.3$ Hz), 123.1, 128.0 (d, $^3J_{CF} = 9.2$ Hz), 129.0, 129.4, 129.8, 130.3, 130.5, 130.9, 137.2, 142.5 (d, $^3J_{CF} = 11.2$ Hz), 153.9, 161.0 (d, $^1J_{CF} = 243$ Hz), 172.0. ^{19}F NMR (DMSO-d_6) δ −(115.5–115.6) (m). IR (KBr) 3448, 1636, 1574, 1522, 1508 and 1320. m/z 283 ($M^{+\cdot}$, $C_{16}H_{10}FNO_3$, 5), 265 (13); 239 (69), 238 (100), 211 (17). HRMS ($M^{+\cdot}$, $C_{16}H_{10}FNO_3$) calcd 283.06445, found 283.05924.

4.1.3.3. 8-Fluoro-3-hydroxy-2-phenylquinoline-4-carboxylic acid hydrochloride 5c. Acid hydrochloride **5c** was obtained from methoxyacid **4c** (0.69 g, 2.1 mmol) in CH_2Cl_2 (12 mL) and BBr_3 (1.86 g, 7.5 mmol) in CH_2Cl_2 (12 mL): yellow solid, mp 150 °C; 75% (0.50 g). ^{1}H NMR (DMSO-d_6) δ 7.35–7.39 (m, 1H), 7.49–7.60 (m, 4H), 8.03–8.06 (m, 2H), 8.49 (d, $^3J_{H5H6} = 8.7$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 111.3 (d, $^2J_{CF} = 18.2$ Hz), 115.7, 121.3 (d, $^4J_{CF} = 4.4$ Hz), 128.0, 128.8, 128.9, 130.0, 130.4, 132.3 (d, $^3J_{CF} = 11.2$ Hz), 138.0, 153.0, 155.0, 158.6 (d, $^1J_{CF} = 252.1$ Hz), 172.0. ^{19}F NMR (DMSO-d_6) δ −(125.1–125.2) (m). IR (KBr) 4374, 4344, 4280, 3060, 1724, 1644, 1448 and 1238. m/z 283 ($M^{+\cdot}$, $C_{16}H_{10}FNO_3$, 27), 265 (34); 239 (59), 238 (100), 237 (69), 208 (24).

HRMS ($M^{+\cdot}$, $C_{16}H_{10}FNO_3$) calcd 283.06445, found 283.06523.

4.1.3.4. 3-Hydroxy-6-iodo-2-phenylquinoline-4-carboxylic acid hydrochloride 5d. Acid hydrochloride **5d** was obtained from methoxyacid **4d** (1 g, 2.5 mmol) in CH_2Cl_2 (15 mL) and BBr_3 (1.85 g, 7.4 mmol) in CH_2Cl_2 (15 mL): yellow solid, mp 236 °C; 70% (0.68 g). ^{1}H NMR (DMSO-d_6) 7.51–7.56 (m, 4H), 7.79 (d, $^3J_{H8H7} = 8.7$ Hz, 1H), 7.85 (dd, $^4J_{H7H5} = 1.6$ Hz, $^3J_{H7H8} = 8.7$ Hz, 1H), 8.00–8.04 (m, 2H), 9.27 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 95.5, 114.0, 128.2, 128.8, 128.9, 130.4, 130.6, 130.7, 131.1, 134.0, 135.3, 153.3, 156.9, 171.9. m/z 391 ($M^{+\cdot}$, $C_{16}H_{10}INO_3$, 5), 347 (100), 346 (94), 219 (29), 192 (20), 165 (15), 110 (13), 85 (61). HRMS ($M^{+\cdot}$, $C_{16}H_{10}INO_3$) calcd 390.97055, found 390.96996.

4.1.4. General procedure for amidation of quinolinic acids 4–5. EDCI (2 equiv) was added slowly at −5 °C to a mixture of Et_3N (2 equiv), (*S*)-phenylpropylamine (1.1 equiv), HOBt (2 equiv) and acid **4** or **5** (1 equiv) in CH_2Cl_2 (20–40 mL). The mixture was stirred at −5 °C for 1 h, then at room temperature for 18 h. After washing with aqueous solution of citric acid 5% (three times), then $NaHCO_3$ 5% (three times) and finally with brine, the organic layer was dried over $MgSO_4$, filtered off and concentrated under vacuum. Purification by column chromatography (pentane/AcOEt 85:15 containing Et_3N: 1‰) yielded to quinoline carboxamides **1**–**2**.

4.1.4.1. (*S*)-*N*-(1-Phenylpropyl)-6-fluoro-3-methoxy-2-phenylquinoline-4-carboxamide 1a. Carboxamide **1a** was obtained from methoxyacid **4a** (1.35 g, 4.0 mmol): white solid, mp 158 °C; 67% (1.1 g). $[\alpha]_D$ −46.8 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.07 (t, $^3J_{HH} = 7.4$ Hz, 3H), 1.95–2.02 (m, 2H), 3.48 (s, 3H), 5.28 (q, $^3J_{HH} = 8.1$ Hz, 1H), 6.68 (d, $^3J_{HH} = 8.5$ Hz, 1H), 7.28–7.54 (m, 10H), 7.95–7.97 (m, 2H), 8.06 (dd, $^4J_{HF} = 3.1$ Hz, $^3J_{H8H7} = 10.0$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 11.3, 29.5, 56.1, 62.5, 108.7 (d, $^2J_{CF} = 23.8$ Hz), 119.4 (d, $^2J_{CF} = 25.9$ Hz), 126.7, 126.8, 127.1, 127.2, 128.1, 129.2, 129.5, 129.7, 132.5 (d, $^3J_{CF} = 9.4$ Hz), 133.7 (d, $^3J_{CF} = 5.8$ Hz), 137.6, 142.7, 149.1, 154.2 (d, $^3J_{CF} = 2.9$ Hz), 161.7 (d, $^1J_{CF} = 249.2$ Hz), 164.7. ^{19}F NMR ($CDCl_3$) δ −111.6 (ddd, $^4J_{FH8} = 3$ Hz, $^3J_{FH5} = 8$ Hz, $^3J_{FH6} = 10$ Hz). IR (KBr) 3262, 2966, 2934, 1636, 1492, 1458, 1446, 1348, 1234, 1186 and 698. m/z 414 ($M^{+\cdot}$, $C_{26}H_{23}FN_2O_2$, 16), 385 (23), 281 (19), 280 (100), 237 (17), 149 (13), 86 (49), 84 (77). HRMS ($M^{+\cdot}$, $C_{26}H_{23}FN_2O_2$) calcd 414.17534, found 414.17465. Anal. ($C_{17}H_{12}FNO_3 \cdot \frac{1}{4}H_2O$) C, H, N.

4.1.4.2. (*S*)-*N*-(1-Phenylpropyl)-7-fluoro-3-methoxy-2-phenylquinoline-4-carboxamide 1b. Carboxamide **1b** was obtained from methoxyacid **4b** (2.24 g, 6.7 mmol): white solid, mp 64 °C; 70% (1.93 g). $[\alpha]_D$ −38.0 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, $^3J_{HH} = 7.3$ Hz, 3H), 1.78–1.91 (m, 2H), 3.33 (s, 3H), 5.09–5.13 (q, $^3J_{HH} = 8.3$ Hz, 1H), 6.65 (d, $^3J_{HH} = 8.5$ Hz, 1H), 7.22–7.40 (m, 9H), 7.56 (dd, $^4J_{H8H6} = 2.5$ Hz, $^3J_{H8F} = 10.0$ Hz, 1H), 7.67 (dd, $^4J_{H5F} = 6.0$ Hz, $^3J_{H5H6} = 9.2$ Hz, 1H), 7.83–7.88 (m, 2H). ^{13}C NMR ($CDCl_3$) 11.3, 29.5, 56.1, 62.5, 113.6 (d, $^2J_{CF} = 20.4$ Hz), 118.2 (d, $^2J_{CF} = 25.2$ Hz), 122.6, 127.1 (d, $^3J_{CF} = 6.1$ Hz), 127.1, 128.0, 128.9, 129.1, 129.7, 129.9, 134.7, 137.6, 142.1, 146.3 (d, $^3J_{CF} = 12.6$ Hz), 147.9 (d, $^4J_{CF} = 2.7$ Hz), 156.0, 162.9 (d, $^1J_{CF} = 149.5$ Hz), 164.8. ^{19}F NMR ($CDCl_3$) −(111.1–111.2) (m). IR (KBr) 3256, 2964, 2934, 1636, 1540, 1504, 1352, 1216 and 698. m/z 414 ($M^{+\cdot}$, $C_{26}H_{23}FN_2O_2$, 47), 385 (59), 281 (54), 280 (100), 237 (38), 210 (33), 105 (81). HRMS ($M^{+\cdot}$, $C_{26}H_{23}FN_2O_2$) calcd 414.17534, found 414.17345. Anal. ($C_{26}H_{23}FN_2O_2$) C, H, N.

4.1.4.3. (*S*)-*N*-(1-Phenylpropyl)-8-fluoro-3-methoxy-2-phenylquinoline-4-carboxamide 1c. Carboxamide **1c** was obtained from methoxyacid **4c** (0.43 g, 1.3 mmol): white solid, mp 68 °C; 73% (0.39 g). $[\alpha]_D$ −44.6 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.03 (t, $^3J_{HH} = 7.3$ Hz, 3H), 1.90–1.99 (m, 2H), 3.46 (s, 3H), 5.20 (q, $^3J_{HH} = 8.3$ Hz, 1H), 6.63 (d, $^3J_{HH} = 8.5$ Hz, 1H), 7.17–7.54 (m, 11H), 8.00–8.01 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 11.3, 29.6, 56.2, 62.5, 113.3 (d, $^2J_{CF} = 18.9$ Hz), 120.6 (d, $^3J_{CF} = 4.8$ Hz), 127.1, 127.3, 127.5, 127.6, 128.0, 128.9, 129.1, 129.8, 129.9, 134.4 (d, $^4J_{CF} = 2.3$ Hz), 135.7 (d, $^3J_{CF} = 12.0$ Hz), 137.6, 142.0, 149.2, 155.0, 158.5 (d, $^1J_{CF} = 257.7$ Hz), 164.8. ^{19}F NMR ($CDCl_3$) δ −124.3 (ddd, $^5J_{FH5} = 3.8$ Hz, $^4J_{FH6} = 11.3$ Hz, $^3J_{FH7} = 15.1$ Hz). IR (KBr) 3422, 3312, 3250, 1636, 1578, 1560, 1540 and 1376. m/z 414 ($M^{+\cdot}$, $C_{26}H_{23}FN_2O_2$, 21), 385 (26), 280 (100), 237 (15), 210 (36), 105 (91). HRMS ($M^{+\cdot}$, $C_{26}H_{23}FN_2O_2$) calcd 414.17534, found 414.17553. Anal. ($C_{26}H_{23}FN_2O_2$) C, H, N.

4.1.4.4. (*S*)-*N*-(1-Phenylpropyl)-6-iodo-3-methoxy-2-phenylquinoline-4-carboxamide 1d. Carboxamide **1d** was obtained from methoxyacid **4d** (0.71 g, 1.60 mmol): white solid, mp 82 °C; 78% (0.65 g). $[\alpha]_D$ −62.4 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.09 (t, $^3J_{HH} = 7.38$ Hz, 3H), 2.00–2.06 (m, 2H), 3.53 (s, 3H), 5.28 (q, $^3J_{HH} = 7.5$ Hz, 1H), 6.43 (d, $^3J_{HH} = 7.6$ Hz, 1H), 7.28–7.55 (m, 8H), 7.84 (d, $^3J_{H8H7} = 8.8$ Hz, 1H), 7.91 (dd, $^4J_{H7H5} = 1.9$ Hz, $^3J_{H7H8} = 8.8$ Hz), 7.99–8.01 (m, 2H), 8.29 (d, $^4J_{H5H7} = 1.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 9.8, 28.0, 54.8, 61.2, 92.7, 125.7, 125.9, 126.7, 127.5, 127.9, 128.2, 128.4, 130.2, 131.6, 132.3, 136.2, 136.6, 140.5, 143.0, 147.4, 154.1, 163.1. IR (KBr) ν 3250, 2932, 1636, 1534 and 1346. m/z 523 ($MH^{+\cdot}$, $C_{26}H_{23}IN_2O_2$, 100), 387 (23), 362 (19), 348 (24), 119 (13). HRMS ($M^{+\cdot}$, $C_{26}H_{23}IN_2O_2$) calcd 522.08044, found 522.08350. Anal. ($C_{26}H_{23}IN_2O_2$) C, H, N.

4.1.4.5. (*S*)-*N*-(1-Phenylpropyl)-8-iodo-3-methoxy-2-phenylquinoline-4-carboxamide 1f. Carboxamide **1f** was obtained from methoxyacid **4f** (0.31 g, 0.70 mmol): white solid, mp 74 °C; 78% (0.65 g). $[\alpha]_D$ −62.4 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.24 (t, $^3J_{HH} = 7.2$ Hz, 3H), 1.92–1.99 (m, 2H), 3.52 (s, 3H), 5.21 (q, $^3J_{HH} = 8.3$ Hz, 1H), 6.50 (d, $^3J_{HH} = 8.5$ Hz, 1H), 7.14 (dd, $^3J_{H6H5} = 8.2$ Hz, $^3J_{H6H7} = 7.4$ Hz, 1H), 7.11–7.39 (m, 5H), 7.48–7.51 (m, 3H), 7.70 (dd, $^4J_{H5H7} = 1.2$ Hz, $^3J_{H5H6} = 8.3$ Hz, 1H), 8.22–8.26 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 11.3, 29.5, 56.1, 62.6, 104.7, 125.7, 125.8, 127.11, 128.0, 128.8, 128.9, 129.1, 130.0, 130.1, 135.1, 137.4, 139.6, 142.0, 143.8, 149.3, 154.8, 164.7. IR (KBr) 2966, 1636, 1526, 1476,

1446, 1344, 1294, 700 and 692. *m/z* 522 ($M^{+\cdot}$, $C_{26}H_{23}IN_2O_2$, 57), 493 (28), 388 (100). HRMS ($M^{+\cdot}$, $C_{26}H_{23}IN_2O_2$) calcd 522.08044, found 522.0773. Anal. ($C_{26}H_{23}IN_2O_2$) C, H, N.

4.1.4.6. (*S*)-*N*-(1-Phenylpropyl)-7-iodo-3-methoxy-2-phenylquinoline-4-carboxamide 1e. EDCI (0.52 g, 2.72 mmol) was added by portions at −5 °C to a solution of DMF (15 mL) containing quinolinic acid **4e** (1.00 g, 2.27 mmol) and *N*-hydroxysuccinimide (0.31 g, 2.72 mmol). After stirring at −5 °C for 1 h, then at room temperature for 6 h, the mixture was concentrated under vacuum. The residue was diluted in ethyl acetate and the organic layer was washed successively with a solution of citric acid 5% (three times), a solution of $NaHCO_3$ (once) and brine (once), dried over $MgSO_4$, filtrated off and concentrated under vacuum to afford 1-{[(7-iodo-3-methoxy-2-phenylquinolin-4-yl)carbonyl]oxy}pyrrolidine-2,5-dione, which was purified by two consecutive recrystallizations in a mixture of MeOH/Et_2O: white solid, mp 72 °C; 99% (1.13 g). ^{1}H NMR ($CDCl_3$) 2.97–2.99 (m, 4H), 3.75 (s, 3H), 7.53–7.55 (m, 3H), 7.92–7.93 (m, 2H), 8.06–8.09 (m, 2H), 8.38 (d, $^4J_{HH} = 0.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.2, 63.0, 95.4, 123.9, 125.7, 126.0, 129.1, 129.6, 130.3, 137.0, 137.6, 139.1, 145.6, 150.7, 155.5, 161.8, 169.1. IR (KBr) 3242, 2941, 1666, 1534, 1527 and 1346. *m/z* 502 ($M^{+\cdot}$, $C_{21}H_{15}IN_2O$, 28), 388 (100), 84 (48). HRMS ($M^{+\cdot}$, $C_{21}H_{15}IN_2O$) calcd 502.00257, found 502.00169. Anal. ($C_{21}H_{15}IN_2O_5$) C, H, N. A solution of this pyrrolidine-2,5-dione (0.375 g, 0.75 mmol) and (*S*)-phenylpropylamine (0.403 g, 3.0 mmol) in CH_2Cl_2 (5 mL) was refluxed for 4 h. After washing with aqueous solution of citric acid 5% (three times), then $NaHCO_3$ 5% (three times) and finally with brine, the organic layer was dried over $MgSO_4$, filtered off and concentrated under vacuum. Purification by column chromatography over silica gel (pentane/AcOEt 85:15) yielded to **1e**: white solid, mp 72 °C, 99% (0.390 g). $[\alpha]_D$ −29.4 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.07 (t, $^3J_{HH} = 7.4$ Hz, 3H), 2.00–2.04 (m, 2H), 3.52 (s, 3H), 5.28 (q, $^3J_{HH} = 8.2$ Hz, 1H), 6.46 (d, $^3J_{HH} = 8.5$ Hz, 1H), 7.29–7.41 (m, 1H), 7.42–7.44 (m, 4H), 7.51–7.53 (m, 3H), 7.63 (d, $^3J_{H5H6} = 8.9$ Hz, 1H), 7.77 (d, $^3J_{H6H5} = 8.9$ Hz, 1H), 7.98–8.00 (m, 2H), 8.57 (d, $^4J_{H8H6} = 1.6$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 9.9, 27.9, 54.6, 60.9, 93.5, 123.3, 124.6, 125.7, 126.6, 127.4, 127.7, 128.3, 128.5, 133.0, 134.9, 136.0, 137.2, 140.6, 144.4, 147.1, 154.1, 163.2. IR (KBr) 3238, 3224, 3144, 3056, 3028, 2962, 2932, 2854, 1632, 1544, 1540 and 696. *m/z* 522 ($M^{+\cdot}$, $C_{26}H_{23}IN_2O_2$, 22), 493 (26), 388 (100), 84 (58). HRMS ($M^{+\cdot}$, $C_{26}H_{23}IN_2O_2$) calcd 522.08044, found 522.07837. Anal. ($C_{26}H_{23}IN_2O_2$) C, H, N.

4.1.5. Synthesis of 3-hydroxy-4-quinoline carboxamides 2 by demethylation of 3-methoxy-4-quinoline carboxamides 1. Demethylation reactions from **1** were carried out according to the procedure described in the quinolinic acid series.

4.1.5.1. (*S*)-*N*-(1-Phenylpropyl)-6-fluoro-3-hydroxy-2-phenylquinoline-4-carboxamide 2a. Carboxamide **2a** was obtained from methoxycarboxamide **1a** (0.200 g, 0.48 mmol) in CH_2Cl_2 (10 mL) and BBr_3 (0.250 g, 1.00 mmol) in CH_2Cl_2 (5 mL): white solid, mp 158 °C; 75% (0.144 g). $[\alpha]_D$ −27.0 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.08 (t, $^3J_{HH} = 7.4$ Hz, 3H), 1.95–2.09 (m, 2H), 5.19 (q, $^3J_{HH} = 7.7$ Hz, 1H), 6.80 (d, $^3J_{HH} = 8.1$ Hz, 1H), 7.27–7.54 (m, 9H), 7.56 (dd, $^4J_{H5H7} = 2.4$ Hz, $^3J_{H5F} = 10.6$ Hz, 1H), 7.98–8.01 (m, 3H), 11.2 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 11.4, 29.4, 56.7, 106.6 (d, $^2J_{CF} = 24.7$ Hz), 116.7 (d, $^2J_{CF} = 25.1$ Hz), 125.0, 125.1, 127.2, 128.4, 128.6, 129.5, 129.8, 130.0, 133.8 (d, $^3J_{CF} = 9.9$ Hz), 136.9, 140.1, 141.2, 151.9, 161.6 (d, $^1J_{CF} = 249.4$ Hz), 168.1. ^{19}F NMR ($CDCl_3$) δ −110.1 (ddd, $^4J_{FH8} = 7.1$ Hz, $^3J_{FH6} = 14.1$ Hz, $^3J_{FH5} = 11.8$ Hz). IR (KBr) 3746, 3530, 3448, 3966, 1624, 1586, 1560 and 1544. *m/z* 400 ($M^{+\cdot}$, $C_{25}H_{21}FN_2O_2$, 20), 282 (35), 265 (41), 237 (78), 135 (53), 119 (55), 91 (100), 84 (81). HRMS ($M^{+\cdot}$, $C_{25}H_{21}FN_2O_2$) calcd 400.15868, found 400.15845. Anal. ($C_{25}H_{21}FN_2O_2$) C, H, N.

4.1.5.2. (*S*)-*N*-(1-Phenylpropyl)-7-fluoro-3-hydroxy-2-phenylquinoline-4-carboxamide 2b. Carboxamide **2b** was obtained from methoxycarboxamide **1b** (0.400 g, 0.97 mmol) in CH_2Cl_2 (20 mL) and BBr_3 (0.500 g, 2.00 mmol) in CH_2Cl_2 (10 mL): white solid, mp 112 °C; 81% (0.315 g). $[\alpha]_D$ −24.0 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.05 (t, $^3J_{HH} = 7.3$ Hz, 3H), 1.99–2.11 (m, 2H), 5.26 (q, $^3J_{HH} = 7.7$ Hz, 1H), 6.63 (d, $^3J_{HH} = 7.8$ Hz, 1H), 7.34–7.46 (m, 4H), 7.50–7.56 (m, 3H), 7.81 (dd, $^4J_{H5F} = 2.7$ Hz, $^3J_{H5H6} = 9.7$ Hz, 1H), 8.50 (dd, $^4J_{H8H6} = 5.6$ Hz, $^3J_{H8F} = 9.3$ Hz, 1H), 8.07–8.09 (m, 2H), 10.9 (sl, 1H). ^{13}C NMR ($CDCl_3$) δ 11.3, 29.5, 56.7, 115.3 (d, $^2J_{CF} = 20.2$ Hz), 118.6 (d, $^2J_{CF} = 24.7$ Hz), 121.1, 123.8 (d, $^3J_{CF} = 8.9$ Hz), 127.1, 128.5, 128.7, 129.5, 130.0, 130.1, 137.0, 141.1, 144.1 (d, $^3J_{CF} = 12.9$ Hz), 153.6, 161.29 (d, $^1J_{CF} = 248$ Hz), 168.0. ^{19}F NMR ($CDCl_3$) δ −(114.6–114.7) (m). IR (KBr) 3318, 3058, 3028, 2964, 2932, 1624, 1578, 1216 and 698. *m/z* 400 ($M^{+\cdot}$, $C_{25}H_{21}FN_2O_2$, 24), 282 (52), 265 (58), 237 (41), 119 (63), 106 (39), 91 (100). HRMS ($M^{+\cdot}$, $C_{25}H_{21}FN_2O_2$) calcd 400.15868, found 400.15811. Anal. ($C_{25}H_{21}FN_2O_2$) C, H, N.

4.1.6. (*S*)-*N*-(1-Phenylpropyl)-8-fluoro-3-hydroxy-2-phenylquinoline-4-carboxamide 2c. Carboxamide **2c** was obtained from methoxycarboxamide **1c** (0.200 g, 0.48 mmol) in CH_2Cl_2 (10 mL) and BBr_3 (0.250 g, 1.00 mmol) in CH_2Cl_2 (5 mL): white solid, mp 136 °C; 65% (0.126 g). $[\alpha]_D$ −7.6 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.00 (t, $^3J_{HH} = 7.4$ Hz, 3H), 2.00–2.09 (m, 2H), 5.25 (q, $^3J_{HH} = 7.6$ Hz), 6.74 (d, $^3J_{HH} = 8.0$ Hz, 1H), 7.21–7.52 (m, 10H), 7.78 (d, $^3J_{H5H6} = 8.6$ Hz, 1H), 8.11–8.13 (m, 2H), 11.4 (sl, 1H). ^{13}C NMR ($CDCl_3$) δ 11.3, 29.5, 53.7, 111.5 (d, $^2J_{CF} = 19.4$ Hz), 116.3, 117.6 (d, $^4J_{CF} = 4.8$ Hz), 126.1, 127.1, 128.4, 128.6, 128.8 (d, $^3J_{CF} = 8.9$ Hz), 129.5, 130.0, 130.3, 133.3 (d, $^3J_{CF} = 11.5$ Hz), 137, 141.1, 152.3, 152.5, 159.4 (d, $^1J_{CF} = 258$ Hz), 168.1. ^{19}F NMR ($CDCl_3$) δ −(124.3–124.4) (m). IR (KBr) 3448, 3442, 3384, 1734, 1718, 1648, 1624, 1578, 1570, 1560, 1540 and 1534. *m/z* 400 ($M^{+\cdot}$, $C_{25}H_{21}FN_2O_2$, 18), 282 (348), 265 (42), 237 (79), 135 (54), 119 (58), 91 (100), 84 (59). HRMS ($M^{+\cdot}$,

$C_{25}H_{21}FN_2O_2$) calcd 400.15868, found: 400.15886. Anal. ($C_{25}H_{21}FN_2O_2$) C, H, N.

4.1.6.1. (*S*)-*N*-(1-Phenylpropyl)-6-iodo-3-hydroxy-2-phenylquinoline-4-carboxamide 2d. Carboxamide **2d** was obtained from methoxycarboxamide **1d** (0.050 g, 0.0958 mmol) in CH_2Cl_2 (6 mL) and BBr_3 (0.100 g, 0.398 mmol) in CH_2Cl_2 (3 mL) after purification by column chromatography (pentane/AcOEt 90:10): white solid, mp 85 °C; 64% (0.031 g). $[\alpha]_D$ −26.4 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.07 (t, $^3J_{HH} = 7.4$ Hz, 3H), 2.01–2.10 (m, 2H), 5.25 (q, $^3J_{HH} = 7.6$ Hz, 1H), 6.67 (d, $^3J_{HH} = 8.2$ Hz, 1H), 7.37–7.53 (m, 8H), 7.82 (dd, $^4J_{H7H5} = 1.6$ Hz, $^3J_{H7H8} = 8.7$ Hz, 1H), 7.86 (d, $^3J_{H8H7} = 8.7$ Hz, 1H), 8.08 (m, 2H), 8.45 (d, $^4J_{H5H7} = 1.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 11.3, 29.6, 56.6, 94.9, 115.0, 126.0, 127.0, 128.4, 128.7, 129.6, 130.0, 130.1, 131.2, 132.9, 135.7, 136.9, 141.2, 142.0, 151.9, 152.6, 153.0, 167.8. IR (KBr) 2852, 1636, 1576, 1492, 1294, 1182 and 698. *m*/*z* 508 ($M^{+\cdot}$, $C_{25}H_{21}IN_2O_2$, 22), 390 (33), 373 (37), 149 (54), 85 (79), 72 (100). HRMS ($M^{+\cdot}$, $C_{25}H_{21}IN_2O_2$) calcd 508.06479, found: 508.06158.

4.1.6.2. (*S*)-*N*-(1-Phenylpropyl)-7-iodo-3-hydroxy-2-phenylquinoline-4-carboxamide 2e. Carboxamide **2e** was obtained from methoxycarboxamide **1e** (0.193 g, 0.37 mmol) in CH_2Cl_2 (10 mL) and BBr_3 (0.370 g, 1.47 mmol) in CH_2Cl_2 (6 mL): white solid, mp 112 °C; 67% (0.126 g). $[\alpha]_D$ −6.6 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.01 (t, $^3J_{HH} = 7.4$ Hz, 3H), 1.94–2.10 (m, 2H), 5.20 (q, $^3J_{HH} = 7.7$ Hz, 1H), 6.67 (d, $^3J_{HH} = 8.1$ Hz, 1H), 7.33–7.42 (m, 5H), 7.48–7.52 (m, 3H), 7.64 (d, $^3J_{H5H6} = 8.9$, 1H), 7.73 (dd, $^4J_{H6H8} = 1.8$ Hz, $^3J_{H6H5} = 9.0$ Hz, 1H), 8.03–8.06 (m, 2H), 8.48 (d, $^4J_{H8H6} = 1.7$ Hz, 1H), 11.17 (sl, 1H). ^{13}C NMR ($CDCl_3$) δ 11.3, 29.4, 56.6, 91.4, 116.5, 123.3, 123.4, 127.1, 128.5, 128.6, 129.5, 130.0, 130.1, 136.8, 137.0, 140.0, 141.0, 143.8, 151.6, 153.0, 167.9. IR (KBr) 3854, 3448, 3344, 1624, 1560 and 698. *m*/*z* 508 ($M^{+\cdot}$, $C_{25}H_{21}IN_2O_2$, 12), 390 (33), 373 (26), 149 (30), 119 (36), 91 (68), 84 (100). HRMS ($M^{+\cdot}$, $C_{25}H_{21}IN_2O_2$) calcd 508.06479, found: 508.06581. Anal. ($C_{25}H_{21}IN_2O_2$) C, H, N.

4.1.6.3. (*S*)-*N*-(1-Phenylpropyl)-8-iodo-3-hydroxy-2-phenylquinoline-4-carboxamide 2f. Carboxamide **2e** was obtained from methoxycarboxamide **1e** (0.034 g, 0.065 mmol) in CH_2Cl_2 (5 mL) and BBr_3 (0.400 g, 1.59 mmol) in CH_2Cl_2 (10 mL): white solid, mp 74 °C; 73% (0.024 g). $[\alpha]_D$ −24.8 (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.00 (t, $^3J_{HH} = 7.4$ Hz, 3H), 1.95–2.09 (m, 2H), 5.19 (q, $^3J_{HH} = 7.7$ Hz, 1H), 6.64 (d, $^3J_{HH} = 7.9$ Hz, 1H), 7.19 (t, $^3J_{H6H5} = {}^3J_{H6H7} = 8.1$ Hz, 1H), 7.25–7.42 (m, 5H), 7.48–7.54 (m, 3H), 7.96 (d, $^3J_{H5H6} = 8.2$ Hz, 1H), 8.18 (dd, $^4J_{H7H5} = 0.7$ Hz, $^3J_{H7H6} = 8.1$ Hz, 1H), 8.34 (m, 2H), 11.34 (sl, 1H). ^{13}C NMR ($CDCl_3$) δ 10.9, 29.1, 56.3, 106.5, 116.4, 122.3, 124.1, 126.7, 128.0, 128.2, 129.0, 129.1, 129.8, 130.2, 136.4, 137.2, 140.7, 141.1, 151.8, 151.9, 167.6. IR (KBr) 2958, 2954, 2852, 2358, 1716, 1700, 1684, 1652, 1622 and 698. *m*/*z* 508 ($M^{+\cdot}$, $C_{25}H_{21}IN_2O_2$, 14), 390 (33), 373 (20), 149 (32), 119 (36), 91 (70), 84 (100). HRMS ($M^{+\cdot}$, $C_{25}H_{21}IN_2O_2$) calcd 508.06479, found: 508.06466.

4.2. Biology

Receptor binding assays were performed with crude membranes from Chinese hamster ovary (CHO) cells expressing the human NK-3 receptor (hNK-3r-CHO) purchased from Amersham Biosciences or with CHO cells stably transfected with the human NK-1 receptor (hNK-1r-CHO) cDNA (generous gift from Dr. J. Grassi and Prof. J. Y. Couraud, CEA Saclay) plated in 24-well plates. [^{3}H]-Senktide and [^{125}I]-Bolton-Hunter-substance P ([^{125}I]-BH-SP) used as radioligands were supplied by Perkin Elmer Life Sciences. The time necessary to reach the steady state was previously determined by kinetic studies; the radioligand dissociation constant (K_d) and the maximum number of binding sites (B_{max}) were obtained by saturation binding experiments.

4.2.1. Radioligand binding assays. Briefly, for hNK3-r competition studies, hNK-3r-CHO membranes (~7 μg of protein) were incubated with 3 nM [^{3}H]-senktide in a total volume of 170 μL of 50 mM Tris HCl (pH 7.4), 3 mM $MnCl_2$, 1 μM phosphoramidon, 40 μg/mL bacitracin and 0.5% bovine serum albumin (BSA), with or without various concentrations of tested compounds, for 60 min at 25 °C. Incubations were stopped by rapid filtration with a Brandell tissue harvester through Whatman GF/C filters that were presoaked for at least 60 min in 0.5% BSA. Membranes were washed three times with ice-cold 50 mM Tris HCl (pH 7.4) and bound radioactivity (dpm) was determined by using liquid scintillation counting.

For hNK-1r competition studies, CHO cells expressing hNK-1r (2×10^5 cells/well) were cultured as previously described[28] and washed three times with Krebs buffer (120 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$, 70 mM NaH_2PO_4, 1.6 mM $CaCl_2$, 0.04 mM BSA, 30 mg/mL bacitracin and 6 g/L glucose). Cells were then incubated for 100 min at room temperature (until equilibrium) in presence of 15 pM [^{125}I]-BH-SP and increasing concentrations of cold competing ligands in a final volume of 200 μL. Finally, cells were washed three times in cold Krebs buffer, lysed with 0.1% Triton X100 containing 1 mg/mL BSA overnight at 4 °C°C and the radioactivity was counted with a Cobra Auto-Gamma counter ard).

Concentration–response curves for each compound, were run using duplicate samples in at least two independent experiments following curve-fitting procedures in SigmaPlot. Specific binding was determined by subtracting total binding from nonspecific binding, which was assessed as the binding in the presence of 10 μM NKB or SP. Percent inhibition of specific binding was determined for each compound concentration and the IC_{50} value defined as the concentration required to inhibit 50% of the specific binding, obtained from concentration–response curves. Values presented in Table 1 were the inhibition constants (K_i), which were calculated

from the IC_{50} according to Cheng and Prusoff procedure.[29]

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