

QUINOLINE DERIVATIVES.

5 The present invention relates to novel compounds, in particular to novel quinoline derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

The mammalian peptide Neurokinin B (NKB) belongs to the Tachykinin (TK) peptide family which also include Substance P (SP) and Neurokinin A (NKA). Pharmacological and molecular biological evidence has shown the existence of three
10 subtypes of TK receptor (NK₁, NK₂ and NK₃) and NKB binds preferentially to the NK₃ receptor although it also recognises the other two receptors with lower affinity (Maggi et al, 1993, *J. Auton. Pharmacol.*, 13, 23-93).

Selective peptidic NK₃ receptor antagonists are known (Drapeau, 1990 *Regul. Pept.*, 31, 125-135), and findings with peptidic NK₃ receptor agonists suggest that NKB,
15 by activating the NK₃ receptor, has a key role in the modulation of neural input in airways, skin, spinal cord and nigro-striatal pathways (Myers and Undem, 1993, *J. Physiol.*, 470, 665-679; Counture et al., 1993, *Regul. Peptides*, 46, 426-429; Mccarson and Krause, 1994, *J. Neurosci.*, 14 (2), 712-720; Arenas et al. 1991, *J. Neurosci.*, 11, 2332-8). However, the peptide-like nature of the known antagonists makes them likely to
20 be too labile from a metabolic point of view to serve as practical therapeutic agents.

We have now discovered a novel class of non-peptide NK-3 antagonists which are far more stable from a metabolic point of view than the known peptidic NK-3 receptor antagonists and are of potential therapeutic utility. These compounds also have NK-2
25 antagonist activity and are therefore considered to be of potential use in the prevention and treatment of a wide variety of clinical conditions which are characterized by overstimulation of the tachykinin receptors, in particular NK-3 and NK-2.

These conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity, cough; inflammatory
30 diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjunctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions
35 such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and urinary incontinence; renal disorders and disorders of the bladder function, (hereinafter referred to as the 'Primary Conditions').

40 In addition, certain of the present compounds are indicated to be particularly selective for the periphery rather than the central nervous system. These compounds are therefore considered to be especially useful in the treatment of those components of the

'Primary Conditions' which require a peripheral-selectivity.

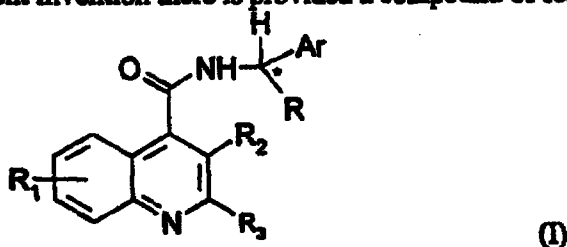
Certain compounds of this invention also show CNS activity and hence are considered to be of particular use in the treatment of disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntington's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of the blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine, (hereinafter referred to as the 'Secondary Conditions').

Certain of these compounds are selective antagonists of the NK-3 receptor relative to the NK-2 receptor.

In an alternative aspect, certain of these compounds are combined NK-2/NK-3 antagonists and hence are considered to be particularly suitable for the treatment and/or prophylaxis of respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity and cough.

The compounds are also considered to be useful as diagnostic tools for assessing the degree to which neurokinin-3 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms.

According to the present invention there is provided a compound of formula (I):



or a solvate thereof, or a salt thereof, wherein, Ar is an optionally substituted aryl or a C₅-7 cycloalkadienyl group, or an optionally substituted single or fused ring aromatic heterocyclic group;

R is C₁-6 alkyl, C₃-7 cycloalkyl, C₃-7 cycloalkylalkyl, optionally substituted phenyl or phenyl C₁-6 alkyl, an optionally substituted five-membered heteroaromatic ring comprising up to four heteroatoms selected from O and N, hydroxy C₁-6 alkyl, amino C₁-6 alkyl, C₁-6 alkylaminoalkyl, di C₁-6 alkylaminoalkyl, C₁-6 acylaminoalkyl, C₁-6 alkoxyalkyl, C₁-6 alkylcarbonyl, carboxy, C₁-6 alkoxyxcarbonyl, C₁-6 alkoxyxcarbonyl

C₁₋₆ alkyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di C₁₋₆ alkylaminocarbonyl, halogeno C₁₋₆ alkyl; or R is a group $-(CH_2)_p-$ wherein p is 2 or 3 which group forms a ring with a carbon atom of Ar;

5 R₁ represents hydrogen or up to four optional substituents selected from the list consisting of: C₁₋₆ alkyl, C₁₋₆ alkenyl, aryl, C₁₋₆ alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C₁₋₆ alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino or mono- and di-C₁₋₆ alkylamino;

10 R₂ represents a moiety $-O-(CH_2)_n-X$ wherein X is alkyl optionally substituted with one or two groups selected from hydroxy and amino; carboxy, cyano, C₁₋₆ alkoxycarbonyl, aminocarbonyl, mono- or di-C₁₋₆ alkylaminocarbonyl, amino-C₁₋₆-alkylaminocarbonyl or mono- or di-C₁₋₆-alkylamino-C₁₋₆-alkylaminocarbonyl; or X is a group $-NX_1X_2$ wherein X₁ and X₂ each independently represent hydrogen, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aryl-C₁₋₆-alkylcarbonyl, heteroaryl C₁₋₆-alkylcarbonyl, aminocarbonyl, mono- or bis-C₁₋₆ alkylaminocarbonyl, amino C₁₋₆-alkylcarbonyl, mono- or bis-C₁₋₆ alkylamino C₁₋₆ alkylcarbonyl, a moiety of formula -CO-T-CO-T₁ or a 5 to 9 membered single or fused ring cycloalkyl group optionally comprising 1 or 2 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O or N and wherein one or two ring atoms are optionally substituted with C₁₋₆ alkyl, said ring being optionally fused to a benzene ring; wherein the above mentioned
20 aryl and heteroaryl groups are optionally substituted with up to two groups selected from: hydroxy, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkyl, amino-C₁₋₆ alkyl, mono- or bis- C₁₋₆-alkylamino, mono- or bis- C₁₋₆-alkylamino-C₁₋₆ alkyl, amino-C₁₋₆-alkoxy, mono- or bis- C₁₋₆-alkylamino-C₁₋₆-alkoxy, carboxy, C₁₋₆-alkylcarbonyl, C₁₋₆-alkoxycarbonyl, carboxy-C₁₋₆ alkyl, carboxy-C₁₋₆ alkoxy and C₁₋₆-alkylcarbonyl C₁₋₆ alkoxy; and
25 wherein the alkyl moiety of any heteroaryl-C₁₋₆-alkyl or aryl-C₁₋₆-alkyl group is optionally substituted with an amino, a mono-C₁₋₆-alkylamino or a bis-C₁₋₆-alkyl amino group; or X is a C-linked single or fused ring heterocyclic group, any ring being saturated or unsaturated and consisting of 5- to 6- ring atoms, said ring atoms comprising 1 or 2 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected
30 from O or N and wherein one or two ring atoms are optionally substituted with C₁₋₆ alkyl, hydroxy, amino, mono- or bis- C₁₋₆-alkylamino or an oxo substituent; and n is zero or an integer in the range of from 1 to 7 providing that when X is a group $-NX_1X_2$, n is only an integer in the range of from 2 to 7 and providing that X₁ and X₂ are not simultaneously hydrogen; or R₂ represents a moiety $-NH-CO-NHY$ wherein Y represents
35 C₁₋₆ -alkyl, aryl, aryl C₁₋₃ -alkyl, a moiety $-(CH_2)_p-X_3$ wherein p is an integer in the range of from 1 to 4 and X₃ is carboxy, C₁₋₆ alkoxycarbonyl, or a moiety $-CO-NH-(CH_2)_q-NX_4X_5$ wherein q is an integer in the range of from 2 to 4 and X₄ and X₅ each independently represent hydrogen, C₁₋₆ alkyl or C₁₋₆ alkylcarbonyl;

40 R₃ is branched or linear C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring aromatic heterocyclic group, ;

T is a C₁₋₆ alkylene or C₂₋₆ alkenylene group; and

T₁ is hydroxy or C₁₋₆ alkoxy.

Suitably, Ar represents phenyl

Suitably, R represents C₁₋₆ alkyl, for example ethyl.

Preferably, R is ethyl.

5 Preferably, R₁ represents hydrogen.

When R₂ represents a moiety -O-(CH₂)_n-X wherein n is an integer in the range of from 1 to 7, such as 1, 2 and 3, suitable values of X include carboxy, C₁₋₆

alkoxycarbonyl, aminocarbonyl, mono- or di- C₁₋₆ alkylaminocarbonyl or X is a C-linked single or fused ring heterocyclic group as defined in relation to formula (I);

10 preferably X is carboxy, C₁₋₆ alkoxycarbonyl, for example ethoxycarbonyl, or the said C-linked single or fused ring heterocyclic group, for example pyridyl; preferably n is 1 or 3.

In one preferred aspect R₂ is a group -O-(CH₂)_n-X wherein X represents carboxy or C₁₋₆ alkoxycarbonyl.

15 In one preferred aspect R₂ is a group -O-(CH₂)_n-X wherein X represents a C-linked single or fused ring heterocyclic group as defined in relation to formula (I).

When R₂ represents a moiety -O-(CH₂)_n-X wherein n is an integer in the range of from 2 to 7, such as 2 and 3, suitable values of X include a group -NX₁X₂ wherein X₁ and X₂ each independently represent hydrogen, alkylcarbonyl, heteroarylcarbonyl,

20 arylcarbonyl, aminocarbonyl, mono- or di-C₁₋₆ alkylaminocarbonyl, a moiety of the above defined formula -CO-T-CO-T₁ or a 5- or 6- membered cycloalkyl group said group being optionally fused to a benzene ring, providing that X₁ and X₂ are not simultaneously hydrogen; preferably one of X₁ and X₂ is hydrogen and the other is selected from heteroarylcarbonyl, arylcarbonyl or a moiety of the above defined formula -CO-T-CO-T₁.

25 Examples of X include carboxy, cyano, ethoxycarbonyl, aminocarbonyl, dimethylaminocarbonyl, (2-indanyl)amino and benzoylamino.

One particular value of R₂ is -O-(CH₂)_n-X wherein n is an integer 1, 2 or 3 and X is carboxy.

30 One particular value of R₂ is -O-(CH₂)_n-X wherein n is an integer 1, 2 or 3 and X is ethoxycarbonyl. One particular value of R₂ is -O-(CH₂)_n-X wherein n is an integer 1, 2 or 3 and X is pyridyl.

35 One particular value of R₂ is -O-(CH₂)_n-X wherein n is an integer 2 or 3 and X is a group -NX₁X₂ wherein X₁ is hydrogen and X₂ is a 5 to 9 membered single ring cycloalkyl group ring fused to a benzene ring, for example a 2-indanylamino group, or an N-methyl-8-azabicyclo[3.2.1]oct-3-yl group

One particular value of R₂ is -O-(CH₂)_n-X wherein n is an integer 2 or 3 and X is a group -NX₁X₂ wherein X₁ is hydrogen and X₂ is amino-C₁₋₆ alkylcarbonyl or mono- or bis-C₁₋₆ alkylamino C₁₋₆ alkylcarbonyl, for example 2-aminoacetyl.

40 One particular value of R₂ is -O-(CH₂)_n-X wherein n is an integer 2 or 3 and X is a group -NX₁X₂ wherein X₁ is hydrogen and X₂ is a moiety of formula -CO-T-CO-T₁ wherein T is a C₁₋₆ alkylene, for example -CH₂CH₂- and T₁ is hydroxy or C₁₋₆ alkoxy, especially hydroxy.

One particular value of R_2 is $-O-(CH_2)_n-X$ wherein n is an integer 2 or 3 and X is a group $-NX_1X_2$ wherein X_1 is hydrogen and X_2 is optionally substituted heteroarylcarbonyl, such as 2-pyrazinylcarbonyl and 3-amino-2-pyrazinylcarbonyl.

One particular value of R_2 is $-O-(CH_2)_n-X$ wherein n is an integer 2 or 3 and X is a group $-NX_1X_2$ wherein X_1 is hydrogen and X_2 is optionally substituted aryl- C_{1-6} -alkylcarbonyl group, such as 2-(methylaminomethyl) benzylcarbonyl, 2-(pyrrolidinomethyl)benzylcarbonyl, 2-(pyrrolidinoethoxy)benzylcarbonyl and (2-carboxy)benzylcarbonyl.

One preferred value of R_2 is $-O-(CH_2)_n-X$ wherein n is an integer 2 or 3 and X is a group $-NX_1X_2$ wherein X_1 is hydrogen and X_2 is a moiety of the above defined formula $-CO-T-CO-T_1$, for example wherein T is ethylene and T_1 is OH.

One preferred value of R_2 is $-O-(CH_2)_n-X$ wherein n is an integer 2 or 3 and X is a group $-NX_1X_2$ wherein X_1 is hydrogen and X_2 is and substituted aryl- C_{1-6} -alkylcarbonyl, for example (2-carboxy)benzylcarbonyl and (2-pyrrolidinomethyl)benzylcarbonyl.

One preferred value of R_2 is $-O-(CH_2)_n-X$ wherein n is an integer 2 or 3 and X is a group $-NX_1X_2$ wherein X_1 is hydrogen and X_2 is heteroarylcarbonyl, for example 2-pyrazinylcarbonyl.

When R_2 represents a moiety $-O-(CH_2)_n-X$ wherein n is zero, suitable values of X include carboxy, C_{1-6} alkoxy carbonyl, for example ethoxycarbonyl.

Y suitably represents aryl, for example phenyl, or a moiety $-(CH_2)_p-X_3$.

When Y is $-(CH_2)_p-X_3$, p is favourably an integer 1.

When Y is $-(CH_2)_p-X_3$, X_3 is suitably C_{1-6} alkoxy carbonyl, for example ethoxycarbonyl.

Preferred compounds of formula (I) are those wherein:

Ar is phenyl, R is ethyl, R_1 is hydrogen and R_2 is a moiety $-O-(CH_2)_n-X$ wherein either:

n is 1, 2 or 3 and X is carboxy, C_{1-6} alkoxy carbonyl, for example ethoxycarbonyl, or the C-linked single or fused ring heterocyclic group defined in relation to formula (I), for example pyridyl;

or

n is 2 or 3 and X is a group $-NX_1X_2$ wherein X_1 is hydrogen and X_2 is moiety of the above defined formula $-CO-T-CO-T_1$, for example wherein T is ethylene and T_1 is OH, or X_2 is substituted aryl- C_{1-6} -alkylcarbonyl, for example (2-carboxy)benzylcarbonyl and (2-pyrrolidinomethyl)benzylcarbonyl or heteroarylcarbonyl, for example 2-pyrazinylcarbonyl.

In particular should be mentioned the compounds of examples 2, 11, 14, 29, 34, 36, 38, 39 and 40, especially 2, 11 and 40.

It should also be stated that compounds 2 and 11, especially, 14 and 29 are particularly active at the periphery and hence are considered to be especially selective for those 'Primary Conditions' which require peripheral selectivity, as discussed above.

Compounds 34, 36 and 38 are particularly selective for the NK-3 receptor relative

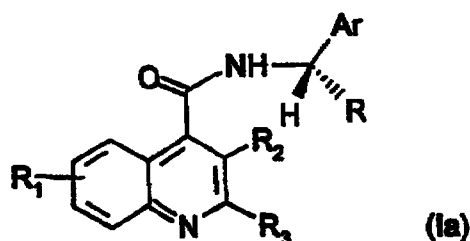
to the NK-2 receptor.

As stated above certain of the compounds of formula (I) are combined NK-2/NK-3 antagonists and are considered to be particularly suitable for the treatment and/or prophylaxis of respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity and cough. Accordingly the present invention also comprises a combined NK-2/NK-3 antagonist, especially for use in the treatment and/or prophylaxis of respiratory diseases. Also within the present invention is a method for the treatment and/or prophylaxis of respiratory diseases in mammals, such as humans, which method comprises the administration of an effective, non-toxic, pharmaceutically acceptable amount of a combined NK-2/NK-3 antagonist.

A suitable, combined NK-2/NK-3 antagonist is an antagonist having an NK-2/NK-3 binding affinity ratio in the range of from 0.05 to 20, favourably 0.1 to 10, preferably 1 to 7 and most preferably 1 to 5; thus preferred compounds are considered to be substantially equipotent antagonists of the NK-2 and NK-3 receptors.

Compounds 39 and 40 are particularly suitable as combined NK-2/NK-3 antagonists and hence are particularly suitable for the treatment and/or prophylaxis of respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity and cough.

The compounds of formula (I) may have at least one asymmetric centre - for example the carbon atom labelled with an asterisk (*) in the compound of formula (I) - and therefore may exist in more than one stereoisomeric form. The invention extends to all such stereoisomeric forms and to mixtures thereof, including racemates. In particular, the invention includes compounds wherein the asterisked carbon atom in formula (I) has the stereochemistry shown in formula (Ia):



wherein Ar, R, R₁, R₂ and R₃ are as defined in relation to formula (I).

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

5 Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

10 Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

15 Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl- β -phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, 20 quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

25 The term 'alkyl' when used alone or when forming part of other groups (such as the 'alkoxy' group) includes straight- or branched-chain alkyl groups containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms, examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl group.

The term 'cycloalkyl' includes groups having 3 to 12, suitably 4 to 6 ring carbon atoms.

30 The term 'aryl' includes phenyl and naphthyl, preferably phenyl which unless specified to the contrary optionally comprise up to five, preferably up to three substituents selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

35 The term 'aromatic heterocyclic group' or 'heteroaryl' includes groups comprising aromatic heterocyclic rings containing from 5 to 12 ring atoms, suitably 5 or 6, and comprising up to four hetero-atoms in the or each ring selected from S, O or N. Unless specified to the contrary suitable substituents for any heterocyclic group includes up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any 40 two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be

substituted or unsubstituted.

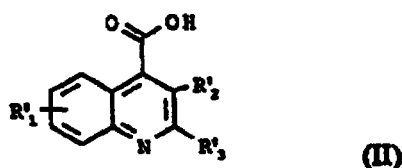
When used herein the term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably fluorine or chlorine.

When used herein the term "acyl" includes residues of acids, in particular a residue of a carboxylic acid such as an alkyl- or aryl- carbonyl group.

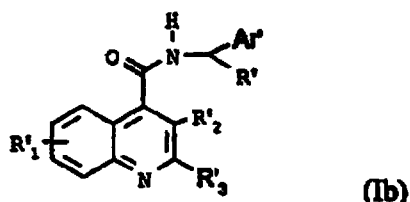
The invention also provides a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (III):



wherein R' and Ar' are R and Ar as defined for formula (I) or a group or atom convertible to R and Ar respectively, with a compound of formula (II) or an active derivative thereof:



wherein R'₁, R'₂ and R'₃ are R₁, R₂ and R₃ respectively as defined in relation to formula (I) or a group convertible to R₁, R₂ and R₃ to form a compound of formula (Ib):



wherein Ar', R', R'₁, R'₂ and R'₃ are as defined above, and optionally thereafter carrying out one or more of the following optional steps:

- (i) converting any one of Ar', R', R'₁, R'₂ and R'₃ to Ar, R, R₁, R₂ or R₃ respectively as required, to obtain a compound of formula (I);
- (ii) converting a compound of formula (I) into another compound of formula (I); and
- (iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Suitable groups convertible into other groups include protected forms of said groups.

Suitably Ar', R', R'₁ or R'₃ each represents Ar, R, R₁, or R₃ respectively or a protected form thereof.

Suitably R'₂ represents a group other than a protected form which is convertible into R₂ by conventional procedures.

It is favoured if the compound of formula (II) is present as an active derivative.

A suitable active derivative of a compound of formula (II) is a transient activated form of the compound of formula (II) or a derivative wherein the carboxy group of the compound of formula (II) has been replaced by a different group or atom, for example
5 by a carboxy halide, preferably a chloride, or an azide or a carboxylic acid anhydride.

Other suitable active derivatives include: a mixed anhydride formed between the carboxyl moiety of the compound of formula (II) and an alkyl chloroformate; an activated ester, such as a cyanomethyl ester, thiophenyl ester, p-nitrophenyl ester, p-nitrothiophenyl ester, 2,4,6-trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-
10 hydroxy-phthalimido ester, N-hydroxypiperidine ester, N-hydroxysuccinimide ester, N-hydroxy benzotriazole ester; alternatively, the carboxy group of the compound of formula (II) may be activated using a carbodiimide or N,N'-carbonyldiimidazole.

The reaction between the compound of formula (II) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate
15 conventional conditions for the particular compounds chosen. Generally, when the compound of formula (II) is present as an active derivative the reaction is carried out using the same solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (Ib) and thereafter the compound of formula (I) or a salt thereof and/or a solvate thereof is
20 prepared.

For example the reaction between an active derivative of the compound of formula (II) and the compound of formula (III) may be carried out:

(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable
25 aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C); or

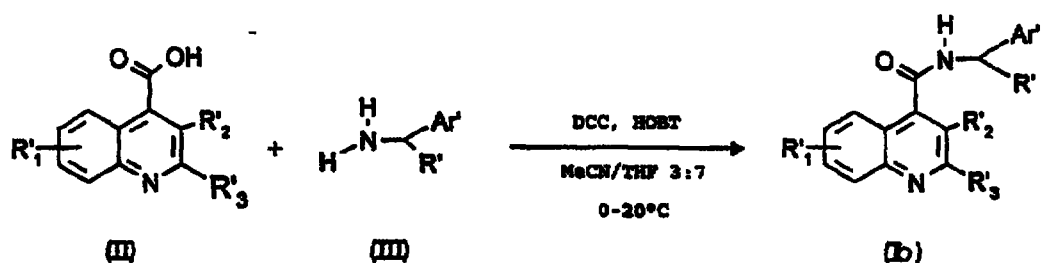
(b) by treating the compound of formula (II) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyldiimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-
30 dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis*, 453, 1972), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a volume ratio of from 1:9 to 7:3 (MeCN:THF), at a temperature in the range of from -70 to 50°C (preferably in a range of
35 from -10 to 25°C).

A preferred reaction is set out in Scheme 1 shown below:

40

Scheme 1

-9-



wherein Ar', R', R₁, R₂ and R₃ are as defined above.

It will be appreciated that a compound of formula (Ib) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I) by interconversion of suitable substituents. Thus, certain compounds of formula (I) and (Ib) are useful intermediates in forming other compounds of the present invention.

Accordingly, in a further aspect the invention provides a process for preparing a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises converting a compound of the above defined formula (Ib) wherein at least one of Ar', R', R₁, R₂ or R₃ is not Ar, R, R₁, R₂ or R₃ respectively, thereby to provide a compound of formula (I); and thereafter, as required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) into another compound of formula (I); and
- (ii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Suitably, in the compound of formula (Ib) the variables Ar', R', R₁ and R₃ are Ar, R, R₁ or R₃ respectively or they are protected forms thereof and R₂ is a group or atom which may be converted into a variable R₂ by one or more steps.

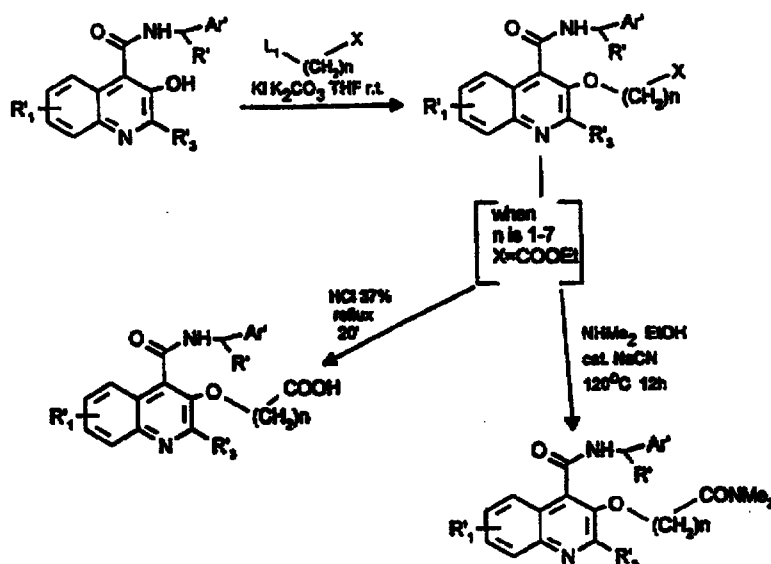
Favourably, R₂ represents OH or NH₂.

The conversion of any group Ar', R', R₁ or R₃ into Ar, R, R₁ or R₃, which as stated above are usually protected forms of Ar, R, R₁ or R₃, may be carried out using appropriate conventional conditions such as the appropriate deprotection procedure.

The conversion of any group R₂ into R₂ may be carried out using appropriate conventional reagents and conditions:

For example, when R₂ is OH, the compounds of formula (Ib) can be converted to compounds of formula (I) as described in Scheme 2.

Scheme 2



- 5 wherein Ar', R', R'₁, R'₂, R'₃ and X are as defined above in relation to formula (I), n is as defined in relation to formula (I) or as particularly specified in the Scheme 2 and L₁ is a leaving group or atom, such as a halogen atom for example a chlorine or bromine atom.

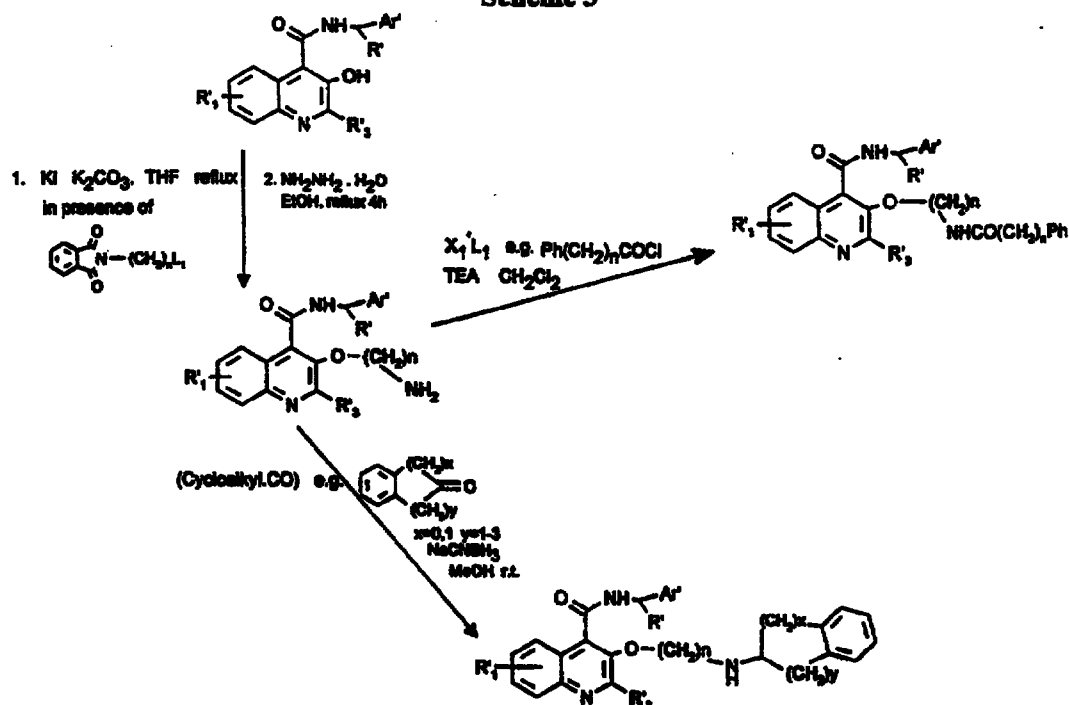
In Scheme 2, an example of X is COOEt.

- 10 In particular, when R'₂ is OH, it can be alkylated with an alkyl haloformate or with an ω-haloalkyl ester or ω-haloalkyl nitrile; for example, when it is alkylated with ethylbromoacetate and K₂CO₃ in THF, the 3-ethoxycarbonylmethoxy derivative is obtained. The resulting ester moiety can be subsequently hydrolyzed by refluxing in concentrated HCl, or transamidated with ammonia, a primary or a secondary amine in ethanol as solvent, at a temperature ranging from 20° to 120°C, optionally in the presence of a catalytic amount of NaCN (*J. Org. Chem.*, 1987, 52, 2033).

15 In Scheme 3, R'₂ = OH is converted to an ω-aminoalkoxy group by reaction with ω-bromoalkylphthalimide and K₂CO₃ in boiling THF to obtain the phthalimidoalkoxy derivative, which is, in turn, hydrolyzed with hydrazine hydrate.

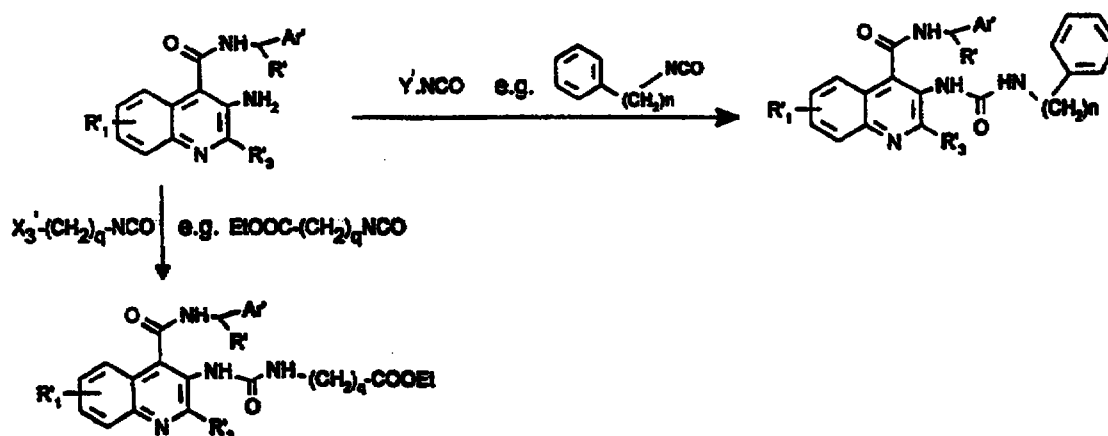
- 20 The amino function of the resulting ω-aminoalkoxy substituent can then be acylated with a phenyl(alkyl) acid chloride, such as benzoyl chloride, and TEA in CH₂Cl₂ or can be submitted to a reductive amination procedure with a benzo-condensed cyclic ketone, for example 2-indanone, and NaCNBH₃ in methanol at room temperature (*J. Am. Chem. Soc.*, 1971, 93, 2897).

Scheme 3



- 5 wherein Ar' , R' , R'_1 , R'_2 and R'_3 are as defined above, X_1 is X_1 as defined in relation to formula (I) or a protected form thereof, (cyclic.CO) is a 5 to 9 membered single or fused ring cycloalkyl group wherein one or two ring atoms are optionally substituted with C_{1-6} alkyl, said ring being optionally fused to a benzene ring and said ring also comprising an oxo group.
- 10 When R'_2 is NH_2 , compounds (Ib) can be converted to other compounds of formula (I) or (Ib) as described in Scheme 4.

Scheme 4



5

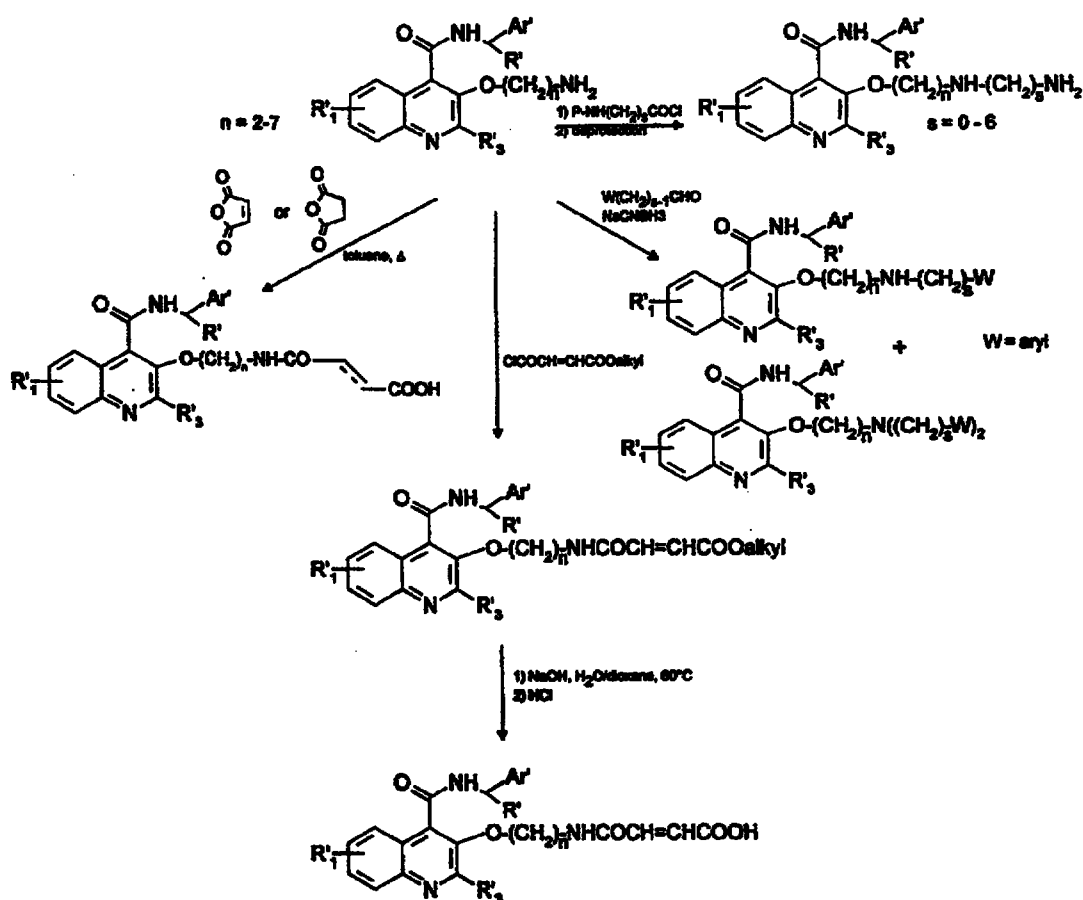
- wherein Ar', R', R'₁, R'₂, R'₃ and n are as defined above, Y' is Y as defined in relation to formula (I) or a protected form thereof, X₃' is X₃ as defined in relation to formula (I) or a protected form thereof and q is as defined in relation to formula (I). In particular,
- 10 when R'₂ is NH₂, the phenyl(alkyl)ureido derivative is obtained by reaction with phenyl(alkyl)isocyanate in CH₂Cl₂/THF/CH₃CN at 40°C. In a similar way the ethoxycarbonylalkyl ureido derivatives are synthesized from the corresponding ethoxycarbonylalkyl isocyanates in THF/DMF at 60°C. In a further aspect, the primary amine intermediate described in Scheme 3 (wherein R₂ is a moiety -O-(CH₂)_n-N
- 15 X₁X₂ in which X₁ and X₂ both represent hydrogen) may be converted into a compound of formula (I) wherein one or both of X₁ and X₂ represent aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl or a moiety -CO-T-CO-T₁ wherein T and T₁ are as defined in relation to formula (I), by using such reactions as those exemplified in Scheme 5:

20

25

30

Scheme 5

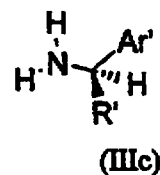
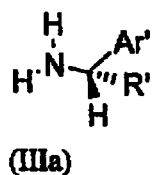


wherein Ar' , R' , R_1' , and R_3' are as defined above.

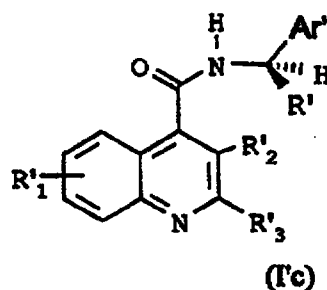
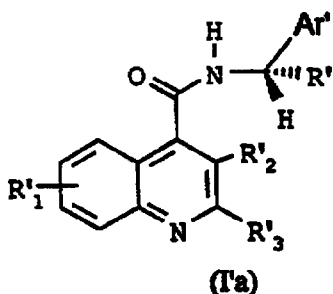
- 5 Suitable conversions of one compound of formula (I) into another compound of formula (I) include conversions wherein one group R , R_1 , R_2 or R_3 is converted into another group R , R_1 , R_2 or R_3 respectively, said conversions conveniently proceeding via appropriate groups Ar' , R' , R_1' , R_2' and R_3' using conventional methodology, for example those methods described in Schemes 2, 3 and 4 above.

- 10 As mentioned before, the compounds of formula (I) may exist in more than one stereoisomeric form - and the process of the invention may produce racemates as well as enantiomerically pure forms. Accordingly, a pure enantiomer of a compound of formula (I) is obtained by reacting a compound of the above defined formula (II) with an appropriate enantiomerically pure primary amine of formula (IIIa) or (IIIc):

15

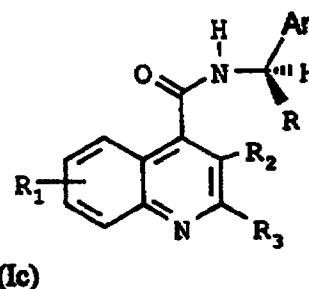
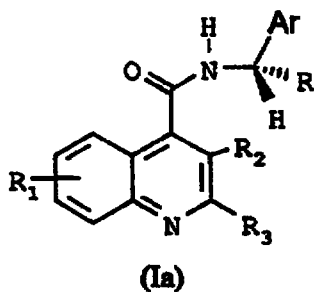


wherein R' and Ar' are as defined above, to obtain a compound of formula (I'a) or (I'e):



wherein Ar', R', R'1, R'2 and R'3 are as defined above.

Compounds of formula (I'a) or (I'e) may subsequently be converted to compounds of formula (Ia) or (Ic):



15 wherein Ar, R, R1, R2 and R3 are as defined above by the methods of conversion mentioned before.

The compounds of formula (II) wherein R2 is OH or NH2 and protected forms of such compounds are either known compounds or they are prepared according to methods used to prepare known compounds, for example 3-hydroxy-2-phenyl-4-quinoline carboxylic acid (R2 is OH, CAS = [485-89-2]) is prepared in accordance with the methods described in U.S. Patent 2,776,290 (1957); and 3-amino-2-phenyl-4-quinoline carboxylic acid (R2 is NH2, CAS = [36735-26-9]) is prepared in accordance with the methods described in Chemical Abstract 77:61769u (c.f. Khim. Geterotsikl. Soedin. (1972), 4, 525-6).

25 It will be appreciated that in any of the abovementioned reactions any reactive group in the substrate molecule may be protected according to conventional chemical practice.

Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. Thus, for example suitable hydroxyl protecting groups include benzyl or trialkylsilyl groups. An amino group is conveniently protected as a (9-fluorenylmethoxycarbonyl)amino [FMOCamino] group.

30 The methods of formation and removal of such protecting groups are those

conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent
5 such as trimethylsilyl iodide or boron tribromide. The FMOCamino group is prepared by reacting the amino compound with FMOC chloride in a solvent such as methylene chloride, preferably in the presence of triethylamine and usually at a low to ambient temperature, for example in the range of from 0°C to ambient temperature. The FMOC group is removed by treating with an organic base such as diethylamine.

10 As indicated above, the compounds of formula (I) have useful pharmaceutical properties, accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising
15 a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

20 In addition as mentioned certain compounds of the invention are selective for the periphery. These compounds are characterised in that they are sufficiently hydrophilic so that substantially they do not pass through the blood-brain barrier. This hydrophilicity is readily measured by use conventional physicochemical methods, such as partition coefficient (logP and ΔLogP) measurements and is readily verified in vivo by for example
25 the assessment of the relative level of compound in the plasma versus the brain after dosing to an animal.

Partition coefficients are determined by conventional methods such as those disclosed by A. Leo *et al* in Chem. Rev. 1971, 71, 525, R.C. Young *et al* in J. Med. Chem. 1988, 31, 656 or by P. Seiler in Eur. J. Med. Chem. 1974, 9, 473.

30 Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the
35 preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

40 The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycolate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free

water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form
5 such as ampoules or disposable injection devices or in multi-dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation
10 comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10
15 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive
20 through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of
25 administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active
30 ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans,
35 which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The activity of the compounds of the present invention, as NK₃ ligands, is determined by their ability to inhibit the binding of the radiolabelled NK₃ ligands, [¹²⁵I]-
40 [Me-Phe⁷]-NKB or [³H]-Senktide, to guinea-pig and human NK₃ receptors (Renzetti et al, 1991, *Neuropeptide*, 18, 104-114; Buell et al, 1992, *FEBS*, 299(1), 90-95; Chung et al, 1994, *Biochem. Biophys. Res. Commun.*, 198(3), 967-972).

The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-[Me-Phe 7]-NKB and [^3H]-Senktide specific binding to NK $_3$ receptor in equilibrium conditions (IC $_{50}$).

Binding assays provide for each compound tested a mean IC $_{50}$ value of 2-5
5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC $_{50}$ values in the range 0.1-1000 nM. The NK $_3$ -antagonist activity of the compounds of the present invention is determined by their ability to inhibit senktide-induced contraction of the guinea-pig ileum (Maggi et al, 1990, *Br. J. Pharmacol.*, 101, 996-1000) and rabbit isolated iris sphincter muscle (Hall et al., 1991,
10 *Eur. J. Pharmacol.*, 199, 9-14) and human NK $_3$ receptors-mediated Ca $^{++}$ mobilization (Mochizuki et al, 1994, *J. Biol. Chem.*, 269, 9651-9658). Guinea-pig and rabbit *in-vitro* functional assays provide for each compound tested a mean K $_B$ value of 3-8 separate experiments, where K $_B$ is the concentration of the individual compound required to produce a 2-fold rightward shift in the concentration-response curve of senktide. Human
15 receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC $_{50}$ values) the Ca $^{++}$ mobilization induced by the agonist NKB. In this assay, the compounds of the present invention behave as antagonists.

20 The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed using rodent disease models.

As stated above, the compounds of formula (I) are also considered to be useful as diagnostic tool. Accordingly, the invention includes a compound of formula (I) for use as diagnostic tools for assessing the degree to which neurokinin-3 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms. Such use comprises
25 the use of a compound of formula (I) as an antagonist of said activity, for example including but not restricted to tachykinin agonist-induced inositol phosphate turnover or electrophysiological activation, of a cell sample obtained from a patient. Comparison of such activity in the presence or absence of a compound of formula (I), will disclose the degree of NK-3 receptor involvement in the mediation of agonist effects in that tissue.

30 The following Descriptions illustrate the preparation of the intermediates, whereas the Examples illustrate the preparation of the compounds of the present invention. The compounds of the Examples are summarised in Table 1-3 below.

35

DESCRIPTION 1

(S)-N-(α -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide

- 5 2.49 g (9.4 mmol) of 3-hydroxy-2-phenylquinoline-4-carboxylic acid (CAS [485-89-2]) were suspended in 150 ml of a 7/3 mixture of THF/CH₃CN; 1.40 g (10.3 mmol) of 1-hydroxybenzotriazole (HOBT) and 1.27 g (9.4 mmol) of (S)- α -ethylbenzylamine dissolved in 20 ml of CH₂Cl₂ were added and the reaction mixture was stirred at room temperature for 30 minutes. 2.13 g (10.3 mmol) of dicyclohexylcarbodiimide (DCC)
- 10 dissolved in 20 ml of CH₂Cl₂ were added dropwise. The reaction was left at room temperature overnight, quenched with 20 ml of H₂O, evaporated *in-vacuo* to dryness and dissolved in EtOAc. The precipitated dicyclohexylurea was filtered off and the organic layer was washed with H₂O, 20% citric acid, sat. sol. NaHCO₃, sat. sol. NaCl. The organic layer was separated, dried over Na₂SO₄ and evaporated *in-vacuo* to dryness; the
- 15 residue was purified by gradient column chromatography on 60-240 mesh silica gel using a mixture of hexane/EtOAc 9:1 as starting eluent and a mixture of hexane/EtOAc 7:3 as final eluent. The crude product was recrystallized from *i*-PrOH to yield 1.75 g of the title compound as a white solid.

C₂₅H₂₂N₂O₂

- 20 M.P. = 168-168.4°C

M.W. = 382.47

$[\alpha]_D^{20} = -28.5$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 78.51; H, 5.80; N, 7.33;

Found C, 78.49; H, 5.84; N, 7.26.

- 25 I.R. (KBr): 3370; 1625; 1525 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 9.80 (s, 1H); 9.11 (d, 1H); 8.00-7.94 (m, 3H); 7.61-7.42 (m, 8H); 7.38 (dd, 2H); 7.28 (dd, 1H); 5.06 (dt, 1H); 1.82 (ddq, 2H); 0.97 (t, 3H).

MS (EI; TSQ 700; source 200 C; 70 V; 200 uA): 382 (M⁺); 264; 247; 219.

30

DESCRIPTION 2

(S)-N-(α -ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide

- 1.5 g (5.7 mmol) of 3-amino-2-phenylquinoline-4-carboxylic acid (CAS [36735-26-9]) were dissolved in 140 ml of a 7/3 mixture of THF/CH₃CN; 1.5 g (11.1 mmol) of 1-hydroxybenzotriazole (HOBT) were added and 1.15 g (8.5 mmol) of (S)- α -ethylbenzylamine dissolved in 10 ml of CH₂Cl₂ were added dropwise. After cooling of the reaction mixture to 0°C, 1.4 g (6.7 mmol) of dicyclohexylcarbodiimide (DCC) dissolved in 10 ml of CH₂Cl₂ were added dropwise. The solution was kept at 0°C for 30 minutes and then at room temperature overnight. The reaction mixture was evaporated *in-vacuo*, the residue was dissolved in CH₂Cl₂ and the solution filtered off, washed with H₂O, 20% citric acid, sat. sol. NaHCO₃ and sat. sol. NaCl.
- 40 The organic layer was separated, dried over Na₂SO₄ and evaporated *in-vacuo* to dryness

to obtain 2.4 g of the crude product. This was triturated with *i*-Pr₂O, then recrystallized with a 10:1 mixture of *i*-Pr₂O/*i*-PrOH to yield 1.7 g of the title compound.

C₂₅H₂₃N₃O

M.P. = 153-155°C

5 M.W. = 381.48

$[\alpha]_D^{20} = -68.0$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 78.71; H, 6.08; N, 11.01;

Found C, 78.45; H, 6.10; N, 10.96.

I.R. (KBr): 3490; 3380; 3260; 1630; 1600 cm⁻¹.

10 300 MHz ¹H-NMR (DMSO-d₆): δ 9.20 (d, 1H); 7.87 (m, 1H); 7.70 (d, 2H); 7.59-7.26 (m, 11H); 5.08 (dt, 1H); 4.80 (s br, 2H); 2.81 (dq, 2H); 0.95 (t, 3H).

MS (EI; TSQ 700; source 200 C; 70 V; 200 uA): 381 (M⁺); 352; 247; 219; 218.

15 DESCRIPTION 3

(S)-N-(α-ethylbenzyl)-2-phenyl-3-(2-phthalimidoethoxy)quinoline-4-carboxamide

1.90 g (5.0 mmol) of (S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (product of Description 1) were dissolved in 20 ml of THF.

20 3.80 g (14.9 mmol) of N-(2-bromoethyl)phthalimide dissolved in 15 ml of THF, 2.00 g (14.5 mmol) of K₂CO₃ and 0.25 g of KI were added and the suspension was stirred at room temperature for 2.5 hours and then refluxed for 2 hours.

Additional 1.90 g (7.4 mmol) of N-(2-bromoethyl)phthalimide and a catalytic amount of KI were added and the reaction refluxed for 3.5 hours; additional 0.50 g (2.0 mmol) of N-(2-bromoethyl)phthalimide and a catalytic amount of KI were added and the reaction
25 refluxed for 5 hours.

The inorganic salts were filtered off and the reaction mixture evaporated *in-vacuo* to dryness, dissolved in CH₂Cl₂ and washed with water; the organic layer was separated, dried over Na₂SO₄ and evaporated *in-vacuo* to dryness. The residue was purified by flash
30 column chromatography on 230-400 mesh silica gel, eluting initially with a mixture of hexane/ethyl acetate 8:2 containing 0.5% NH₄OH (28%) and then with a mixture of hexane/ethyl acetate 3:2 containing 0.5% NH₄OH (28%). The purified solid obtained (2.60 g) was triturated with *i*-Pr₂O, filtered, washed and dried to yield 2.5 g of the title compound.

35 C₃₅H₂₉N₃O₄

M.P. = 172-175°C

M.W. = 555.64

$[\alpha]_D^{20} = -16.3$ (c=0.5, MeOH)

I.R. (KBr): 3280; 3060; 2960; 1780; 1715; 1660; 1530 cm⁻¹.

40 300 MHz ¹H-NMR (DMSO-d₆): δ 9.27 (d, 1H); 8.03 (d, 1H); 7.92-7.84 (m, 4H); 7.78-7.69 (m, 3H); 7.60-7.53 (m, 2H); 7.46-7.38 (m, 4H); 7.27 (dd, 1H); 7.13-7.04 (m, 3H); 4.96 (dt, 1H); 3.92-

3.78 (m, 2H); 3.72-3.55 (m, 2H); 1.78 (dq, 2H); 0.93 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 555 (M+), 526, 421, 174.

5 DESCRIPTION 4

(S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide

2.2 g (3.9 mmol) of (S)-N-(α -ethylbenzyl)-2-phenyl-3-(2-phthalimidoethoxy) quinoline-4-carboxamide (compound of Description 3) were dissolved in 150 ml of 96% EtOH; the solution was heated to reflux; 0.38 ml (7.8 mmol) of hydrazine hydrate were added and the reaction mixture refluxed for 4 hours.

Additional 0.4 ml (8.2 mmol), 0.2 ml (4.1 mmol), 0.2 ml (4.1 mmol), 0.4 ml (8.2 mmol), 0.4 ml (8.2 mmol) of hydrazine hydrate were added every 12 hours while refluxing the reaction mixture. Then it was evaporated *in-vacuo* to dryness and 20 ml of H₂O were added; it was cooled with an ice bath and 10 ml of conc. HCl were added.

15 The reaction mixture was refluxed for 1 hour and then, after cooling, the phthalhydrazide was filtered off. The resulting aqueous filtrate was washed with EtOAc, basified with 2N NaOH and extracted with EtOAc. The organic layer was washed with sat. sol. NaCl, dried over Na₂SO₄ and evaporated *in-vacuo* to dryness. The residue was purified by flash column chromatography on 230-400 mesh silica gel, eluting with a mixture of EtOAc/MeOH 96:4 containing 1.2% NH₄OH (28%) to yield 1.2 g of the title compound.

C₂₇H₂₇N₃O₂

M.P. = 62-66°C

M.W. = 425.54

I.R. (KBr): 3360; 3250; 3060; 3020; 2960; 2920; 2870; 1640; 1540 cm⁻¹.

25 300 MHz ¹H-NMR (DMSO-d₆): δ 9.45 (d, 1H); 8.09 (d, 1H); 8.00 (dd, 1H); 7.94 (s br, 3H); 7.76 (ddd, 1H); 7.65-7.51 (m, 4H); 7.48-7.40 (m, 3H); 7.31 (dd, 1H); 5.09 (dt, 1H); 3.83 (t, 2H); 2.72 (m, 2H); 1.93-1.80 (m, 2H); 0.99 (t, 3H).

MS (FAB POS; thioglycerine matrix; FAB gas Xe; 8 kV; source 50): 426 (MH+).

30

EXAMPLE 1

(S)-N-(α -ethylbenzyl)-3-(ethoxycarbonylmethoxy)-2-phenylquinoline-4-carboxamide

35 2.0 g (5.2 mmol) of (S)-N-(α -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (compound of Description 1) were dissolved, under nitrogen atmosphere and magnetic stirring, in 20 ml of THF. 2.0 g (14.5 mmol) of K₂CO₃, 0.87 ml (7.8 mmol) of ethyl bromoacetate and a small amount of KI were added and the reaction mixture was left at room temperature under magnetical stirring for 2.5 hours.

40 The precipitate was filtered off and the solution was evaporated *in-vacuo* to dryness; the residue was dissolved in water and extracted with EtOAc; the organic phase was separated, dried over Na₂SO₄ and evaporated *in-vacuo* to dryness to obtain 3.3 g of a

dense yellow oil.

The oil was purified by flash chromatography on 230-400 mesh silica gel, eluting with a mixture of hexane/EtOAc 70:30 containing 0.5% of 28% NH₄OH, and the purified product was triturated with *i*-Pr₂O/*i*-PrOH to yield 2.1 g of the title compound as a white solid.

C₂₉H₂₈N₂O₄

M.P. = 103-105°C

M.W. = 468.56

[α]_D²⁰ = -42.5 (c=0.5, MeOH)

10 Elemental analysis: Calcd. C, 74.34; H, 6.02; N, 5.98;

Found C, 74.44; H, 6.01; N, 6.00.

I.R. (KBr): 3320-3140; 3100-3020; 2980-2920; 1758; 1630; 1550 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 9.28 (d, 1H); 8.08 (d, 1H); 8.05-7.98 (m, 2H); 7.80-7.71 (m, 1H); 7.60 (d, 2H); 7.55-7.48 (m, 3H); 7.43 (d, 2H); 7.35 (dd, 2H); 7.28 (dd, 1H); 5.06 (dt, 1H); 4.26 (ABq, 2H); 4.04 (q, 2H); 1.86-1.67 (m, 2H); 1.12 (t, 3H); 0.96 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 468 (M+); 439; 334; 306; 278.

20 EXAMPLE 2

(S)-N-(α-ethylbenzyl)-3-(carboxymethoxy)-2-phenylquinoline-4-carboxamide hydrochloride

25 0.35 g (0.7 mmol) of (S)-N-(α-ethylbenzyl)-3-(ethoxycarbonylmethoxy)-2-phenylquinoline-4-carboxamide (compound of Example 1) were dissolved in 20 ml of 37% HCl and the reaction mixture was refluxed under magnetical stirring for 20'.

The solution was evaporated *in-vacuo* to dryness and the crude product was triturated with warm EtOAc/*i*-PrOH to yield 0.17 g of the title compound as a white solid.

C₂₇H₂₄N₂O₄.HCl

30 M.P. = 203-204°C

M.W. = 476.96

[α]_D²⁰ = -30.2 (c=0.5, MeOH)

Elemental analysis: Calcd. C, 67.99; H, 5.28; N, 5.87;

Found C, 67.44; H, 5.29; N, 5.84.

35 I.R. (Nujol): 3280-3120; 3100-3000; 1740; 1670; 1635; 1545 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 9.30 (d, 1H); 8.11-8.01 (m, 3H); 7.80-7.71 (m, 1H); 7.59 (d, 2H); 7.56-7.48 (m, 3H); 7.44 (d, 2H); 7.36 (dd, 2H); 7.27 (dd, 1H); 5.07 (dt, 1H); 4.26 (ABq, 2H); 1.81 (dq, 2H); 0.97 (t, 3H).

40 MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 440 (M+); 411; 396; 306; 278.

EXAMPLE 3

(S)-N-(α -ethylbenzyl)-3-(aminocarbonylmethoxy)-2-phenylquinoline-4-carboxamide

0.5 g (1.3 mmol) of (S)-N-(α -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (compound of Description 1) were dissolved, under nitrogen atmosphere and magnetic stirring, in 5 ml of THF; 0.5 g (3.6 mmol) of K_2CO_3 , 0.27 g (1.9 mmol) of 2-bromoacetamide and a small amount of KI were added.

The reaction mixture was left overnight under magnetical stirring; the precipitate was filtered off and the residue dissolved in H_2O and extracted with EtOAc; the organic layer was washed with sat. sol. NaCl, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness. The crude product was triturated with hexane and then recrystallized from EtOH to yield 0.29 g of the title compound as a white solid.

$C_{27}H_{25}N_3O_3$

M.P. = 237-240°C

M.W. = 439.51

$[\alpha]_D^{20} = -35.9$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 73.78; H, 5.73; N, 9.56;

Found C, 73.75; H, 5.75; N, 9.54.

I.R. (KBr): 3440; 3310; 3220; 3100-3020; 2980-2920; 1688; 1650; 1550 cm^{-1} .

300 MHz 1H -NMR (DMSO- d_6): δ 9.30 (d, 1H); 8.08 (d, 1H); 8.05-8.00 (m, 2H); 7.80-7.70 (m, 1H); 7.60 (d, 2H); 7.57-7.50 (m, 3H); 7.43 (d, 2H); 7.38 (dd, 2H); 7.37 (s br, 1H); 7.28 (dd, 1H); 7.12 (s br, 1H); 5.07 (dt, 1H); 4.03 (ABq, 2H); 1.81 (m, 2H); 0.80 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 439 (M⁺); 410; 305; 277; 248.

EXAMPLE 4

(S)-N-(α -ethylbenzyl)-3-(dimethylaminocarbonylmethoxy)-2-phenylquinoline-4-carboxamide

30

0.6 g (1.3 mmol) of (S)-N-(α -ethylbenzyl)-3-(ethoxycarbonylmethoxy)-2-phenylquinoline-4-carboxamide (compound of Exemple 1) were dissolved in 30 ml of $Me_2NH/EtOH$ (~28%); a small amount of NaCN was added and the reaction mixture was heated in a Parr apparatus to 100°C (external temperature) for 2 hours, then to 120°C for 12 hours. The reaction mixture was evaporated *in-vacuo* to dryness, the residue was dissolved in EtOAc and washed with H_2O , 20% citric acid, sat. sol. $NaHCO_3$ and sat. sol. NaCl. The organic layer was dried over Na_2SO_4 and evaporated *in-vacuo* to dryness to obtain 0.45 g of a residue which was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/EtOAc 50:50 containing 0.5% of 28% NH_4OH . The crude product was triturated with Et_2O , filtered, washed and dried to yield 80 mg of the title compound as a white solid.

40

$C_{29}H_{29}N_3O_3$

M.P. = 86-88°C

M.W. = 467.57

$[\alpha]_D^{20} = -41.2$ (c=0.25, MeOH)

I.R. (KBr): 3240; 3060; 2980-2820; 1685; 1625; 1550 cm⁻¹.

5 300 MHz ¹H-NMR (DMSO-d₆): δ 9.40 (d, 1H); 8.04 (m, 3H); 7.72 (ddd, 1H); 7.65-7.47 (m, 5H); 7.44 (d, 2H); 7.26 (dd, 2H); 7.28 (dd, 1H); 5.05 (dt, 1H); 4.43 (ABq, 2H); 2.70 (s, 3H); 2.50 (s, 3H); 1.80 (m, 2H); 0.94 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 467 (M⁺); 438; 333; 305; 262.

10

EXAMPLE 5

(S)-N-(α-ethylbenzyl)-3-(ethoxycarbonyloxy)-2-phenylquinoline-4-carboxamide

0.5 g (1.3 mmol) of (S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (compound of Description 1) were dissolved in 10 ml of pyridine; 0.5 ml (5.2 mmol) of ethyl chloroformate were added dropwise and the solution was refluxed under magnetical stirring for 8 hours. The reaction mixture was allowed to reach room temperature and left overnight. 1.0 ml (10.4 mmol) of ethyl chloroformate were added and the solution refluxed for 4 hours. The pyridine was evaporated off with toluene; the residue was dissolved in CH₂Cl₂, washed with H₂O and the organic layer dried over Na₂SO₄ and evaporated *in-vacuo* to dryness. The crude product was triturated with warm *i*-Pr₂O to yield 0.25 g of the title compound as a yellow solid.

C₂₈H₂₆N₂O₄

M.P. = 119-121°C

25 M.W. = 454.53

$[\alpha]_D^{20} = -57.8$ (c=0.25, MeOH)

I.R. (Nujol): 3280; 1765; 1645; 1550 cm⁻¹.

30 300 MHz ¹H-NMR (DMSO-d₆): δ 9.30 (d, 1H); 8.15 (d, 1H); 7.89-7.77 (m, 3H); 7.70 (m, 2H); 7.59-7.49 (m, 3H); 7.42 (d, 2H); 7.33 (dd, 2H); 7.28 (dd, 1H); 5.05 (dt, 1H); 3.93 (q, 2H); 1.78 (m, 2H); 0.97 (t, 1H); 0.95 (t, 1H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 454 (M⁺); 425; 382; 320; 247; 219.

EXAMPLE 6

(S)-N-(α-ethylbenzyl)-3-(3-phenylureido)-2-phenylquinoline-4-carboxamide

1.5 g (3.9 mmol) of (S)-N-(α-ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide (compound of Description 2) were dissolved in 30 ml of dry CH₂Cl₂, 10 ml of dry THF and 10 ml of dry CH₃CN.

0.47 ml (4.3 mmol) of phenylisocyanate dissolved in 10 ml of CH₂Cl₂ were added and the reaction mixture heated to 40°C for 4 hours.

40 After cooling of the reaction mixture, the precipitate was collected by filtration and washed with CH₂Cl₂ to yield 0.9 g of the title compound.

$C_{32}H_{28}N_4O_2$

M.P. = 257-258°C

M.W. = 500.61

$[\alpha]_D^{20} = -64.6$ (c = 0.25, DMF)

5 I.R. (KBr): 3250; 3060; 2960; 1680; 1630; 1600; 1550 cm^{-1} .

300 MHz 1H -NMR (DMSO- d_6): δ 9.06 (d, 1H); 8.71 (s br, 1H); 8.13-8.05 (m, 2H); 7.83-7.69 (m, 4H); 7.62 (dd, 1H); 7.48-7.35 (m, 5H); 7.23-7.10 (m, 7H); 6.91 (m, 1H).

MS (FAB POS; matrix thioglycerine; FAB gas Xe; 8 kV; source 50): 501 (MH⁺).

10

EXAMPLE 7

(S)-N-(α -ethylbenzyl)-3-(3-ethoxycarbonylmethylureido)-2-phenylquinoline-4-carboxamide

15 2.0 g (5.2 mmol) of (S)-N-(α -ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide (compound of Description 2) were dissolved in 10 ml of dry THF and 5 ml of dry DMF. 1.71 ml (15.2 mmol) of phenylisocyanate neat were added and the reaction mixture heated to 60°C for 3 days; 1.0 ml (10.3 mmol) of phenylisocyanate neat were added again and the reaction mixture stirred at 60°C for additional 2 days.

20 After cooling of the reaction mixture, the precipitate was collected by filtration and washed with CH_2Cl_2 to yield 0.8 g of a white powder. The residue was recrystallized from toluene containing traces of EtOH and then from EtOH containing traces of H_2O to yield 0.45 g of the title compound.

$C_{30}H_{30}N_4O_4$

25 M.P. = 237-238°C

M.W. = 510.60

$[\alpha]_D^{20} = -45$ (c = 0.1, DMF)

I.R. (KBr): 3360; 3310; 3250; 3060; 2960; 1740; 1655; 1560 cm^{-1} .

30 300 MHz 1H -NMR (DMSO- d_6): δ 8.83 (d, 1H); 8.16 (s, 1H); 8.06 (d, 1H); 7.80-7.70 (m, 3H); 7.66-7.54 (m, 2H); 7.50-7.23 (m, 8H); 6.60 (t br, 1H); 5.00 (dt, 1H); 4.09 (q, 2H); 3.66 (m, 2H); 1.75 (m, 2H); 1.19 (t, 3H); 0.90 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 510 (M⁺); 407; 290.

35 EXAMPLE 8

(S)-N-(α -ethylbenzyl)-3-[2-(2-indanylamino)ethoxy]-2-phenylquinoline-4-carboxamide hydrochloride

40 1.0 g (2.3 mmol) di (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) were dissolved, under nitrogen atmosphere and magnetical stirring, in 15 ml of MeOH; 0.47 g (3.5 mmol) of 2-indanone and a small amount of triturated molecular sieves were added and the mixture was stirred at room

temperature for 30 minutes. 0.15 g (2.3 mmol) of NaCNBH₃ were added portionwise over 30 minutes and the mixture was left under stirring at room temperature overnight.

The reaction was quenched with 20 ml of 2N NaOH and, after stirring at room temperature for 20 minutes, was evaporated *in-vacuo* to dryness. The residue was dissolved in 2N NaOH and extracted with CH₂Cl₂; the organic layer was washed with sat. sol. NaCl and extracted with 20% citric acid. The acid aqueous layer was basified with conc. NaOH and extracted with EtOAc; the organic layer was washed several times with sat. sol. NaCl, dried over Na₂SO₄, and evaporated *in-vacuo* to dryness to obtain 1.0 g of the title compound as free base. This was dissolved in EtOAc and the solution acidified with HCl/Et₂O to yield 0.84 g of the corresponding hydrochloride, which was recrystallized from acetone/EtOH to obtain 0.49 g of the title compound as a white powder.

C₃₆H₃₅N₃O₂ · HCl

M.P. = 156-160°C

M.W. = 578.16

[α]_D²⁰ = -11.0 (c=0.5, MeOH)

I.R. (KBr): 3700-3250; 3240-3100; 3080-2900; 2850-2000; 1670-1630; 1550 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 9.52 (d, 1H); 9.40 (s br, 1H); 8.10 (d, 1H); 7.97 (dd, 2H); 7.81-7.73 (m, 1H); 7.65-7.19 (m, 14H); 5.05 (dt, 1H); 3.98 (m, 2H); 3.69 (m, 1H); 3.18-3.06 (m, 2H); 3.02-2.80 (m, 4 H); 1.94-1.74 (m, 2H); 0.96 (t, 3H).

MS (FAB POS; matrix thioglycerine; FAB gas Xe; 8 kV; source 50 C): 542 (MH⁺).

EXAMPLE 9

(S)-N-(α-ethylbenzyl)-3-(2-benzoylaminoethoxy)-2-phenylquinoline-4-carboxamide

0.95 g (2.2 mmol) of (S)-N-(α-ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) were dissolved, under nitrogen atmosphere and magnetical stirring, in 12 ml of dry CH₂Cl₂; 0.37 ml (2.6 mmol) of TEA were added, the solution cooled to 0°C and 0.3 ml (2.6 mmol) of benzoyl chloride, dissolved in in 3 ml dry CH₂Cl₂ were added dropwise.

The reaction was left 30 minutes at 0°C, then allowed to reach room temperature and left overnight. The mixture was evaporated *in-vacuo* to dryness, the residue was dissolved in CH₂Cl₂, and washed with H₂O, 20% citric acid, sat. sol. NaHCO₃, sat. sol. NaCl; the organic layer was dried over Na₂SO₄ and evaporated *in-vacuo* to dryness. The residue was triturated with hot *i*-Pr₂O/*i*-PrOH to yield 0.8 g of the title compound as a white solid.

C₃₄H₃₁N₃O₃

M.P. = 157-160°C

M.W. = 529.64

[α]_D²⁰ = -27.3 (c=0.5, MeOH)

Elemental analysis: Calcd C, 77.10; H, 5.90; N, 7.93;
Found C, 76.92; H, 5.88; N, 7.88.

I.R. (KBr): 3300; 3240; 3100-3020; 2980-2920; 1632; 1545 cm^{-1} .

5 300 MHz ^1H -NMR (DMSO- d_6): δ 9.31 (d, 1H); 8.32 (t, 1H); 8.05 (d, 1H); 7.90 (m, 2H);
7.79-7.69 (m, 3H); 7.60-7.33 (m, 12H); 7.29 (dd, 1H);
5.05 (dt, 1H); 3.80 (m, 2H); 3.42-3.29 (m, 1H); 3.25-
3.15 (m, 1H); 1.89-1.72 (m, 2H); 0.93 (t, 3H).

MS (EI; TSQ 700; source 180 C; 10 V; 200 uA): 529 (M⁺); 382; 148.

10 DESCRIPTION 5

methyl 3-chlorocarbonylpropenoate

5.0 g (51.0 mmol) of maleic anhydride were heated to 100°C in 2.2 ml of MeOH for 1 hour [*J. Chem. Soc.*, 1964, 526-528]. The reaction mixture was cooled to room
15 temperature and 37 ml (50.7 mmol) of SOCl_2 were added dropwise. The reaction was
refluxed for 1.5 hours and then distilled collecting the fraction boiling at 42-44°C/2mbar
to obtain 5.3 g of the title compound, possibly as a mixture of E and Z diastereoisomers.
This compound was used without further purification in the subsequent reaction to
prepare Examples 18 and 19.

20

EXAMPLE 10

(S)-N-(α -ethylbenzyl)-3-[3-(ethoxycarbonyl)propoxy]-2-phenylquinoline-4-carboxamide

25 2.0 g (5.23 mmol) of (S)-N-(α -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide
(compound of Description 1), 2.17 g (15.70 mmol) of K_2CO_3 , 0.26 g (1.57 mmol) of KI
and 1.13 ml (7.84 mmol) of ethyl 4-bromobutyrate were suspended in 50 ml of dry THF
and the reaction was stirred at room temperature for 24 hours.

30 The solid was filtered off and the solvent was evaporated *in vacuo* to dryness. The residue
was dissolved in CH_2Cl_2 and the organic phase was washed with H_2O , separated, dried
over Na_2SO_4 and evaporated *in vacuo* to dryness. The crude product was triturated with
hot *i*-Pr $_2\text{O}$ to yield 2.10 g of the title compound as a white powder.

$\text{C}_{31}\text{H}_{32}\text{N}_2\text{O}_4$

M.P. = 140-142°C.

35 M.W. = 496.61

$[\alpha]_D^{20} = -41.6$ (c=1, MeOH)

I.R. (KBr): 3110; 2960-2850; 1740; 1650 cm^{-1} .

40 300 MHz ^1H -NMR (DMSO- d_6): δ 9.25 (d, 1H); 8.06 (d, 1H); 7.92 (dd, 2H); 7.72 (ddd,
1H); 7.63-7.50 (m, 5H); 7.44 (d, 2H); 7.39 (dd, 2H);
7.28 (dd, 1H); 5.08 (dt, 1H); 3.99 (q, 2H); 3.61 (m,
2H); 2.15-1.98 (m, 2H); 1.90-1.74 (m, 2H); 1.60-1.51
(m, 2H); 1.16 (t, 3H); 0.98 (t, 3H).

MS (EI; TSQ 700; source 180 C;70 V; 200 uA): 496 (M⁺); 115.

EXAMPLE 11

(S)-N-(α -ethylbenzyl)-3-(carboxypropoxy)-2-phenylquinoline-4-carboxamide

0.6 g (1.21 mmol) of (S)-N-(α -ethylbenzyl)-3-[3-(ethoxycarbonyl)propoxy]-2-phenylquinoline-4-carboxamide (compound of Example 10) were dissolved in 30 ml of 6N HCl and the solution was refluxed for 4 hours.

The reaction mixture was evaporated *in vacuo* to dryness and the crude compound was recrystallized from toluene with traces of THF to yield 0.5 g of the title compound as a yellow solid.

$C_{29}H_{28}N_2O_4$

M.P. = 149-151°C.

M.W. = 468.56

$[\alpha]_D^{20} = -42.3$ (c=1, MeOH)

I.R. (KBr): 3249; 3065; 2971-2840; 1709; 1633; 1544 cm^{-1} .

300 MHz 1H -NMR (DMSO- d_6): δ 11.98 (s, 1H); 9.24 (d, 1H); 8.07 (d, 1H); 7.93 (dd, 2H); 7.72 (ddd, 1H); 7.61-7.50 (m, 5H); 7.44 (d, 2H); 7.38 (dd, 2H); 7.28 (dd, 1H); 5.08 (dt, 1H); 3.62 (m, 2H); 2.01 (m, 2H); 1.90-1.72 (m, 2H); 1.55 (m, 2H); 0.99 (t, 3H).

MS (EI; TSQ 700; source 180 C;70 V; 200 uA): 468 (M⁺); 439; 382; 334; 264; 247; 219; 134; 119; 91.

EXAMPLE 12

(S)-N-(α -ethylbenzyl)-3-[2-(2'-hydroxymethylphenylacetyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

0.7 g (4.7 mmol) of isochromanone were dissolved in 25 ml of abs. EtOH; 2.0 g (4.7 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) were added and the reaction was refluxed for 12 hours. Additional 0.3 g (2.0 mmol) of isochromanone were added and the reaction mixture was refluxed for 5 hours; additional 0.5 g (3.4 mmol) of isochromanone were added and the reaction refluxed for 10 hours. After cooling, it was evaporated *in vacuo* to dryness and the residue was purified by gradient flash column chromatography on 230-400 mesh silica gel utilising a mixture of hexane/EtOAc 50:50 containing 0.5% NH_4OH (28%) as starting eluent and a mixture of hexane/EtOAc 20:80 containing 0.5% NH_4OH (28%) as final eluent. The crude product so obtained was triturated with *i*-Pr₂O/*i*-PrOH to yield 1.8 g of the title compound.

$C_{36}H_{35}N_3O_4$

M.P. = 160-163°C

M.W. = 573.69

$[\alpha]_D^{20} = -31.5$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 75.36; H, 6.15; N, 7.32;

Found C, 75.09; H, 6.14; N, 7.34.

I.R. (KBr): 3600-3100; 3100-3000; 1641; 1558 cm^{-1} .

300 MHz ^1H -NMR (DMSO- d_6): δ 9.30 (d, 1H); 8.08 (d, 1H); 7.98 (m, 2H); 7.89 (t br, 1H); 7.73 (ddd, 1H); 7.59 (m, 2H); 7.57-7.48 (m, 3H); 7.45 (m, 2H); 7.41-7.33 (m, 3H); 7.28 (dd, 1H); 7.19 (dd, 1H); 7.15 (dd, 1H); 7.09 (dd, 1H); 5.09 (t, 1H); 5.08 (dt, 1H); 4.48 (d, 1H); 3.70-3.59 (m, 2H); 3.37 (s, 2H); 3.12-2.92 (m, 2H); 1.90-1.75 (m, 2H); 0.99 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 μA): 555; 438; 411; 382; 247; 218; 192; 174; 119.

EXAMPLE 13

(S,Z)-N-(α -ethylbenzyl)-3-[2-(3-carboxypropenoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

2.0 g (4.7 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) and 0.61 g (6.2 mmol) of maleic anhydride were dissolved in 50 ml of toluene. Some molecular sieves were added and the reaction mixture was refluxed for 5 hours. After cooling, the reaction mixture was evaporated *in vacuo* to dryness, dissolved in CH_2Cl_2 and washed with sat. sol. NaCl, 20% citric acid, sat. sol. NaCl. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The crude product was purified by flash column chromatography on 230-400 mesh silica gel, eluting with a mixture of *i*-Pr $_2\text{O}$ /EtOAc 70:30 containing 0.5% of 85% formic acid, and then triturated with *i*-Pr $_2\text{O}$ to yield 2.0 g of the title compound.

$\text{C}_{31}\text{H}_{29}\text{N}_3\text{O}_5$

M.P. = 158-162°C

M.W. = 523.59

$[\alpha]_D^{20} = -38.6$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 71.11; H, 5.58; N, 8.03;

Found C, 70.90; H, 5.56; N, 7.95.

I.R. (KBr): 3280; 3150-3000; 1710; 1640-1620 cm^{-1} .

300 MHz ^1H -NMR (DMSO- d_6): δ 14.80 (s br, 1H); 9.30 (d, 1H); 9.08 (t br, 1H); 8.07 (d, 1H); 7.94 (dd, 2H); 7.79-7.70 (m, 1H); 7.60 (m, 2H); 7.52-7.38 (m, 7H); 7.29 (dd, 1H); 6.32 (d, 1H); 6.27 (d, 1H); 5.07 (dt, 1H); 3.76-3.64 (m, 2H); 3.28-3.00 (m, 2H); 1.90-1.74 (m, 2H); 1.00 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 μA): 425; 407.

EXAMPLE 14

(S)-N-(α -ethylbenzyl)-3-[2-(3-carboxypropanoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

5 2.0 g (4.7 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) and 0.6 g (6.2 mmol) of succinic anhydride were dissolved in 50 ml of toluene; some tritured molecular sieves were added and the reaction mixture was refluxed in a Dean Stark apparatus for 4 hours. The reaction mixture
 10 was evaporated *in vacuo* to dryness, dissolved in 100 ml of CH₂Cl₂ and washed with sat. sol. NaCl, 20% citric acid and sat. sol. NaCl. The organic layer was dried over Na₂SO₄ and evaporated *in vacuo* to dryness to yield 2.3 g of the crude product which was purified by flash column chromatography on 230-400 mesh silica gel, eluting initially with a mixture of CH₂Cl₂/MeOH 9:1 and then with a mixture of CH₂Cl₂/MeOH 8:2. The crude
 15 solid obtained was tritured with *i*-Pr₂O/*i*-PrOH, filtered, washed and dried to yield 1.4 g of the title compound.

C₃₁H₃₁N₃O₅

M.P. = 118-122°C

M.W. = 525.60

20 $[\alpha]_D^{20} = -32.1$ (c=0.5, MeOH)I.R. (KBr): 3600-3120; 3100-3000; 1740-1700; 1680-1600 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 11.98 (s br, 1H); 9.28 (d, 1H); 8.07 (d, 1H); 7.99 (dd, 2H); 7.73 (ddd, 1H); 7.66 (t br, 1H); 7.61-7.48 (m, 5H); 7.46 (d, 2H); 7.39 (dd, 2H); 7.30 (dd, 1H); 5.05 (dt, 1H); 3.69-3.57 (m, 2H); 3.12-2.91 (m, 2H); 2.34 (m, 2H); 2.21 (m, 2H); 1.90-1.75 (m, 2H); 1.00 (t, 3H).

MS (FAB POS; thioglycerine matrix; FAB gas Xe; 8 kV; source 50): 526 (MH⁺); 383; 291.

30

EXAMPLE 15

(S)-N-(α -ethylbenzyl)-3-[2-(N-methyl-8-azabicyclo[3.2.1]oct-3-yl)aminoethoxy]-2-phenylquinoline-4-carboxamide hydrochloride

35 1.50 g (3.53 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) and 0.98 g (7.06 mmol) of tropinone were dissolved in 30 ml MeOH and 100 ml toluene; 0.22 g (3.53 mmol) of NaCNBH₃ were added portionwise and the reaction was refluxed for 24 hours in a Dean-Stark apparatus. The reaction was quenched with 5 ml of 2N NaOH and, after stirring at room temperature
 40 for 20 minutes, was evaporated *in vacuo* to dryness. The residue was dissolved in 20% citric acid and extracted twice with EtOAc; the aqueous layer was basified with solid K₂CO₃ and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and

evaporated *in vacuo* to dryness to afford 1.8 g of a yellow solid which was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of EtOAc/MeOH 80:20 containing 2% of 28% NH₄OH.

- 5 The crude product (0.17 g) was dissolved in MeOH and the solution acidified with HCl/Et₂O to yield the corresponding hydrochloride, which was recrystallized from EtOAc/abs. EtOH to obtain 0.10 g of the title compound as a slightly brown powder.

C₃₅H₄₀N₄O₂·HCl

M.P. = 200-203°C

M.W. = 585.19

- 10 I.R. (KBr): 3403; 2966-2760; 1637; 1558 cm⁻¹.

- 300 MHz ¹H-NMR (DMSO-d₆, free base): δ 9.29 and 9.26 (d, 1H); 8.05 (d, 1H); 7.92 (dd, 2H); 7.71 (ddd, 1H); 7.61-7.50 (m, 5H); 7.45 (d, 2H); 7.38 (dd, 2H); 7.28 (dd, 1H); 5.09 (dt, 1H); 3.70-3.60 (m, 2H); 3.32 (m, 2H); 2.95 (m, 1H); 2.82 (m, 1H); 2.41 (t, 2H); 2.11 and 2.08 (s, 3H); 1.90-1.65 (m, 6H); 1.41-1.31 (m, 2H); 1.23-1.03 (m, 2H); 0.98 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 548(M⁺); 386; 305; 166; 124; 82.

20

EXAMPLE 16

(S)-N-(*a*-ethylbenzyl)-3-[2-(2'-carboxybenzoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

- 25 0.85 g (2.0 mmol) of (S)-N-(*a*-ethylbenzyl)-3-[2-(2'-methoxycarbonylbenzoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide (compound of Example 17) were dissolved in 25 ml of 10% NaOH and 5 ml of 1,4-dioxane. The solution was warmed to 60°C for 15 minutes, then it was extracted with CH₂Cl₂, washed with 10% citric acid and sat. sol. NaCl, dried over Na₂SO₄ and evaporated *in vacuo* to dryness. The residue was purified by gradient flash column chromatography on 230-400 mesh silica gel utilising a mixture of *i*-Pr₂O/EtOAc/HCOOH (85%)/H₂O 70:30:0.5:0.5 as starting eluent and a mixture of *i*-Pr₂O/EtOAc/HCOOH (85%)/H₂O 60:40:0.5:0.5 as final eluent. The crude product so obtained was triturated with *i*-Pr₂O/*i*-PrOH to yield 0.2 g of the title compound.

C₃₅H₃₁N₃O₅

- 35 M.P. = 96-115°C dec.

M.W. = 573.65

[α]_D²⁰ = -33.3 (c=0.5, MeOH)

I.R. (KBr): 3400; 3257; 3100-3000; 1723; 1637; 1581 cm⁻¹.

- 40 300 MHz ¹H-NMR (DMSO-d₆): δ 12.75 (s br, 1H); 9.31 (d, 1H); 8.07 (d, 1H); 8.00 (m, 3H); 7.76-7.69 (m, 2H); 7.57 (m, 2H); 7.55-7.37 (m, 9H); 7.29 (dd, 1H); 7.18 (m, 1H); 5.06 (dt, 1H); 3.79 (t, 2H); 3.34-3.15 (m, 2H); 1.90-1.75 (m, 2H); 0.97 (t,

3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 555; 526; 422; 382; 262; 247; 219; 174; 119; 91.

5 EXAMPLE 17

(S)-N-(α -ethylbenzyl)-3-[2-(2'-methoxycarbonylbenzoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

2.4 g (5.7 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) were dissolved, under nitrogen atmosphere, in 50 ml of dry CH_2Cl_2 ; 0.88 ml (6.2 mmol) of TEA were added and the solution was cooled to 0°C. 1.1 g (5.8 mmol) of methyl 2-chlorocarbonylbenzoate (obtained by treating the corresponding mono acid mono ester with oxalyl chloride), dissolved in 50 ml of CH_2Cl_2 , were added dropwise at 0°C and the solution was then stirred at room temperature for 4 hours. The reaction mixture was washed with H_2O , 20% citric acid, sat. sol. NaHCO_3 , sat. sol. NaCl , dried over Na_2SO_4 and evaporated *in vacuo* to dryness. 1.0 g of the residue were purified by flash column chromatography on 230-400 mesh silica gel, eluting with a mixture of hexane/EtOAc 1:1, and then triturated with *i*-Pr₂O to yield 0.9 g of the title compound.

20 $\text{C}_{36}\text{H}_{33}\text{N}_3\text{O}_5$

M.P. = 133-135°C

M.W. = 587.68

 $[\alpha]_D^{20} = -35.6$ ($c=0.5$, MeOH)

Elemental analysis: Calcd. C, 73.22; H, 5.20; N, 6.57;

25 Found C, 73.30; H, 5.61; N, 7.08.

I.R. (KBr): 3500-3120; 3100-3000; 1730; 1660-1620 cm^{-1} .

300 MHz ^1H -NMR (DMSO- d_6): δ 9.30 (d, 1H); 8.10 (t, 1H); 8.08 (d, 1H); 8.01 (d, 2H); 7.70-7.68 (m, 2H); 7.59-7.38 (m, 11H); 7.30 (m, 2H); 5.06 (dt, 1H); 3.79 (t, 2H); 3.61 (s, 3H); 3.30-3.13 (m, 2H); 1.90-1.75 (m, 2H); 0.95 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 422; 382; 264; 247; 219; 206; 174; 163; 147.

EXAMPLE 18

35 (S,E)-N-(α -ethylbenzyl)-3-[2-(3-methoxycarbonylpropenoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

1.4 g (3.3 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) were dissolved, under nitrogen atmosphere, in 35 ml of dry CH_2Cl_2 . 0.77 ml (5.5 mmol) of TEA were added, the solution was cooled to 0°C and 0.4 g (3.4 mmol) of methyl 3-chlorocarbonylpropenoate (compound of Description 5), dissolved in 25 ml of CH_2Cl_2 , were added dropwise. The reaction was

stirred at room temperature for 2 days, washed with H₂O, 20% citric acid, sat. sol. NaHCO₃, sat. sol. NaCl, dried over Na₂SO₄ and evaporated *in vacuo* to dryness. The residue was purified by gradient flash column chromatography on 230-400 mesh silica utilising a mixture of hexane/EtOAc 8:2 as starting eluent and a mixture of hexane/EtOAc 3:7 as final eluent. The crude product so obtained was further purified by preparative HPLC to yield 0.30 g of the title compound.

C₃₂H₃₁N₃O₅

M.P. = 122-125°C

M.W. = 537.62

10 $[\alpha]_D^{20} = -37.7$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 71.49; H, 5.81; N, 7.82;

Found C, 71.19; H, 5.86; N, 7.77.

I.R. (KBr): 3500-3120; 3100-3000; 1730; 1670-1620; 1550 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 9.30 (d, 1H); 8.47 (t br, 1H); 8.06 (d, 1H); 7.97 (dd, 2H); 7.73 (ddd, 1H); 7.60 (m, 2H); 7.50-7.37 (m, 7H); 7.29 (dd, 1H); 6.95 (d, 1H); 6.51 (d, 1H); 5.07 (dt, 1H); 3.75 (s, 3H); 3.69 (m, 2H); 3.25-3.00 (m, 2H); 1.90-1.75 (m, 2H); 0.97 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 537 (M⁺); 507; 404; 382; 301; 249; 156.

20

EXAMPLE 19

(S,Z)-N-(α-ethylbenzyl)-3-[2-(3-methoxycarbonylpropenoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

25 By continuing the elution of the flash column chromatography of Example 18, 0.31 g of the title compound were isolated.

C₃₂H₃₁N₃O₅

M.P. = 80-90°C

M.W. = 537.62

30 $[\alpha]_D^{20} = -37.2$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 71.49; H, 5.81; N, 7.82;

Found C, 71.05; H, 5.93; N, 7.68.

I.R. (KBr): 3500-3120; 3100-3000; 1730; 1670-1620; 1550 cm⁻¹.

35 300 MHz ¹H-NMR (DMSO-d₆): δ 9.31 (d, 1H); 8.07 (d, 1H); 8.05 (t br, 1H); 7.98 (dd, 2H); 7.73 (ddd, 1H); 7.59 (m, 2H); 7.55-7.38 (m, 7H); 7.29 (dd, 1H); 6.22 (Abq, 2H); 5.09 (dt, 1H); 3.66 (m, 2H); 3.58 (s, 3H); 3.20-2.95 (m, 2H); 1.83 (m, 2H); 0.99 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 537 (M⁺); 476; 371; 247; 156; 124.

40

EXAMPLE 20

(S,E)-N-(α -ethylbenzyl)-3-[2-(3-carboxypropenoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

- 0.2 g (0.4 mmol) of (S,E)-N-(α -ethylbenzyl)-3-[2-(3-methoxycarbonylpropenoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide (compound of Example 18) were dissolved in 25 ml of 10% NaOH and 5 ml of 1,4-dioxane and warmed to 60°C for 15 minutes. After cooling, the reaction mixture was extracted with CH₂Cl₂ and washed with 10% citric acid and sat. sol. NaCl. The organic layer was dried over Na₂SO₄, evaporated *in vacuo* to dryness and triturated with *i*-Pr₂O to yield 83 mg of the title compound.
- C₃₁H₂₉N₃O₅**
M.P. = 230-233°C
M.W. = 523.59
 $[\alpha]_D^{20} = -39.6$ (c=0.5, MeOH)
I.R. (KBr): 3500-3120; 3100-3000; 1740-1700; 1680-1600; 1550-1520 cm⁻¹.
- 300 MHz ¹H-NMR (DMSO-d₆): δ 9.30 (d, 1H); 8.42 (t br, 1H); 8.06 (d, 1H); 7.97 (dd, 2H); 7.73 (ddd, 1H); 7.59 (m, 2H); 7.50-7.37 (m, 7H); 7.29 (dd, 1H); 6.88 (d, 1H); 6.45 (d, 1H); 5.09 (dt, 1H); 3.68 (m, 2H); 3.24-2.99 (m, 2H); 1.80 (m, 2H); 0.96 (t, 3H).**
- MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 523 (M⁺); 382; 264; 247; 219; 119; 91.**
- EXAMPLE 21**

(S)-N-(α -ethylbenzyl)-3-(cyanomethoxy)-2-phenylquinoline-4-carboxamide

- 2.0 g (5.23 mmol) of (S)-N-(α -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (compound of Description 1), 2.21 g of K₂CO₃, 0.26 g (1.57 mmol) of KI and 0.52 ml (7.85 mmol) of bromoacetonitrile were stirred in 30 ml of dry THF for 5 hours. The inorganic salts were filtered off and the filtrate was evaporated *in vacuo* to dryness. The residue was dissolved in CH₂Cl₂ and the organic phase was washed with H₂O, sat. sol. NaHCO₃, sat. sol. NaCl, separated, dried over Na₂SO₄ and evaporated *in vacuo* to dryness to afford 2.10 g of a brown oil which was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/EtOAc 70:30. The crude product was triturated with hexane, filtered, washed and dried to yield 0.75 g of the title compound as a white solid.
- C₂₇H₂₃N₃O₂**
M.P. = 70-72 °C
M.W. = 421.50
 $[\alpha]_D^{20} = -40.4$ (c=1, MeOH)
I.R. (KBr): 3413; 3264; 3053; 2943; 1645; 1529 cm⁻¹.
- 300 MHz ¹H-NMR (DMSO-d₆): δ 9.37 (d, 1H); 8.11 (d, 1H); 7.95 (dd, 2H); 7.80 (ddd, 1H); 7.67-7.55 (m, 5H); 7.45-7.38 (m, 4H); 7.20 (dd, 1H); 5.10 (dt, 1H); 4.60 (Abq, 2H); 1.85 (dq, 2H); 1.00 (t, 3H).**

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 421 (M⁺); 392; 381; 287; 247; 219; 190; 134.

EXAMPLE 22

5 (S)-N-(α -ethylbenzyl)-3-(2-phenylacetyl aminoethoxy)-2-phenylquinoline-4-carboxamide

1.0 g (2.3 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) were dissolved in 20 ml of dry CH₂Cl₂; 0.37 ml (2.6 mmol) of TEA were added and the reaction mixture was cooled to 0°C. 0.4 g (2.6 mmol) of phenylacetyl chloride, dissolved in 20 ml of CH₂Cl₂, were added dropwise and the reaction mixture was stirred at room temperature for 4 hours and then washed with 20% citric acid, sat. sol. NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, evaporated *in vacuo* to dryness and triturated with *i*-Pr₂O to yield 0.9 g of the title compound.

15 C₂₅H₃₃N₃O₃

M.P. = 95-105°C

M.W. = 543.66

[α]_D²⁰ = -32.6 (c=0.5, MeOH)

Elemental analysis: Calcd. C, 77.32; H, 6.12; N, 7.73;

20 Found C, 76.89; H, 6.19; N, 7.61.

I.R. (KBr): 3400-3100; 3100-3000; 1650-1620 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 9.30 (d, 1H); 8.06 (d, 1H); 7.98 (m, 2H); 7.86 (t br, 1H); 7.72 (ddd, 1H); 7.59 (m, 2H); 7.51 (m, 3H); 7.45 (d, 2H); 7.39 (dd, 2H); 7.30-7.12 (m, 6H); 5.09 (dt, 1H); 3.62 (m, 2H); 3.29 (s, 2H); 3.12-2.91 (m, 2H); 1.90-1.75 (m, 2H); 0.98 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 543 (M⁺); 410; 382; 162.

EXAMPLE 23

30 (S)-N-(α -ethylbenzyl)-3-[2-((S)- α -aminophenylacetyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

The reaction to obtain the Fmoc-protected title compound was conducted as described in Example 25, starting from 2.8 g (6.7 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4), 1.1 ml (8.0 mmol) of TEA and 3.1 g (8.0 mmol) of (S)-Fmoc-phenylglyciny chloride. The reaction was stirred at room temperature for 20 hours and worked up as described in Example 25 to yield 4.5 g of the Fmoc protected title compound, which was deprotected by stirring at room temperature for 30 minutes with 90 ml of a 10% solution of diethylamine in DMF.

40 The reaction mixture was then evaporated *in vacuo* and purified by gradient flash column chromatography on 230-400 mesh silica gel, utilising EtOAc as starting eluent and a mixture of EtOAc/MeOH 9:1 as final eluent, to yield, after trituration with *i*-Pr₂O, 1.4 g

of the title compound.

$C_{35}H_{34}N_4O_3$

M.P. = 140-145°C

M.W. = 558.68

5 $[\alpha]_D^{20} = -17.0$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 75.25; H, 6.13; N, 10.03;

Found C, 72.70; H, 6.11; N, 9.80.

I.R. (KBr): 3440-3110; 3100-3000; 1650-1630; 1585 cm^{-1} .

10 300 MHz 1H -NMR (DMSO- d_6): δ 9.30 (d, 1H); 8.08 (d, 1H); 7.97 (dd, 2H); 7.92 (t br, 1H); 7.72 (dd, 1H); 7.60-7.48 (m, 5H); 7.45 (d, 2H); 7.38 (dd, 2H); 7.30-7.20 (m, 6H); 5.09 (dt, 1H); 4.21 (s, 1H); 3.65 (t, 2H); 3.07 (dt, 2H); 2.10 (s br, 2H); 1.90-1.75 (m, 2H); 0.95 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 541; 453; 382; 292; 291; 247; 219; 106.

EXAMPLE 24

20 (S)-N-(α -ethylbenzyl)-3-[2-((R)- α -aminophenylacetyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

The reaction was conducted exactly as described in Example 23, utilising the (R)-FMOC-phenylglyciny chloride instead of the (S). The same amounts of all the reagents were used. 0.8 g of the title compound were obtained.

25 $C_{35}H_{34}N_4O_3$

M.P. = 92-94°C

M.W. = 558.68

$[\alpha]_D^{20} = -52.8$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 75.25; H, 6.13; N, 10.03;

30 Found C, 74.15; H, 6.19; N, 9.91.

I.R. (KBr): 3440-3110; 3100-3000; 1670-1630 cm^{-1} .

35 300 MHz 1H -NMR (DMSO- d_6): δ 9.30(d, 1H); 8.07 (d, 1H); 7.96 (d, 2H); 7.90 (t br, 1H); 7.72 (m, 1H); 7.60-7.50 (m, 5H); 7.44 (d, 2H); 7.38 (dd, 2H); 7.29-7.19 (m, 6H); 5.09 (dt, 1H); 4.20 (s, 1H); 3.60 (m, 2H); 3.16-2.91 (m, 2H); 2.11 (s br, 2H); 1.90-1.75 (m, 2H); 0.96 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 541; 453; 382; 292; 291; 247; 219; 106.

EXAMPLE 25

40 (S)-N-(α -ethylbenzyl)-3-(2-aminoacetyl)aminoethoxy)-2-phenylquinoline-4-carboxamide

3.0 g (7.1 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-

carboxamide (compound of Description 4) were dissolved, under nitrogen atmosphere, in 60 ml of CH_2Cl_2 and 1.2 ml (8.5 mmol) of TEA were added; the solution was cooled to 0°C and 2.7 g (8.5 mmol) of (9-fluorenylmethoxy carbonyl)glycinyll chloride (Fmoc-glycinyll chloride), dissolved in 60 ml of CH_2Cl_2 , were added dropwise. The reaction mixture was stirred at room temperature for 3 hours and then washed with sat. sol. NaCl, 20% citric acid, sat. sol. NaHCO_3 , sat. sol. NaCl, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The crude product was purified by gradient flash column chromatography on 230-400 mesh silica gel, utilising a mixture of hexane/EtOAc 1:1 as starting eluent and a mixture of EtOAc/MeOH 9:1 as final eluent. The product (5.0 g) was dissolved in 100 ml of a 10% solution of diethylamine in DMF and stirred at room temperature for 30 minutes. The reaction mixture was then evaporated *in vacuo* and purified by gradient flash column chromatography on 230-400 mesh silica gel, utilising a mixture of EtOAc/MeOH 9:1 as starting eluent and a mixture of EtOAc/MeOH 7:3 as final eluent, to yield 0.6 g of the title compound.

$\text{C}_{29}\text{H}_{30}\text{N}_4\text{O}_3$

M.P. = $55-60^\circ\text{C}$ dec.

M.W. = 482.58

$[\alpha]_D^{20} = -33.7$ ($c=0.5$, MeOH)

Elemental analysis: Calcd. C, 72.12; H, 6.27; N, 11.61;

Found C, 70.12; H, 6.45; N, 10.81.

I.R. (KBr): 3500-3110; 3100-3000; 1680-1650; 1638 cm^{-1} .

300 MHz $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 9.29 (d, 1H); 8.06 (d, 1H); 7.98 (dd, 2H); 7.74 (ddd, 1H); 7.68 (t br, 1H); 7.60-7.38 (m, 9H); 7.30 (dd, 1H); 5.09 (dt, 1H); 3.70-3.55 (m, 2H); 3.18-3.00 (m, 2H); 2.99 (s, 2H); 1.90-1.78 (m, 2H); 1.00 (t, 3H).

MS (EI; TSQ 700; source 180°C ; 70 V; 200 μA): 482 (M^+); 382; 291; 264; 247; 219; 190; 141; 119; 101; 91.

EXAMPLE 26

(S)-N-(α -ethylbenzyl)-3-[2-(4-pyridylacetyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

0.41 g (2.4 mmol) of 4-pyridylacetic acid hydrochloride were suspended in 80 ml of CH_2Cl_2 ; the suspension was cooled to 0°C and 0.33 ml (2.4 mmol) of TEA, 0.64 g (4.7 mmol) of HOBT and 1.0 g (2.4 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) were added. 0.58 g (2.8 mmol) of DCC, dissolved in 10 ml of CH_2Cl_2 , were added dropwise and the reaction mixture was stirred at 0°C for 1 h and at room temperature overnight. The precipitated dicyclohexylurea was filtered off and the filtrate was washed with 20% citric acid, sat. sol. NaCl and brine, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The crude product was purified by flash column chromatography on 230-400 mesh silica gel, eluting with a mixture of CH_2Cl_2 /MeOH 95:5 containing 0.5% NH_4OH (28%), to yield, after

trituration with *i*-Pr₂O, 0.85 g of the title compound.

C₃₄H₃₂N₄O₃

M.P. = 76°C dec.

M.W. = 544.65

5 $[\alpha]_D^{20} = -28.6$ (c=0.5, MeOH)

Elemental analysis: Calcd. C, 74.98; H, 5.92; N, 10.29;

Found C, 74.21; H, 5.95; N, 10.17.

I.R. (KBr): 3269; 3100-3000; 1646; 1603 cm⁻¹.

10 300 MHz ¹H-NMR (DMSO-d₆): δ 9.30 (d, 1H); 8.41 (d, 2H); 8.08 (d, 1H); 8.00 (m, 3H);
7.74 (ddd, 1H); 7.62-7.48 (m, 5H); 7.45 (d, 2H); 7.40
(dd, 2H); 7.28 (dd, 1H); 7.18 (d, 2H); 5.10 (dt, 1H);
3.63 (m, 2H); 3.34 (s, 2H); 3.14-2.92 (m, 2H); 1.80 (m,
2H); 0.98 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 544 (M⁺); 411; 382; 163.

15

EXAMPLE 27

(S)-N-(α -ethylbenzyl)-3-[2-(3-pyridylacetyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

20 Prepared as described in Example 26 from 0.41 g (2.4 mmol) of 3-pyridylacetic acid hydrochloride, 1.0 g (2.4 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4), 0.33 ml (2.4 mmol) of TEA, 0.64 g (4.7 mmol) of HOBT and 0.58 g (2.8 mmol) of DCC.

25 The work up and the purification of the reaction mixture were conducted as described in Example 26. After trituration with *i*-Pr₂O, 0.76 g of the title compound were obtained.

C₃₄H₃₂N₄O₃

M.P. = 89°C dec.

M.W. = 544.65

$[\alpha]_D^{20} = -31.7$ (c=0.5, MeOH)

30 Elemental analysis: Calcd. C, 74.98; H, 5.92; N, 10.29;

Found C, 74.14; H, 6.00; N, 10.17.

I.R. (KBr): 3275; 3100-3000; 1643; 1548 cm⁻¹.

35 300 MHz ¹H-NMR (DMSO-d₆): δ 9.29 (d, 1H); 8.40 (m, 2H); 8.06 (d, 1H); 7.98 (m, 3H); 7.72 (ddd, 1H); 7.60-7.48 (m, 6H); 7.45 (d, 2H);
7.39 (dd, 2H); 7.29 (m, 2H); 5.08 (dt, 1H); 3.65 (m, 2H); 3.33 (s, 2H); 3.13-2.91 (m, 2H); 2.90-2.75 (m, 2H); 1.00 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 544 (M⁺); 515; 411; 382; 353; 264; 247; 163.

40

EXAMPLE 28

(S)-N-(α -ethylbenzyl)-3-[2-(2-pyridylacetyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

Prepared as described in Example 26 from 0.41 g (2.4 mmol) of 2-pyridylacetic acid hydrochloride, 1.0 g (2.4 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4), 0.33 ml (2.4 mmol) of TEA, 0.64 g (4.7 mmol) of HOBT and 0.58 g (2.8 mmol) of DCC.

The work up and the purification of the reaction mixture were conducted as described in Example 26. After trituration with *i*-Pr₂O, 0.10 g of the title compound were obtained.

C₃₄H₃₂N₄O₃

M.P. = 74°C dec.

M.W. = 544.65

$[\alpha]_D^{20} = -34.1$ (c=0.5, MeOH)

I.R. (KBr): 3269; 3100-3000; 1645; 1592; 1540 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 9.28 (d, 1H); 8.44 (d, 1H); 8.08-7.90 (m, 4H); 7.75-7.65 (m, 2H); 7.60-7.37 (m, 9H); 7.30-7.20 (m, 3H); 5.10 (dt, 1H); 3.62 (m, 2H); 3.50 (s, 2H); 3.12-2.95 (m, 2H); 1.80 (m, 2H); 0.98 (t, 3H).

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 514; 452; 382; 247; 163.

20

EXAMPLE 29

(S)-N-(α -ethylbenzyl)-3-[2-(2'-carboxyphenylacetyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

1.0 g (2.4 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) were dissolved in 10 ml of toluene; 0.51 g (2.8 mmol) of homophthalic acid were added and the reaction mixture was refluxed for 3.5 hours. After cooling, the solvent was evaporated *in vacuo* to dryness and the residue was dissolved in CH₂Cl₂ and washed with brine. The organic layer was dried over Na₂SO₄ and evaporated *in vacuo* to dryness. The residue was purified by gradient flash column chromatography on 230-400 mesh silica gel, utilising a mixture of hexane/EtOAc 7:3 containing 0.5% NH₄OH (28%) as starting eluent and a mixture of EtOAc/MeOH 8:2 containing 2% NH₄OH (28%) as final eluent, to yield 0.89 g of a mixture of the title compound and of (S)-N-(α -ethylbenzyl)-3-[2-(2'-carboxymethylbenzoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide (compound of Example 30). 0.4 g of this mixture were purified by preparative HPLC to yield 0.17 g of the title compound.

C₃₆H₃₃N₃O₅

M.P. = 108°C dec.

M.W. = 587.67

$[\alpha]_D^{20} = -28.3$ (c=0.5, MeOH)

I.R. (KBr): 3247; 3100-3000; 1710-1650; 1635; 1547 cm⁻¹.

300 MHz ¹H-NMR (DMSO-d₆): δ 12.80 (s br, 1H); 9.29 (d, 1H); 8.08 (d, 1H); 7.99 (d,

2H); 7.79 (d, 1H); 7.75 (t br, 1H); 7.72 (ddd, 1H); 7.60-7.50 (m, 5H); 7.48-7.25 (m, 7H); 7.17 (d, 1H); 5.09 (dt, 1H); 3.72 (s, 2H); 3.65 (m, 2H); 3.12-2.92 (m, 2H); 1.81 (m, 2H); 0.90 (t, 3H).

5 MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 569; 425; 407; 396; 383; 291; 277; 262; 247; 219; 188; 165; 118; 91.

EXAMPLE 30

(S)-N-(α -ethylbenzyl)-3-[2-(2'-carboxymethylbenzoyl)aminoethoxy]-2-phenylquinoline-4-carboxamide

10

By continuing the preparative HPLC of Example 29, 0.063 g of the title compound were obtained.

$C_{36}H_{33}N_3O_5$

M.P. = 83°C dec.

15

M.W. = 587.67

$[\alpha]_D^{20} = -33.5$ (c=0.5, MeOH)

I.R. (KBr): 3273; 3100-3000; 1733; 1641; 1612; 1594; 1538 cm^{-1} .

300 MHz 1H -NMR (DMSO- d_6): δ 12.20 (s br, 1H); 9.31 (d, 1H); 8.30 (s br, 1H); 8.06 (d, 1H); 7.99 (m, 2H); 7.72 (ddd, 1H); 7.57 (m, 2H); 7.48-7.38 (m, 8H); 7.30-7.20 (m, 4H); 5.04 (dt, 1H); 3.79 (t, 2H); 3.63 (s, 2H); 3.32-3.15 (m, 2H); 1.88-1.75 (m, 2H); 0.94 (t, 3H).

20

MS (EI; TSQ 700; source 180 C; 70 V; 200 uA): 569; 425; 407; 396; 383; 291; 277; 262; 247; 219; 188; 165; 118; 91.

25

EXAMPLE 31

(S)-N-(α -ethylbenzyl)-3-(2-benzylaminoethoxy)-2-phenylquinoline-4-carboxamide hydrochloride

1.5 g (3.52 mmol) of (S)-N-(α -ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide (compound of Description 4) and 0.71 ml (7.04 mmol) of benzaldehyde were dissolved in 40 ml of MeOH; after cooling to 10°C, 2.21 g (3.52 mmol) of NaCNBH₃ were added portionwise, under nitrogen atmosphere, and the reaction stirred at room temperature overnight.

30

The reaction was quenched with 50 ml of 2N NaOH and extracted with ether; the organic layer was separated, dried over Na₂SO₄ and evaporated *in vacuo* to dryness.

35

The crude product was purified by 230-400 mesh silica gel gradient column chromatography, eluting with hexane/EtOAc (from 20 to 30%).

The crude product (0.64 g) was dissolved in MeOH and the solution acidified with HCl/Et₂O to yield the corresponding hydrochloride, which was recrystallized from *i*-

40

Pr₂O/*i*-PrOH to obtain 0.50 g of the title compound as a pale yellow powder.

$C_{34}H_{33}N_3O_2 \cdot HCl$

M.P. = 165-169°C

M.W. = 552.110

$[\alpha]_D^{20} = -27.7$ (c=1.1, MeOH)

I.R. (KBr): 3498; 3185; 2968-2637; 1650; 1535 cm^{-1} .

300 MHz $^1\text{H-NMR}$ 353 K (DMSO- d_6): δ 8.89 (d, 1H); 8.01 (d, 1H); 7.74 (m, 2H); 7.62 (dd, 2H); 7.57-7.44 (m, 6H); 7.39 (dd, 2H); 7.29 (dd, 1H); 7.20-7.10 (m, 3H); 6.89 (m, 2H); 5.13 (dt, 1H); 3.70 (s, 2H); 3.10 (s, 2H); 2.02-1.80 (m, 2H); 1.68 (s, 3H); 0.98 (t, 3H).

MS (EI, TSQ 700, source $^{\circ}180$ C, 70 V, 200 μA): 408; 273; 380.

EXAMPLE 32

15 (S)-N-(α -ethylbenzyl)-3-(2-dibenzylaminoethoxy)-2-phenylquinoline-4-carboxamide hydrochloride

By continuing the elution of the chromatographic column of Example 31, 0.40 g of the crude title compound were obtained.

20 This product was dissolved in MeOH and the solution acidified with HCl/Et₂O to yield the corresponding hydrochloride, which was recrystallized from Et₂O/MeOH to obtain 0.26 g of the title compound.

$\text{C}_{41}\text{H}_{39}\text{N}_3\text{O}_2\cdot\text{HCl}$

M.P. = 144-145 $^{\circ}\text{C}$

25 M.W. = 642.28

$[\alpha]_D^{20} = -25.3$ (c=0.25, MeOH)

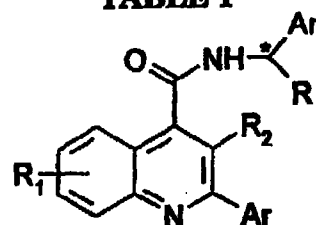
I.R. (KBr): 3419; 3163; 3059-2933; 1656; 1542 cm^{-1} .

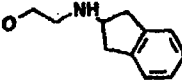
300 MHz $^1\text{H-NMR}$ DMSO- d_6): δ 9.52 (d, 1H); 8.10 (d, 1H); 7.86 (dd, 2H); 7.79 (ddd, 1H); 7.63 (m, 2H); 7.49-7.36 (m, 16H); 7.30-7.20 (m, 3H); 5.01 (dt, 1H); 4.09 (m, 4H); 3.99 (m, 2H); 3.00 (m, 2H); 1.81-1.71 (m, 2H); 0.82 (t, 3H).

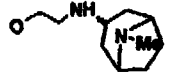
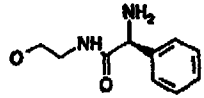
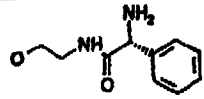
MS (EI, TSQ 700, source $^{\circ}180$ C, 70 V, 200 μA): 514; 223; 210; 132; 91.

35

TABLE 1



Ex	Ar	R	R ₁	R ₂	*	Molecular formula	Melting point °C	[α] _D ²⁰ c=0.5, MeOH
1	Ph	Et	H	OCH ₂ CO ₂ Et	(S)	C ₂₉ H ₂₈ N ₂ O ₄	103-105	-42.5
2	Ph	Et	H	OCH ₂ CO ₂ H	(S)	C ₂₇ H ₂₄ N ₂ O ₄ · HCl	203-204	-30.2
3	Ph	Et	H	OCH ₂ CONH ₂	(S)	C ₂₇ H ₂₅ N ₃ O ₃	237-240	-35.9
4	Ph	Et	H	OCH ₂ CONMe ₂	(S)	C ₂₉ H ₂₉ N ₃ O ₃	86-88	-41.2
5	Ph	Et	H	OCO ₂ Et	(S)	C ₂₈ H ₂₆ N ₂ O ₄	119-121	-57.8 ^a
6	Ph	Et	H	NHCONHPh	(S)	C ₃₂ H ₂₈ N ₄ O ₂	257-258	-64.6 ^b
7	Ph	Et	H	NHCONHCH ₂ CO ₂ Et	(S)	C ₃₀ H ₃₀ N ₄ O ₄	237-238	-45.0 ^c
8	Ph	Et	H		(S)	C ₃₆ H ₃₅ N ₃ O ₂ · HCl	156-160	-11.0
9	Ph	Et	H	OCH ₂ CH ₂ NHCOPh	(S)	C ₃₄ H ₃₁ N ₃ O ₃	157-160	-27.3
10	Ph	Et	H	OCH ₂ CH ₂ CH ₂ COOEt	(S)	C ₃₁ H ₃₂ N ₂ O ₄	140-142	-41.6 ^d
11	Ph	Et	H	OCH ₂ CH ₂ CH ₂ COOH	(S)	C ₂₉ H ₂₈ N ₂ O ₄	149-151	-42.3 ^d

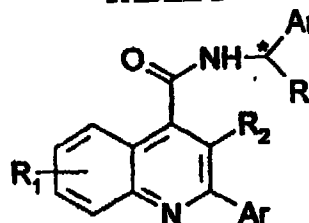
Ex	Ar	R	R ₁	R ₂	*	Molecular formula	Melting point °C	[α] _D ²⁰ c=0.5, MeOH
12	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ Ph(o-CH ₂ OH)	(S)	C ₃₆ H ₃₅ N ₃ O ₄	160-163	-31.5
13	Ph	Et	H	(Z) OCH ₂ CH ₂ NHCOCH=CHCOOH	(S)	C ₃₁ H ₂₉ N ₃ O ₅	158-162	-38.6
14	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ CH ₂ COOH	(S)	C ₃₁ H ₃₁ N ₃ O ₅	118-122	-32.1
15	Ph	Et	H		(S)	C ₃₅ H ₄₀ N ₄ O ₂ · HCl	200-203	—
16	Ph	Et	H	OCH ₂ CH ₂ NHCOPh(o-COOH)	(S)	C ₃₅ H ₃₁ N ₃ O ₅	96-115	-33.3
17	Ph	Et	H	OCH ₂ CH ₂ NHCOPh(o-COOMe)	(S)	C ₃₆ H ₃₃ N ₃ O ₅	133-135	-35.6
18	Ph	Et	H	(E) OCH ₂ CH ₂ NHCOCH=CHCOOMe	(S)	C ₃₂ H ₃₁ N ₃ O ₅	122-125	-37.7
19	Ph	Et	H	(Z) OCH ₂ CH ₂ NHCOCH=CHCOOMe	(S)	C ₃₂ H ₃₁ N ₃ O ₅	80-90	-37.2
20	Ph	Et	H	(E) OCH ₂ CH ₂ NHCOCH=CHCOOH	(S)	C ₃₁ H ₂₉ N ₃ O ₅	230-233	-39.6
21	Ph	Et	H	OCH ₂ C≡N	(S)	C ₂₇ H ₂₃ N ₃ O ₂	70-72	-40.4 ^d
22	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ Ph	(S)	C ₃₅ H ₃₃ N ₃ O ₃	95-105	-32.6
23	Ph	Et	H		(S)	C ₃₅ H ₃₄ N ₄ O ₃	140-145	-17.0
24	Ph	Et	H		(S)	C ₃₅ H ₃₄ N ₄ O ₃	92-94	-52.8
25	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ NH ₂	(S)	C ₂₉ H ₃₀ N ₄ O ₃	55-60	-33.7

Ex	Ar	R	R ₁	R ₂	*	Molecular formula	Melting point °C	[α] _D ²⁰ c=0.5, MeOH
26	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ -(4-pyridyl)	(S)	C ₃₄ H ₃₂ N ₄ O ₃	76 dec.	-28.6
27	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ -(3-pyridyl)	(S)	C ₃₄ H ₃₂ N ₄ O ₃	89 dec.	-31.7
28	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ -(2-pyridyl)	(S)	C ₃₄ H ₃₂ N ₄ O ₃	74 dec.	-34.1
29	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ Ph(o-COOH)	(S)	C ₃₆ H ₃₃ N ₃ O ₅	108 dec.	-28.3
30	Ph	Et	H	OCH ₂ CH ₂ NHCOPh(o-CH ₂ COOH)	(S)	C ₃₆ H ₃₃ N ₃ O ₅	83 dec.	-33.5
31	Ph	Et	H	OCH ₂ CH ₂ NHCH ₂ Ph	(S)	C ₃₄ H ₃₃ N ₃ O ₂ · HCl	165-169	-27.7
32	Ph	Et	H	OCH ₂ CH ₂ N(CH ₂ Ph) ₂	(S)	C ₄₁ H ₃₉ N ₃ O ₂ · HCl	144-145	-25.3

a: C = 0.25, MeOH; b: C = 0.25, DMF; c: C = 0.1, DMF; d: C = 1, MeOH

Following synthetic procedures described in Examples 1-32, the compounds listed below have been prepared:

TABLE 2



Ex	Ar	R	R ₁	R ₂	*	Molecular formula	Molecular weight	Melting point °C	[α] _D ²⁰ c=0.5, MeOH
33	Ph	Et	H	OCH ₂ CH ₂ NHCH ₂ CH ₂ Ph	(S)	C ₃₅ H ₃₅ N ₃ O ₂ · HCl	529.680	113-115	- 10.4
34	Ph	Et	H	OCH ₂ -(4-pyridyl)	(S)	C ₃₁ H ₂₇ N ₃ O ₂	473.573	182-184	- 38.2
35	Ph	Et	H	OCH ₂ CH ₂ CH ₂ NHCO-(3-carboxamidopyrazin-2-yl)	(S)	C ₃₄ H ₃₂ N ₆ O ₄	588.665	121-123	- 30.9
36	Ph	Et	H	OCH ₂ CH ₂ NHCO-(2-pyrazinyl)	(S)	C ₃₂ H ₂₉ N ₅ O ₃	531.613	68-70	- 38.9
37	Ph	Et	H	OCH ₂ CH ₂ NHCO-(3-aminopyrazin-2-yl)	(S)	C ₃₂ H ₃₀ N ₆ O ₃	546.628	80-85	- 44.2
38	Ph	Et	H	OCH ₂ CH ₂ CH ₂ NHCO-(2-pyrazinyl)	(S)	C ₃₃ H ₃₁ N ₅ O ₃	545.640	70-75	- 31.6

Ex	Ar	R	R ₁	R ₂	*	Molecular formula	Molecular weight	Melting point °C	[α] _D ²⁰ c=0.5, MeOH
39	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ Ph(o-CH ₂ NHMe)	(S)	C ₃₇ H ₃₈ N ₄ O ₃	586.732	58 dec.	- 30.5
40	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ Ph(o-CH ₂ pyrrolidino)	(S)	C ₄₀ H ₄₂ N ₄ O ₃	626.797	89-95	- 34.2
41	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ Ph(o-OCH ₂ CH ₂ pyrrolidino)	(S)	C ₄₁ H ₄₄ N ₄ O ₄	656.823	132-134	- 30.1
42	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ Ph(o-OH)	(S)	C ₃₅ H ₃₃ N ₃ O ₄	559.663	160-161	- 34.7
43	Ph	Et	H	OCH ₂ CH ₂ NHCOCH ₂ Ph(o-OMe)	(S)	C ₃₆ H ₃₅ N ₃ O ₄	573.690	106-108	- 31.6

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Table 3. Analytical and spectroscopic data of compounds of Examples 33-43.

Ex.	Elemental analysis	IR (Kbr); cm^{-1}	MS (EI; TSQ 700; source 180 °C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
33		3388; 2930; 1630; 1563.	438 ; 383; 320; 303; 291; 247; 219; 204; 119; 105; 91; 56.	9.48(d,1H); 8.91(s br,1H); 8.09(d,1H); 7.98(dd,2H); 7.76(ddd,1H); 7.61(m,2H); 7.58-7.50(m,3H); 7.48- 7.25(m,8H); 7.21(d,2H); 5.07(dt,1H); 3.98-3.85 (m,2H); 2.85(s br,6H); 1.90-1.74(m,2H); 0.93(t,3H).
34		3230; 3063-2868; 1626; 1586; 1541.	473 (M ⁺); 444; 381; 339; 312; 248; 220;219; 190; 134; 91.	9.37(d,1H); 8.41(d,2H); 8.11(d,1H); 7.94(m,2H); 7.79(ddd,1H); 7.70-7.60(m,2H); 7.50(m,3H); 7.40(m,2H); 7.30-7.20(m,3H); 6.98(d,2H); 5.07(dt,1H); 4.68(s,2H); 1.76(dq,2H); 0.90(t,3H).
35	Calcd. C,69.37; H,5.48; N,14.28; Found C,68.47; H,5.50; N,13.96.	3280; 2965; 2877; 1700-1610.	383; 247; 207; 190; 162; 91.	9.28(d,1H); 8.73(s,2H); 8.25(t,1H); 8.05(d,1H); 7.95(m,3H); 7.71(ddd,1H); 7.60-7.37(m,10H); 7.28(dd,1H); 5.08(dt,1H); 3.70(t,2H); 3.05(dt,2H); 1.90-1.75(m,2H); 1.65-1.58(m,2H); 0.98(t,3H).
36		3276; 3062;2969; 2879; 1690-1630; 1577.	219; 150.	9.30(d,1H); 9.11(d,1H); 8.88(d,1H); 8.70(m,1H); 8.60(t,1H); 8.04(d,1H); 7.92(dd,2H); 7.71(ddd,1H); 7.59(m,2H); 7.45- 7.23(m,8H); 5.08(dt,1H); 3.89-3.78(m,2H); 3.41-3.25(m,2H); 1.89-1.72(m,2H); 0.92(t,3H).
37		3296; 3063; 2967; 2932; 2877; 1670; 1660; 1642; 1596.	247; 219; 190; 165; 150; 119.	9.29(d,1H); 8.41(t,1H); 8.21(d,1H); 8.03(d,1H); 7.92(dd,2H); 7.80(d,1H); 7.71(ddd,1H); 7.58(m,2H); 7.55-7.35(m,9H); 7.26(dd,1H); 5.08(dt,1H); 3.85-3.73 (m,2H); 3.32-3.20(m,2H); 1.89-1.72(m,2H); 0.91(t,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; TSQ 700; source 180 °C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
38		3393; 3289; 3060; 2965; 2932; 2876; 1680-1640; 1582.	219; 164; 136.	9.27(d,1H); 9.15(d,1H); 8.88(d,1H); 8.70(m,1H); 8.61(t,1H); 8.07(d,1H); 7.92(d,2H); 7.71(ddd,1H); 7.60-7.54(m,2H); 7.50-7.32(m,7H); 7.24(dd,1H); 5.08(dt,1H); 3.67(t,2H); 3.12(dt,2H); 1.89-1.72 (m,2H); 1.68-1.59(m,2H); 0.98(t,3H).
39		3266; 2929; 1660- 1650; 1541.	586 (M ⁺); 383; 264; 247; 219; 161; 119; 104; 91.	9.29(d,1H); 8.33(t,1H); 8.08(d,1H); 7.97(m,2H); 7.72(ddd,1H); 7.59(m,2H); 7.51(m,3H); 7.43(d,2H); 7.36(dd,2H); 7.27(m,2H); 7.19-7.09(m,3H); 5.08(dt,1H); 3.60(m,4H); 3.40(s,2H); 3.10-2.90 (m,2H); 2.21(s,3H); 1.81- 1.75(m,2H); 0.96(t,3H).
40		3256; 3063; 2965; 2790; 1640; 1539.	383; 264; 247; 219; 175; 119; 105; 91.	9.28(d,1H); 8.24(s br,1H); 8.08(d,1H); 7.97(m,2H); 7.72(ddd,1H); 7.59(m,2H); 7.51(m,3H); 7.44(d,2H); 7.38(dd,2H); 7.30-7.10(m,5H); 5.08(dt,1H); 3.60(m,4H); 3.43(s,2H); 3.10-2.90(m,2H); 2.42(m,4H); 1.88-1.78(m,2H); 1.68-1.59(m,4H); 0.98(t,3H).
41	Calcd. C,74.97; H,6.75; N,8.53; Found C,72.86; H,6.56; N,8.21.	3230; 3061; 2963; 2874; 1640-1630; 1601; 1536.	559; 382; 177; 97; 84.	DMSO (+TFA): 9.67(s br,1H); 9.31(d,1H); 8.09(d,1H); 8.02(t,1H); 7.98(m,2H); 7.73(dd,1H); 7.60(m,2H); 7.51(m,3H); 7.44(d,2H); 7.39(dd,2H); 7.30-7.20(m,2H); 7.11(d,1H); 6.99(d,1H); 6.90(dd,1H); 5.08(dt,1H); 4.29(t,2H); 3.70-3.60 (m,2H); 3.56-3.45(m,4H); 3.38(s,2H); 3.10- 2.94(m,4H); 2.00-1.70(m,6H); 0.99(t,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; TSQ 700; source 180 °C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
42	Calcd. C, 75.11; H, 5.94; N, 7.51; Found C, 75.07; H, 5.95; N, 7.43.	3430; 3400-3100; 3061; 2964; 1660; 1632; 1520.	559 (M ⁺); 426; 408; 383; 264; 248; 178; 106; 100; 134; 91.	9.60(s br, 1H); 9.29(d, 1H); 8.08(d, 1H); 7.98(dd, 2H); 7.80-7.70(m, 2H); 7.59(m, 2H); 7.51(m, 3H); 7.44(d, 2H); 7.38(dd, 2H); 7.28(dd, 1H); 7.02(dd, 1H); 6.99(d, 1H); 6.79(d, 1H); 6.70(dd, 1H); 5.09(dt, 1H); 3.70-3.60(m, 2H); 3.29(s, 2H); 3.13-2.93(m, 2H); 1.90-1.75(m, 2H); 0.99(t, 3H).
43	Calcd. C, 75.37; H, 6.15; N, 7.32; Found C, 75.43; H, 6.26; N, 7.19.	3285; 3062; 2966; 2837; 1670-1630; 1603; 1587.	573 (M ⁺); 382; 264; 247; 220; 192; 160; 133; 91.	9.30(d, 1H); 8.08(d, 1H); 7.99(dd, 2H); 7.72(ddd, 1H); 7.58(m, 2H); 7.52(m, 4H); 7.45(d, 2H); 7.39(dd, 2H); 7.29(dd, 1H); 7.19(dd, 1H); 7.02(d, 1H); 6.91(d, 1H); 6.83(dd, 1H); 5.08(dt, 1H); 3.70(s, 3H); 3.70-3.55 (m, 2H); 3.28(s, 2H); 3.03-2.94(m, 2H); 1.90-1.75 (m, 2H); 0.98(t, 3H).

Table 4. Pharmacological data

Example n.	Binding affinity in hNK-3-CHO ^a
	IC ₅₀ (nM)
2	1.9
8	1.3
9	2.2
11	1.7
14	2.3
22	0.6
25	2.6
26	0.9
29	0.8
30	1.5
34	1.6
36	0.2
38	0.4
40	1.3
42	0.4

^a hNK-3-CHO = human neurokinin-3 receptors expressed in CHO cell lines; radioligand used was [¹²⁵I]-[Me-Phe⁷]-NKB.

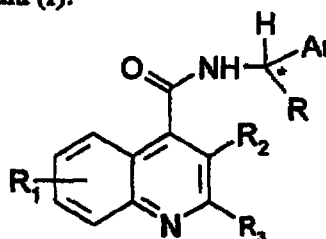
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15



1. A compound of formula (I):



(I)

- 5 or a salt thereof, or a solvate thereof, wherein, Ar is an optionally substituted aryl or a C₅-7 cycloalkdienyl group, or an optionally substituted single or fused ring aromatic heterocyclic group;

- R is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, optionally substituted phenyl or phenyl C₁₋₆ alkyl, an optionally substituted five-membered heteroaromatic ring comprising up to four heteroatoms selected from O and N, hydroxy C₁₋₆ alkyl, amino C₁₋₆ alkyl, C₁₋₆ alkylaminoalkyl, di C₁₋₆ alkylaminoalkyl, C₁₋₆ acylaminoalkyl, C₁₋₆ alkoxyalkyl, C₁₋₆ alkylcarbonyl, carboxy, C₁₋₆ alkoxyxcarbonyl, C₁₋₆ alkoxycarbonyl C₁₋₆ alkyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di C₁₋₆ alkylaminocarbonyl, halogeno C₁₋₆ alkyl; or R is a group -(CH₂)_p- wherein p is 2 or 3 which group forms a ring with a carbon atom of Ar;

- R₁ represents hydrogen or up to four optional substituents selected from the list consisting of: C₁₋₆ alkyl, C₁₋₆ alkenyl, aryl, C₁₋₆ alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C₁₋₆ alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino or mono- and di-C₁₋₆ alkylamino;

- R₂ represents a moiety -O-(CH₂)_n-X wherein X is alkyl optionally substituted with one or two groups selected from hydroxy and amino; carboxy, cyano, C₁₋₆ alkoxycarbonyl, aminocarbonyl, mono- or di-C₁₋₆ alkylaminocarbonyl, amino-C₁₋₆-alkylaminocarbonyl or mono- or di-C₁₋₆-alkylamino-C₁₋₆-alkylaminocarbonyl; or X is a group -NX₁X₂ wherein X₁ and X₂ each independently represent hydrogen, carboxyalkylcarbonyl, alkoxycarbonylalkylcarbonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aryl-C₁₋₆-alkylcarbonyl, heteroaryl C₁₋₆-alkylcarbonyl, aminocarbonyl, mono- or bis-C₁₋₆ alkylaminocarbonyl, amino C₁₋₆ alkylcarbonyl, mono- or bis-C₁₋₆ alkylamino C₁₋₆ alkylcarbonyl, a moiety of formula -CO-T-CO-T₁ or a 5 to 9 membered single or fused ring cycloalkyl group optionally comprising 1 or 2 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O or N and wherein one or two ring atoms are optionally substituted with C₁₋₆ alkyl, said ring being optionally fused to a benzene ring; wherein the above mentioned aryl and heteroaryl groups are optionally substituted with up to two groups selected from: hydroxy, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkyl, amino-C₁₋₆-alkyl, mono- or bis- C₁₋₆-alkylamino, mono- or bis- C₁₋₆-alkylamino-C₁₋₆-alkyl, amino-C₁₋₆-alkoxy, mono- or bis- C₁₋₆-alkylamino-C₁₋₆-alkoxy, carboxy, C₁₋₆-alkylcarbonyl, C₁₋₆-alkoxycarbonyl, carboxy-C₁₋₆ alkyl, carboxy-C₁₋₆ alkoxy and C₁₋₆-alkylcarbonyl C₁₋₆ alkoxy; and wherein the alkyl moiety of any heteroaryl-C₁₋₆-alkyl or aryl-C₁₋₆-alkyl group is optionally substituted with an amino, a mono-C₁₋₆-alkylamino or a bis-C₁₋₆-alkyl amino group; or X is a C-linked single or fused ring heterocyclic group, any ring being saturated or unsaturated and



- consisting of 5- to 6- ring atoms, said ring atoms comprising 1 or 2 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O or N and wherein one or two ring atoms are optionally substituted with C₁₋₆ alkyl, hydroxy, amino, mono- or bis- C₁₋₆-alkylamino or an oxo substituent; and n is zero or an integer in the range of from 1 to 7
- 5 providing that when X is a group -NX₁X₂, n is only an integer in the range of from 2 to 7 and providing that X₁ and X₂ are not simultaneously hydrogen; or R₂ represents a moiety-NH-CO-NHY wherein Y represents C₁₋₆-alkyl, aryl, aryl C₁₋₃-alkyl, a moiety -(CH₂)_p-X₃ wherein p is an integer in the range of from 1 to 4 and X₃ is carboxy, C₁₋₆ alkoxycarbonyl, or a moiety -CO-NH-(CH₂)_q-NX₄X₅ wherein q is an integer in the range
- 10 of from 2 to 4 and X₄ and X₅ each independently represent hydrogen, C₁₋₆ alkyl or C₁₋₆ alkylcarbonyl;
- R₃ is branched or linear C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring aromatic heterocyclic group, ;
- 15 T is a C₁₋₆ alkylene or C₂₋₆ alkenylene group; and
- T₁ is hydroxy or C₁₋₆ alkoxy.
2. A compound according to claim 1, wherein Ar represents phenyl
- 20 3. A compound according to claim 1 or claim 2, wherein R represents ethyl.
4. A compound according to any one of claims 1 to 3, wherein R₁ represents hydrogen.
- 25 5. A compound according to any one of claims 1 to 4, wherein R₂ is a group -O-(CH₂)_n-X wherein X represents carboxy or C₁₋₆ alkoxycarbonyl or a C-linked single or fused ring heterocyclic group as defined in relation to formula (I).
- 30 6. A compound according to any one of claims 1 to 4, wherein R₂ is -O-(CH₂)_n-X wherein n is an integer 2 or 3 and X is a group -NX₁X₂ wherein X₁ is hydrogen and X₂ is a moiety of the above defined formula -CO-T-CO-T₁, substituted aryl-C₁₋₆-alkylcarbonyl or heteroarylcarbonyl.
7. A compound according to any one of claims 1 to 4, wherein Ar is phenyl, R is ethyl, R₁ is hydrogen and R₂ is a moiety -O-(CH₂)_n-X wherein either:
- 35 n is 1, 2 or 3 and X is carboxy, C₁₋₆ alkoxycarbonyl, for example ethoxycarbonyl, or the C-linked single or fused ring heterocyclic group defined in relation to formula (I), for example pyridyl; or
- n is 2 or 3 and X is a group -NX₁X₂ wherein X₁ is hydrogen and X₂ is moiety of the
- 40 above defined formula -CO-T-CO-T₁, for example wherein T is ethylene and T₁ is OH, or X₂ is substituted aryl-C₁₋₆-alkylcarbonyl, for example (2-carboxy)benzylcarbonyl and (2-pyrrolidinomethyl)benzylcarbonyl or heteroarylcarbonyl, for example 2-pyrazinylcarbonyl.

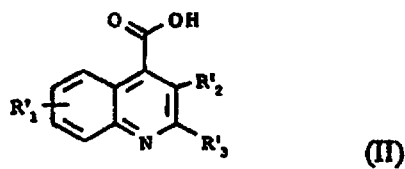


8. A compound according to claim 1, selected from Examples 1-43, or a salt thereof, or a solvate thereof.
- 5 9. A compound according to claim 1, selected from Examples 2, 11, 14, 29, 34, 36, 38, 39 and 40, or a salt thereof, or a solvate thereof.
10. A process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (III):

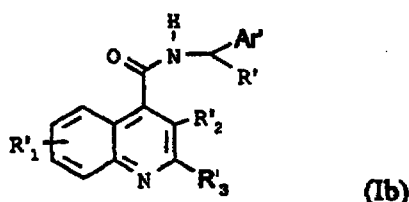
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- wherein R' and Ar' are R and Ar as defined for formula (I) or a group or atom convertible to R and Ar respectively, with a compound of formula (II) or an active derivative thereof:
- 15



- wherein R'1, R'2 and R'3 are R1, R2 and R3 respectively as defined in relation to formula (I) or a group convertible to R1, R2 and R3 to form a compound of formula (Ib):
- 20



wherein Ar', R', R'1, R'2 and R'3 are as defined above, and optionally thereafter carrying out one or more of the following optional steps:

- 25 (i) converting any one of Ar', R', R'1, R'2 and R'3 to Ar, R, R1, R2 or R3 respectively as required, to obtain a compound of formula (I);
- (ii) converting a compound of formula (I) into another compound of formula (I); and
- (iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.
- 30 11. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier.



12. A method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, which method comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof.
13. A compound of formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.
14. A compound of formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of Primary and Secondary Conditions.
15. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.
16. A combined NK-2/NK-3 antagonist.
17. An antagonist according to claim 16, having an NK-2/NK-3 binding affinity ratio in the range of from 0.05 to 20.
18. An antagonist according to claim 16, having an NK-2/NK-3 binding affinity ratio in the range of from 0.1 to 10.
19. An antagonist according to claim 16, having substantially equal binding affinities for the NK-2 and NK-3 receptors.
20. A method for the treatment and/or prophylaxis of respiratory diseases in mammals which method comprises the administration of an effective, non-toxic, pharmaceutically acceptable amount of a combined NK-2/NK-3 antagonist.