Title: A QUINOLINE AMIDE DERIVATIVE AS AGENT AGAINST DISORDERS OF THE CNS

Abstract: A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, is provided (Formula I) as a process for its preparation and methods for its use in therapy, particularly in treating CNS or CNS-mediated disorders.
A QUINOLINE AMIDE DERIVATIVE AS AGENT AGAINST DISORDERS OF THE CNS

Field of the Invention
The present invention relates to a novel quinoline derivative, processes for its preparation, pharmaceutical compositions containing it, and its use in medicine.

Background of the Invention
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 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, 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. Phisiol., 470, 665-679; Couture 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).

WO-A-95/32948, herein incorporated by reference, discloses certain selective, non-peptide NK₃ antagonists of formula (A) or salts or solvates thereof

![Chemical Structure](image)

(A)

in which X, R, Ar, and R₁ to R₅ are as defined therein, which are of potential therapeutic utility in treating various disorders, including pulmonary disorders, skin disorders and itch, neurogenic inflammation and CNS disorders, and convulsive disorders, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders, allergic rhinitis, neurodegenerative disorders, psoriasis, Huntington's disease and depression. *Intera alia*, in formula (A) disclosed in WO-A-95/32948 independently X may represent oxygen; Ar may represent an optionally substituted phenyl group; R may represent a
linear or branched C1-alkyl group; R1 may represent hydrogen; R2 may represent hydrogen; R3 may represent hydrogen; R4 may represent amino; and R5 may represent an optionally substituted aryl group.

5 Surprisingly, it has now been found that a compound generically encompassed by the formula (A) disclosed in WO 95/32948, but having a specific substitution pattern, exhibits advantageous properties over compounds specifically disclosed in WO 95/32948.

Summary of the Invention

10 Accordingly, the present invention provides a compound of formula (I):

or a salt or solvate thereof.

Further aspects of the invention include:

15 - A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carrier(s), diluent(s) and/or excipient(s);

20 - A process for preparing a compound of formula (I) according to the methods disclosed herein;

- A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof for use in therapy;

25 - 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 a patient suffering from certain CNS or CNS-mediated disorders as hereinafter described;

30 - A method of treating a patient suffering from certain CNS or CNS-mediated disorders as hereinafter described comprising administering a therapeutically
effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

Detailed Description of the Invention

The compound of formula (I) has S stereochemistry at the chiral centre, as depicted above. The invention also extends to any tautomeric forms and mixtures thereof.

The compound of the present invention shows advantageous properties. In particular it possesses one or more of the following characteristics as compared to prior art compounds, including those compounds specifically disclosed in WO 95/32948:

(i) it provides a higher *in vivo* brain concentration of pharmacologically active compound after appropriate dosing;

(ii) it provides a higher *in vivo* brain:blood concentration ratio of pharmacologically active compound after appropriate dosing;

(iii) it achieves a higher level of NK3 receptor occupancy at a given dose; this may mean that a lower dose would be needed for effective treatment of e.g. a CNS disorder than a compound with lower receptor occupancy;

(iv) it results in a lower level of adverse peripheral effects at a given dose;

(v) it has improved selectivity for the NK3 receptor;

(vi) it has greater ability to effectively reverse behavioural effects driven by an NK3 agonist *in vivo*;

(vii) it has superior properties in appropriate models predictive of therapeutic efficacy in CNS disorders or CNS-mediated disorders;

(viii) it has an improved duration of action;

(ix) it has other properties which make it a superior candidate for development as a medicament, including physical characteristics which would aid its formulation.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use. The compound of formula (I) or salt or solvate thereof is
preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is also meant, inter alia, of 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 a salt or solvate thereof.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form. A preferred pharmaceutically acceptable form is a crystalline form.

The compound of formula (I) can form acid addition salts thereof. It will be appreciated that for use in therapy the salts of the compound of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, benzoic, ascorbic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. The compound of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms. The compound of formula (I) can be converted into a pharmaceutically acceptable addition salt by reaction with the appropriate organic or mineral acid.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of formula (I), including hydrates, are included within the scope of the invention. Solvates of the compound of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example, hydrates may be formed by crystallization or recrystallization from aqueous solutions, or from aqueous organic solvents, i.e. organic solvents containing water. This invention includes within its scope stoichiometric hydrates or solvates as well as compounds containing variable amounts of water and/or solvent.

Solvates of a compound of formula (I) which are suitable for use in therapy are those wherein the associated solvent is pharmaceutically acceptable.
Salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of the compound of formula (I) and its pharmaceutically acceptable salts and solvates.

The compound of formula (I) has been shown to have NK₃ antagonistic activity and NK₃ selectivity. Such activity and selectivity may be demonstrated by the measurement of NK binding affinity via a scintillation proximity assay (SPA) as described in the experimental section below, or by published methods (as described or referenced in H. M. Sarau et al, J. Pharmacol. Experimental Therapeutics 1997, 281(3), 1303-1311; H. M. Sarau et al, J. Pharmacol. Experimental Therapeutics 2000, 295(1), 373-381; G. A. M. Giardina et al J. Med. Chem. 1999, 42, 1053-1065).

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

The compound of formula (I) and salts and solvates thereof (hereinafter "compounds of the invention") may be useful in the treatment of CNS disorders such as depression (which term includes bipolar (manic) depression (including type I and type II), unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features (e.g. lethargy, over-eating/obesity, hypersomnia) or postpartum onset, seasonal affective disorder and dysthymia, depression-related anxiety, psychotic depression, and depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion); anxiety disorders (including generalised anxiety disorder (GAD), social anxiety disorder (SAD), agitation, tension, social or emotional withdrawal in psychotic patients, panic disorder, and obsessive compulsive disorder); phobias (including agoraphobia and social phobia); psychosis and psychotic disorders (including schizophrenia, schizo-affective disorder, schizophreniform diseases, acute psychosis, alcohol psychosis, autism, delerium, mania (including acute mania), manic depressive psychosis, hallucination, endogenous psychosis, organic psychosyndrome, paranoid and delusional disorders, puerperal psychosis, and psychosis associated with neurodegenerative diseases such as Alzheimer's disease); post-traumatic stress disorder; attention deficit hyperactive disorder (ADHD); cognitive impairment (e.g. the treatment of impairment of cognitive functions including attention, orientation, memory (memory disorders, amnesia, amnesic disorders and age-associated memory impairment) and language function, and including cognitive impairment as a result of stroke,
Alzheimer's disease, Aids-related dementia or other dementia states, as well as other acute or sub-acute conditions that may cause cognitive decline such as delirium or depression (pseudodementia states); convulsive disorders such as epilepsy (which includes simple partial seizures, complex partial seizures, secondary generalised seizures, generalised seizures including absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic clonic seizures and atonic seizures); psychosexual dysfunction (including inhibited sexual desire (low libido), inhibited sexual arousal or excitement, orgasm dysfunction, inhibited female orgasm and inhibited male orgasm, hypoactive sexual desire disorder (HSDD), female sexual desire disorder (FSDD), and sexual dysfunction side-effects induced by treatment with antidepressants of the SSRI-class); sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy); disorders of eating behaviours (including anorexia nervosa and bulimia nervosa); neurodegenerative diseases (such as Alzheimer's disease, ALS, motor neuron disease and other motor disorders such as Parkinson's disease (including relief from locomotor deficits and/or motor disability, including slowly increasing disability in purposeful movement, tremors, bradykinesia, hyperkinesia (moderate and severe), akinesia, rigidity, disturbance of balance and co-ordination, and a disturbance of posture), dementia in Parkinson's disease, dementia in Huntington's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like, and demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis); withdrawal from abuse of drugs including smoking cessation or reduction in level or frequency of such activities (such as abuse of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine and phencyclidine-like compounds, opiates such as cannabis, heroin, morphine, sedative, hypnotic, amphetamine or amphetamine-related drugs such as dextroamphetamine, methylamphetamine or a combination thereof); pain (which includes neuropathic pain (including diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; pain associated with fibromyalgia or cancer; AIDS-related and HIV-related neuropathy; chemotherapy-induced neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; sympathetically maintained pain and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis; reflex sympathetic dystrophy such as shoulder/hand syndrome), acute pain (e.g. musculoskeletal pain, post operative pain and surgical pain), inflammatory pain and chronic pain, pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli.
(thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia), pain associated with migraine, and non-cardiac chest pain); and certain CNS-mediated disorders such as emesis, irritable bowel syndrome, and non-ulcer dyspepsia.

Preferably the compounds of the invention are useful for the treatment of depression; anxiety disorders; phobias; psychosis and psychotic disorders; post-traumatic stress disorder; attention deficit hyperactive disorder (ADHD); withdrawal from abuse of drugs including smoking cessation or reduction in level or frequency of such activities; and irritable bowel syndrome.

More preferably the compounds of the invention are useful for the treatment of depression; anxiety disorders; phobias; and psychosis and psychotic disorders (especially schizophrenia, schizo-affective disorder, and schizophreniform diseases).

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for use in the treatment of depression; anxiety disorders; phobias; psychosis and psychotic disorders; post-traumatic stress disorder; attention deficit hyperactive disorder (ADHD); cognitive impairment; convulsive disorders; psychosexual dysfunction; sleep disorders; disorders of eating behaviours; neurodegenerative diseases; withdrawal from abuse of drugs including smoking cessation or reduction in level or frequency of such activities; pain; emesis; irritable bowel syndrome; and non-ulcer dyspepsia.

In a yet further aspect of the invention, there is provided a method for the treatment of a mammal, including man, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in particular in the treatment of depression; anxiety disorders; phobias; psychosis and psychotic disorders; post-traumatic stress disorder; attention deficit hyperactive disorder (ADHD); cognitive impairment; convulsive disorders; psychosexual dysfunction; sleep disorders; disorders of eating behaviours; neurodegenerative diseases; withdrawal from abuse of drugs including smoking cessation or reduction in level or frequency of such activities; pain; emesis; irritable bowel syndrome; and non-ulcer dyspepsia.

It will be appreciated that references herein to “treatment” extend to prophylaxis, prevention of recurrence and suppression or amelioration of symptoms (whether mild,
moderate or severe) as well as the treatment of established conditions. The compound of
formula (I) may be administered as the raw chemical but the active ingredient is preferably
presented as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical composition
comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate
thereof, in association with one or more pharmaceutically acceptable carrier(s), diluents(s)
and/or excipient(s). The carrier, diluent and/or excipient must be "acceptable" in the sense
of being compatible with the other ingredients of the composition and not deleterious to the
recipient thereof.

There is further provided by the present invention a process of preparing a
pharmaceutical composition, which process comprises mixing a compound of formula (I)
or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically
acceptable carrier, diluent and/or excipient.

Thus a compound of formula (I) or pharmaceutically acceptable salt or solvate thereof
may be formulated for oral, buccal, parenteral, transdermal; topical (including ophthalmic
and nasal), depot or rectal administration or in a form suitable for administration by
inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for
example, tablets, capsules, lozenges, sachets, vials, granules, powders or reconstituted
powders, prepared by conventional means with pharmaceutically acceptable excipients
such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or
hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium
hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants
(e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl
sulphate). The tablets may be coated by methods well known in the art. Liquid
preparations for oral administration may take the form of, for example, solutions,
suspensions, syrups or suspensions or they may be presented as a dry product for
constitution with water or other suitable vehicles before use. Such liquid preparations
may be prepared by conventional means with pharmaceutically acceptable additives such
as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible
fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil,
oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or
propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in a conventional manner.

The compound according to the present invention may be formulated for parenteral administration by injection, e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compound according to the present invention may be formulated for topical administration by insufflation and inhalation. Examples of types of preparation for topical administration include sprays and aerosols for use in an inhaler or insufflator.

Powders for external application may be formed with the aid of any suitable powder base, for example, lactose, talc or starch. Spray compositions may be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as metered dose inhalers, with the use of a suitable propellant.

The compound according to the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compound may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compound according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for
example as an emulsion in an acceptable oil) or ion exchange resins or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinary 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.

The daily dose of the compound of formula (I) or of a pharmaceutically acceptable salt or solvate thereof will depend on several factors such as the seriousness of the disease, the individual response of the patient, the kind of formulation or the route of administration, but it is usually comprised between 0.05 mg and 10 mg per kg of body weight divided into a single dose or into more daily doses, e.g. 2, 3 or 4 times daily. For a 70 kg adult, the total daily dose will normally be in the range of 5 to 500 mg, more preferred 5 to 200 mg.

In the case of a unit dose (which may be administered singly or if desired in multiples to achieve the desired total daily dose), the unit dose may contain from 1 to 500 mg, in particular 2.5, 5, 7.5, 10, 15, 20, 50, 100, 150, or 200, 250, 300, 350, 400, 450 or 500 mg, more preferred being those dosages less than or equal to 200 mg.

The compound of formula (I) and pharmaceutically acceptable salts or solvates thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention.

According to a further aspect of the present invention, there is provided a process (A) for preparing a compound of formula (I) as defined above or a salt or solvate thereof, which process comprises reacting a compound of formula (II) or an activated derivative thereof with a compound of formula (III) (of S-stereochemistry at the chiral centre illustrated (°) or a racemate):

![Chemical Structures]

It is preferred that the compound of formula (II) is present as an activated derivative. A suitable activated derivative is a transient activated form of a compound of formula (II) where the carboxylic acid group has been replaced by e.g. an acyl halide (preferably chloride) or a mixed anhydride.
For example, a compound of formula (II) can be:

(a) converted to an acyl chloride by reaction with oxalyl chloride in an aprotic solvent such as dichloromethane and then coupled to a compound of formula (III) in the presence of an organic base such as disopropylethylamine in an aprotic solvent such as dichloromethane; or

(b) reacted with a compound of formula (III) in the presence of suitable condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)/hydroxybenzotriazole (HOBr) and a base such as N-methylmorphline in a suitable solvent such as tetrahydrofuran.

Where a racemic form of the compound of formula (III) is used, resolution of the resulting stereoisomers (enantiomers) will be required (by standard methods well-known to the person skilled in the art, e.g. chiral HPLC) to prepare the compound of formula (I). Preferably, however, the compound of formula (II) used will be of the appropriate stereochemistry (S-) to prepare the compound of formula (I) directly without the need for an additional resolution step.

Those skilled in the art will appreciate that in the preparation of the compound of formula (I) or a salt or solvate thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. The protecting groups used in the preparation of the compound of formula (I) may be used in a conventional manner. See for example Protective Groups in Organic Chemistry, Ed. J.F.W. McOmie, Plenum Press, London (1973) or Protective Groups in Organic Synthesis, Theodora Green, John Wiley and Sons, New York (1981). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzylxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl, chlorotrityl). Examples of suitable oxygen protecting groups may include for example alky silyl groups, e.g. trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers e.g. tetrahydropyranyl or tert-butyl; or esters e.g. acetate.
Biological Data

No toxicological effects are indicated/expected when a compound of the present invention is administered in the above-mentioned dosage range.

The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed, for example, by measurement of brain penetration and ex vivo NK-3 receptor occupancy, or by measurement of the reversal of NK-3 agonist driven behaviours (e.g. contralateral turning in gerbils as described in Life Sciences 1995, 56, PL27-PL32 and Can. J. Physiol. Pharmacol. 2002, 80, 482-488; or guinea pig wet dog shakes as described in Br. J. Pharmacol. 1997, 122, 715-725) or by mechanistic correlates (e.g. electrophysiology of the dopamine cell firing as described in Gueudet et al., Synapse, 1999, 33, 71-79).

Measurement of NK binding affinity

\(^{125}\)I Substance P, \(^{125}\)I NKA and \(^{125}\)I [MePhe7]-NKB were used in the binding scintillation proximity assay (SPA) of NK1, NK2 and NK3 receptor, respectively. Polystyrene Leadseeker WGA-SPA beads (Amersham Biosciences) were mixed with plasma membrane prepared from CHO cell lines expressing NK-1, NK-2 or NK-3 in a bead/membrane ratio of 20:1 (w/w) in assay buffer (75mM Tris pH 7.8, 75mM NaCl, 4mM MnCl\(_2\), 1mM EDTA, 0.05% Chaps, 1mM PMSF). The mixture was placed on ice for 30 minutes to allow the formation of membrane/bead complex before BSA was added to a final concentration of 1%. After another 30 minutes incubation on ice, the bead/membrane complex was washed twice and suspended in assay buffer. \(^{125}\)I-labelled ligands were then added to the bead/membrane complex. 30 µl of the resulting mixture is then dispensed to each well of Nalgen NUNC 384-well plate with 1 µl compound pre-dispensed in 50% DMSO. The plates were then sealed and pulse spun at 1100 rpm. After 3 hours incubation at room temperature with shaking, the plates were spun for 2 min at 1100 rpm and measured in Viewlux imager (PerkinElmer) for 5 minutes with a 618-nm filter. Inhibition of radioactive ligand binding to its respective receptor was measured by the reduction of signal. IC\(_{50}\) of each compound was determined by an 11-point 3x-dilution inhibition curve. pKi was calculated using Kd of each radioactive ligand determined in a separate experiment.

Measurement of brain and blood drug levels (rat pharmacokinetic study)

Compounds were dosed orally as 1% methylcellulose suspensions. Blood and brain measurements were taken at several timepoints post-dosing. Blood samples and brain
homogenates were extracted by protein precipitation and the extracts analysed by LC-MS-MS against standards prepared in blood or brain homogenate as appropriate.

**Ex-vivo measurement of receptor occupancy in guinea pigs**

Guinea pigs are dosed with drug and sacrificed 1h later. Brains are removed, regions dissected and homogenised. The tissue homogenates are then incubated with $^3$H labelled (−)-(S)-N-(alpha-Ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboxamide (available from Tocris) at 37°C prior to harvesting onto filter mats. Receptor occupancy can be calculated from the amount of label which is retained by the homogenate after corrections for non-specific binding.

The compound of formula (I) has been shown to have the following advantageous properties, by reference to various of the assay/studies described above:

- high NK$_3$ antagonistic activity (pKi greater than 8);
- high NK$_3$ selectivity vs. other NK receptors (NK$_2$ pKi less than 6.5; NK$_1$ pKi less than 4);
- high in vivo brain concentration of physiologically active compound achieved after appropriate dosing (brain concentration of greater than 300 ng/g in a guinea pig ex vivo binding study when dosed at 3mg/kg; and AUC$_{\text{brain}}$ of greater than 800 ng.h/ml in a rat pharmacokinetic study);
- high in vivo brain: blood concentration ratio of physiologically active compound achieved after appropriate dosing (greater than 2.0 in a rat pharmacokinetic study).

**Example**

The following non-limiting example illustrates aspects of the present invention.

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

- g (grams);
- mg (milligrams);
- L (litres);
- ml (millilitres);
- μL (microlitres);
- psi (pounds per square inch);
- M (molar);
- mM (millimolar);
i. v. (intravenous); Hz (Hertz);
MHz (megahertz); mol (moles);
mmol (millimoles); RT (room temperature);
min (minutes); h (hours);
5 mp (melting point); TLC (thin layer chromatography);
T<sub>R</sub> (retention time); RP (reverse phase);
MeOH (methanol); l-PrOH (isopropanol);
TEA (triethylamine); TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride); THF (tetrahydrofuran);
10 DMSO (dimethylsulfoxide); EtOAc (ethyl acetate);
DME (1,2-dimethoxyethane); DCM (dichloromethane);
DCE (dichloroethane); DMF (N,N-dimethylformamide);
DMPU (N,N'-dimethylpropyleneurea);
CDI (1,1-carbonyldiimidazole);
15 IBCF (isobutyl chloroformate); HOAc (acetic acid);
HOSu (N-hydroxysuccinimide); HOBT (1-hydroxybenzotriazole);
mCPBA (meta-chloroperbenzoic acid);
EDC (ethylcarbodiimide hydrochloride);
BOC (tert-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl);
20 DCC (dicyclohexylcarbodiimide); CBZ (benzyloxy carbonyl);
Ac (acetyl); atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl);
TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl);
Me (methyl);
25 HPLC (high pressure liquid chromatography);
Et (ethyl); tBu (tert-butyl).

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees)

Centigrade). All reactions conducted under an inert atmosphere at room temperature unless otherwise noted.

<sup>1</sup>H NMR spectra were recorded on a Bruker B-ACS 60 400MHz, Bruker DPX 400 or a
Bruker DPX 250. Chemical shifts are expressed in parts per million (ppm, δ units).

Coupling constants (J) are in units of hertz (Hz). Splitting patterns describe apparent
multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd
(double doublet), dt (double triplet), m (multiplet), br (broad).
Low-resolution mass spectra (MS) were recorded on a HP1100 series spectrometer; MS and liquid chromatography MS were recorded on a Micromass MS2 Platform LC spectrometer. All mass spectra were taken under electrospray ionisation (ESI), chemical ionisation (CI), electron impact (EI) or by fast atom bombardment (FAB) methods. All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualised with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution. Flash column chromatography was performed on silica gel.

Intermediate 1: 2-Amino-1-(4-fluoro-phenyl)-ethanone hydrochloride
To a solution of 2-bromo-1-(4-fluoro-phenyl)-ethanone (6.51 g, 30 mmol) in chloroform (130 ml) was added hexamethylenetetramine (4.62 g, 33 mmol) in portions over 30 min and the mixture was then stirred at RT for 17 h. The resulting solid was collected by filtration and washed with chloroform. Afterwards, the solid was suspended in a mixture of ethanol/(36%) hydrochloric acid (150 ml/10 ml) and this was heated at reflux for 3.5 h. After cooling to RT the precipitate was removed by filtration and washed with ethanol. The combined filtrates were evaporated to dryness and the residue was co-evaporated with toluene (2 x 50 ml) to give the title compound as a cream solid (6.6 g) contaminated with ammonium hydrochloride; 1H NMR δH (400 MHz, DMSO-d₆), 4.6 (2H, br s), 7.4 (3H, t, J 50.8 Hz), 7.44 (2H, m), 8.12 (2H, m), 8.38 (3H, br s); MS: m/z (MH⁺) = 154/155.

Intermediate 2: 3-Amino-2-(4-fluoro-phenyl)-quinoline-4-carboxylic acid
A mixture of isatin (2.6 g, 17.7 mmol) and potassium hydroxide (5.6 g, 99.8 mmol) in ethanol (60 ml) was sonicated at RT for 15 min and then stirred at 85 °C for a further 15 min. A solution of 2-amino-1-(4-fluoro-phenyl)-ethanone hydrochloride (3.6 g, 70% pure, 12.7 mmol) in ethanol/water/tetrahydrofuran mixture (50 ml/50 ml/10 ml) was added dropwise over 2 h to the mixture at 85 °C. After the addition was complete the stirring at 85 °C was continued for another 5 h. The mixture was then cooled to RT concentrated to a small volume, diluted with water (30 ml), extracted with diethyl ether (6 x 20 ml), and acidified to pH 3.5 with acetic acid. The resulting precipitate was collected, washed with water and dried to give the title compound as a yellowish solid; (0.98 g, 27%); 1H NMR δH (400 MHz, DMSO-d₆), 7.35 (3H, m), 7.50 (1H, q, J 8.4 Hz, 1.5 Hz), 7.73 (2H, m), 7.83 (1H, m), 8.38 (1H, m); MS: m/z (MH⁺) = 283/284.

Example 1: 3-Amino-2-(4-fluoro-phenyl)-quinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide
A mixture of 3-amino-2-(4-fluoro-phenyl)-quinoline-4-carboxylic acid (0.25 g, 0.9 mmol), (S)-1-phenylpropylamine (0.14 g, 1 mmol), HOBT hydrate (0.21 g, 1.37 mmol), 4-methylmorpholine (0.14 g, 1.38 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.26 g 1.37 mmol) in tetrahydrofuran (25 mL) was stirred at RT for 17 h.

The solvent was removed, the residue was dissolved in dichloromethane (100 ml), washed with water (3 x 30 ml), aqueous saturated sodium hydrogen carbonate (1 x 30 ml) and dried (MgSO₄). The solvent was evaporated and the resulting mixture was separated by column chromatography on silica gel (eluting with ethyl acetate-hexane gradient) to give the title compound as a cream solid (0.23 g, 65% yield); ¹H NMR (500 MHz, CDCl₃-δ), 1.03 (3H, t, J 7.8 Hz), 2.0 (2H, m), 5.24 (1H, q, J 7.8), 7.21, (2H, t, J 8.8Hz), 7.32 (1H, m), 7.39 (2H, m), 7.40 (2H, m), 7.43 (1H, m), 7.45 (1H, m), 7.70 (2H, dd, J 8.8Hz, 5.4 Hz), 7.74 (1H, m), 7.89 (1H, m); MS: m/z (MH⁺) = 400. C28H27FN2O requires 399.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims:
Claims

1. A compound of formula (I)

   \[
   \begin{array}{c}
   \text{O} \\
   \text{N} \\
   \text{H} \\
   \text{N} \\
   \text{H} \\
   \text{F}
   \end{array}
   \]  

   (I)

   or a salt or solvate thereof.

2. A pharmaceutical composition comprising a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof according to claim 1 together with one or more pharmaceutically acceptable carrier(s), diluents(s) and/or excipient(s).

3. A process for preparing a compound of formula (I) as claimed in claim 1, comprising reacting a compound of formula (II) or an activated derivative thereof with a compound of formula (III) (of S-stereochemistry at the chiral centre illustrated (*) or a racemate):

   \[
   \begin{array}{c}
   \text{CO}_2\text{H} \\
   \text{NH}_2 \\
   \text{F}
   \end{array}
   \]  

   (II)

   \[
   \begin{array}{c}
   \text{NH}_2
   \end{array}
   \]  

   (III)

   followed, where the compound of formula (III) is a racemate, by resolution using standard methods of the stereoisomers (enantiomers) produced.

4. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof according to claim 1, for use in therapy.

5. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof according to claim 1, in the manufacture of a medicament for the treatment of depression; anxiety disorders; phobias; psychosis and psychotic disorders; post-traumatic stress disorder; attention deficit hyperactive disorder (ADHD); cognitive impairment; convulsive disorders; psychosexual dysfunction; sleep
disorders; disorders of eating behaviours; neurodegenerative diseases; withdrawal from abuse of drugs including smoking cessation or reduction in level or frequency of such activities; pain; emesis; irritable bowel syndrome; and non-ulcer dyspepsia.

6. A method of treating a patient suffering from depression; anxiety disorders; phobias; psychosis and psychotic disorders; post-traumatic stress disorder; attention deficit hyperactive disorder (ADHD); cognitive impairment; convulsive disorders; psychosexual dysfunction; sleep disorders; disorders of eating behaviours; neurodegenerative diseases; withdrawal from abuse of drugs including smoking cessation or reduction in level or frequency of such activities; pain; emesis; irritable bowel syndrome; or non-ulcer dyspepsia comprising administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, according to claim 1.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

* Special categories of cited documents:

*A* document defining the general state of the art which is not considered to be of particular relevance

*E* earlier document but published on or after the international filing date

*L* document which may throw doubts on priority claims or which is cited to establish the publication date of another citation or other special reason (as specified)

*O* document referring to an oral disclosure, use, exhibition or other means

*P* document published prior to the international filing date but later than the priority date claimed

*"* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search: 22 March 2004

Date of mailing of the international search report: 01/04/2004

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV The Hague
Tel: (+31-70) 340-2400, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer: Hanisch, I
Continuation of Box I.1

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
**INTERNATIONAL SEARCH REPORT**

**Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   
   see FURTHER INFORMATION sheet PCT/ISA/210

2. **☐** Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant’s protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
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