ALKYLNITRILE QUINOLINES, AS NK-3 RECEPTOR LIGANDS

Compounds of Formula (I) wherein $R^1$, $A$, $R^2$, $R^3$, $R^4$, $R^5$, $n$, $m$, and $q$ are as described in the specification, pharmaceutically-acceptable salts, methods of making, pharmaceutical compositions containing and methods for using the same.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
ALKYNITRILE QUINOLINES, AS NK-3 RECEPTOR LIGANDS.

FIELD OF THE INVENTION

This invention relates to quinoline derivatives, pharmaceutical compositions comprising them, and the use of such compounds in the treatment of central nervous system and peripheral diseases or disorders. This invention also relates to the use of such compounds in combination with one or more other CNS agents to potentiate the effects of the other CNS agents. The compounds of this invention are also useful as probes for the localization of cell surface receptors.

BACKGROUND OF THE INVENTION

Tachykinin receptors are the targets of a family of structurally related peptides which include substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), collectively "tachykinins." Tachykinins are synthesized in the central nervous system (CNS), and peripheral tissues, where they exert a variety of biological activities. Three tachykinin receptors are known which are named neurokinin-1 (NK-I), neurokinin-2 (NK-2) and neurokinin-3 (NK-3) receptors. NK-I and NK-2 receptors are expressed in a wide variety of peripheral tissues and NK-I receptors are also expressed in the CNS whereas NK-3 receptors are primarily expressed in the CNS.

The neurokinin receptors mediate a variety of tachykinin-stimulated biological effects that include: transmission of excitatory neuronal signals in the CNS and periphery (e.g. pain signals), modulation of smooth muscle contractile activity, modulation of immune and inflammatory responses, induction of hypotensive effects via dilation of the peripheral vasculature, and stimulation of endocrine and exocrine gland secretions.

In the CNS, activation of NK-3 receptors has been shown to modulate dopamine, acetylcholine and serotonin release, suggesting a therapeutic utility for NK-3 ligands for the treatment of a variety of disorders including anxiety, depression, schizophrenia and obesity. Studies in primate brain have shown the presence of NK-3 mRNA in a variety of regions relevant to these disorders. Studies in rats have shown NK-3 receptors to be located on MCH-containing neurons in the lateral hypothalamus and zona incerta, again suggesting a therapeutic utility for NK-3 ligands for obesity.

Non-peptide ligands have been developed for each of the tachykinin receptors, however known non-peptide NK-3 receptor antagonists suffer from a number of problems
such as species selectivity which limits the potential to evaluate these compounds in many appropriate disease models. New non-peptide NK-3 receptor ligands are therefore desirable for use as therapeutic agents and as tools to investigate the biological consequences of NK-3 receptor modulation.

SUMMARY OF THE INVENTION

Disclosed are compounds, particularly quinoline derivatives with affinity for NK-3 receptors (NK-3r). These compounds have potential for the treatment of a broad array of diseases, disorders and conditions including but not limited to depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases including irritable bowel syndrome and inflammatory bowel disorder, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders associated with excessive gonadotrophins and/or androgens including dysmenorrhea, benign prostatic hyperplasia, prostatic cancer, and testicular cancer in which modulation of the activity of NK-3 receptors is beneficial.

Ligands for NK-3 receptors disclosed and stereoisomers, enantiomers, in vivo-hydrolysable precursors and pharmaceutically-acceptable salts thereof are compounds of Formula I,

\[
\begin{align*}
R^1 & \text{ is cyanomethyl;} \\
A & \text{ is phenyl or } C_{3-7}\text{-CyClOallCy}-; \\
R^2 & \text{ at each occurrence is independently selected from } H, \text{-OH, } \text{-NH}_2, \text{-CN, halogen, } \\
& C_{1-6}\text{-alkyl-}, C_{3-7}\text{-cycloalkyl-}, C_{1-6}\text{-alkoxy- and } C_{1-6}\text{-alkoxyC}_{1-6}\text{-alkyl-}; \\
n & \text{ is } 1, 2 \text{ or } 3; \\
R^3 & \text{ at each occurrence is independently selected from } H, \text{-OH, } \text{-NH}_2, \text{-NO}_2, \text{-CN, halogen, } \\
& C_{1-6}\text{-alkyl-}, C^{\text{all}}\text{-alkoxy- and } C^{\text{galkoxyC}}\text{-alkyl-}; \\
m & \text{ is } 1, 2 \text{ or } 3;
\end{align*}
\]
R\(^4\) is selected from H, -OH, -OSO\(_2\)R\(^5\), C\(_{1-6}\)alkyl-, C\(_{1-6}\)alkoxy-, C\(_{1-6}\)alkoxyC\(_{1-6}\)alkyl-, and E-(CH\(_2\))^p-, where E is selected from -NR\(^6\)R\(^7\), -NR\(^6\)SO\(_2\)R\(^7\), -N\(^+$\)O\(^−\))R\(^6\)R\(^7\), aryl and an N- or C-linked 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 nitrogen atoms or an N-oxide thereof, and p is 0, 1, 2, 3, 4 or 5;

R\(^5\) at each occurrence is independently selected from H, -OH, -CN, halogen, -R\(^6\), -OR\(^6\), -NR\(^6\)R\(^7\), -SR\(^6\), -SOR\(^6\) and -SO\(_2\)R\(^6\);

q is 1, 2 or 3;

wherein:

R\(^6\) and R\(^7\) at each occurrence are independently selected from H, a C\(_{1-6}\) straight or branched alkyl group, a C\(_{2-6}\) straight or branched alkenyl or alkynyl group and a C\(_{3-7}\)carbocyclic group having zero, one or two double- or triple-bonds, wherein said groups are either unsubstituted or substituted with one or more moieties selected from -OH, =O, -NH\(_2\), -CN, halogen, aryl and C\(_{1-3}\)alkoxy-;

and,

when R\(^2\), R\(^3\) or R\(^4\) is a C\(_{2-6}\)alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH\(_2\), -CN, phenyl and halogen.

Also disclosed are pharmaceutical compositions and formulations containing the compounds, methods of using them to treat diseases and conditions either alone or in combination with other therapeutically-active compounds or substances, processes and intermediates used to prepare them, uses of them as medicaments, uses of them in the manufacture of medicaments and uses of them for diagnostic and analytic purposes. In particular are disclosed compounds, compositions containing them, and methods using them for treating or preventing conditions and disorders associated with a wide range of diseases or disorders in which NK-3 receptors are considered to have a role.
DETAILED DESCRIPTION OF THE INVENTION

Compounds of the invention are compounds of Formula I.

\[
\begin{align*}
\text{R}^1 & \quad \text{A} \quad \text{(R}^2)_{n} \\
\text{O} & \quad \text{NH} \\
\text{R}^4 & \quad (\text{R}^5)_{q} \\
(\text{R}^3)_{m} & \quad \text{I}
\end{align*}
\]

wherein:

- \text{R}^1 is cyanomethyl;
- \text{A} is phenyl or C\text{\textsubscript{3-7}}cycloalkyl-;
- \text{R}^2 at each occurrence is independently selected from H, -OH, -NH\textsubscript{2}, -CN, halogen, C\text{\textsubscript{1-6}}alkyl-, C\text{\textsubscript{3-7}}cycloalkyl-, C\text{\textsubscript{1-6}}alkoxy- and C\text{\textsubscript{1-6}}alkoxyC\text{\textsubscript{1-6}}alkyl-;
- \text{n} is 1, 2 or 3;
- \text{R}^3 at each occurrence is independently selected from H, -OH, -NH\textsubscript{2}, -NO\textsubscript{2}, -CN, halogen, C\text{\textsubscript{1-6}}alkyl-, C\text{\textsubscript{1-6}}alkoxy- and C\text{\textsubscript{1-6}}alkoxyC\text{\textsubscript{1-6}}alkyl-;
- \text{m} is 1, 2 or 3;
- \text{R}^4 is selected from H\textsubscript{3}-OH, -OSO\textsubscript{2}R\textsubscript{6}, C\text{\textsubscript{i-6}}alkyl-, C\text{\textsubscript{1-6}}alkoxy-, C\text{\textsubscript{1-6}}alkoxyC\text{\textsubscript{i-6}}alkyl-, and E-(CH\textsubscript{2})\text{p}-, where E is selected from -NR\textsubscript{6}R\textsubscript{7}, -NR\textsubscript{6}SO\textsubscript{2}R\textsubscript{7}, -N\textsubscript{4}(OR\textsubscript{6}R\textsubscript{7}, aryl and an N- or C-linked 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 nitrogen atoms or an N-oxide thereof, and p is 0, 1, 2, 3, 4 or 5;
- \text{R}^5 at each occurrence is independently selected from H, -OH, -CN, halogen, -R\textsubscript{6}, -OR\textsubscript{6}, -NR\textsubscript{6}R\textsubscript{7}, -SR\textsubscript{6}, -SOR\textsubscript{6} and -SO\textsubscript{2}R\textsubscript{6};
- \text{q} is 1, 2 or 3;

wherein:

- \text{R}^6 and \text{R}^7 at each occurrence are independently selected from H, a C\text{\textsubscript{1-6}} straight or branched alkyl group, a C\text{\textsubscript{2-6}} straight or branched alkenyl or alkynyl group and a C\text{\textsubscript{3-7}}carbocyclic group having zero, one or two double- or triple-bonds, wherein said groups are either unsubstituted or substituted with one or more moieties selected from -OH, =0, -NH\textsubscript{2}, -CN, halogen, aryl and C\text{\textsubscript{1-6}}alkoxy-; and,
when $R^2$, $R^3$ or $R^4$ is a C$_{2-6}$ alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH$_2$, -CN, phenyl and halogen;

stereoisomers, enantiomers, *in vivo*-hydrolysable precursors and pharmaceutically-
acceptable salts thereof.

Particular compounds are those wherein:
A is phenyl;
$R^2$ is selected from H, halogen and unsubstituted C$_{1-6}$ alkoxy-;
$R^3$ is H or halogen;
n and m are both 1, and

when $R^4$ is a C$_{2-6}$ alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH$_2$, -CN and halogen;

stereoisomers, enantiomers, *in vivo*-hydrolysable precursors and pharmaceutically-
acceptable salts thereof.

Other particular compounds are those wherein:
A is phenyl;
$R^2$ is selected from H, halogen and unsubstituted C$_{1-6}$ alkoxy-;
$R^3$ is H or halogen;
n and m are both 1, and

$R^5$ is H;

stereoisomers, enantiomers, *in vivo*-hydrolysable precursors and pharmaceutically-
acceptable salts thereof.

Still other particular compounds are those wherein:

$A$ is phenyl;
$R^2$ is selected from H, F and -OCH$_3$;
$R^3$ is H or F;

$n$, $m$ and $q$ are each 1;

$R^5$ at each occurrence is independently selected from H, -OH and halogen;

stereoisomers, enantiomers, *in vivo*-hydrolysable precursors and pharmaceutically-
acceptable salts thereof.

Still other particular compounds are enantiomers in accord with Formula H
wherein $R_1$, $A$, $R_2$, $n$, $R_3$, $m$, $R_4$, $R_5$ and $q$ are as defined for Formula I:

stereoisomers, enantiomers, in v/v-o-hydrolysable precursors and pharmaceutically-acceptable salts thereof.

Particular compounds are selected from those described in Table 1, stereoisomers, enantiomers, in v/v-o-hydrolysable precursors and pharmaceutically-acceptable salts thereof.

Compounds of the present invention have the advantage that they may be more soluble, be more easily absorbed and more efficacious in vivo, produce fewer side effects, be less toxic, be more potent, more selective, be longer acting, be less metabolized and/or have a better pharmacokinetic profile than, or have other useful pharmacological or physicochemical properties over known compounds. Using assays for functional activity described herein, compounds of the invention will be found to have IC50's of less than about 1 µM for NK-3 receptors and many compounds will be found to have IC50's of less than about 100 nM for NK-3 receptors.

ABBREVIATIONS AND DEFINITIONS

As used herein, unless otherwise indicated, $C_{1-6}$ alkyl includes $C_1$, $C_2$, $C_3$, $C_4$, $C_5$ and $C_6$-alkyl moieties and is not limited to methyl, ethyl, $\langle$-propyl, n-butyl, $z$-propyl, $t$-butyl, $s$-butyl moieties, whether alone or part of another group and alkyl groups may be straight-chained or branched.

As used herein, unless otherwise indicated, $C_{2-6}$ alkenyl includes but is not limited to 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl and 3-butenyl.

As used herein, unless otherwise indicated, $C_{3-7}$ cycloalkyl groups include but are not limited to the cyclic alkyl moieties cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, unless otherwise indicated, $C_{2-6}$ alkenyl includes but is not limited to 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl and 3-butenyl.
As used herein, unless otherwise indicated, C\textsubscript{2-6} alkynyl includes but is not limited to ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and 3-butynyl.

As used herein, unless otherwise indicated, halo or halogen refers to fluorine, chlorine, bromine, or iodine;

As used herein, aryl includes to phenyl and naphthyl;

As used herein, aromatic or non-aromatic heterocyclic rings include but are not limited to N- or C-linked furyl, imidazolyl, oxazolyl, pyrrolidinyl, thiazolyl, thiophenyl, pyrrolyl, morpholinyl, piperidinyl, pyrazinyl, pyridyl, pyrimidinyl, indanyl, indolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, benzo[b]thiophenyl, benzoazoyl, or benzthiazoyl;

DCM refers to dichloromethane;

EtOAc refers to ethyl acetate;

EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide;

EDTA refers to ethylenediaminetetraacetic acid;

HEPES refers to 4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid, monosodium salt, and

TEA refers to triethylamine.

In processes described herein, where necessary, hydroxy, amino, or other reactive groups may be protected using a protecting group as described in the standard text "Protecting groups in Organic Synthesis", 3\textsuperscript{rd} Edition (1999) by Greene and Wuts.

Unless otherwise stated, reactions are conducted under an inert atmosphere, preferably under a nitrogen atmosphere and are usually conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

The compounds of the invention and intermediates may be isolated from their reaction mixtures by standard techniques.

Acid addition salts of the compounds of Formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts.

Acid addition salts of compounds of Formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol,
tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

Certain compounds of Formula I may exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallization, or chiral HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemization.

SYNTHESIS AND SCHEMES

Compounds of Formula I may be prepared by a general method as follows, reacting an amino alcohol with benzyl chloroformate to afford a carbbenzyloxy alcohol; reacting said carbbenzyloxy alcohol with toluenesulfonyl chloride to afford a toluene sulfonate; reacting said toluene sulfonate with potassium cyanide to afford an N-protected amine nitrile which can be deprotected with hydrogen in the presence of palladium catalyst to afford an amine nitrile which can be reacted with a quinoline-carboxylic acid in the presence of suitable coupling conditions, such as by first reacting the quinoline-carboxylic acid with thionyl chloride to afford the corresponding acid chloride, and then reacting the acid chloride with the amine nitrile to afford a compound of Formula I.

An exemplary process, to form a particular compound of Formula I is shown in Scheme 1:

Scheme 1
Thus as illustrated in Scheme I, reaction of (R)-2-amino-2-phenyl-ethanol with benzyl chloroformate in the presence of triethylamine in methylene chloride will afford \(((R)-(2-hydroxy-l-phenyl-ethyl)-carbamic \text{ acid benzyl ester. This material can be reacted with toluenesulfonyl chloride in the presence of base to afford toluene-4-sulfonic acid (R)-2-benzyloxy carbonylamino-2-phenyl-ethyl ester, which can be reacted with potassium cyanide to afford ((S)-2-cyano-l-phenyl-ethyl)-carbamic \text{ acid benzyl ester, then deprotected with hydrogen in the presence of catalytic palladium in an appropriate solvent such as methanol to afford (S)-3-amino-3-phenyl-propionitrile.}}\)

3-Methyl-2-phenyl-quinoline-4-carboxylic \text{ acid can be reacted with thionyl chloride to afford 3-methyl-2-phenyl-quinoline-4-carbonyl chloride which can be reacted with (S)-3-amino-3-phenyl-propionitrile to afford N-((S)-2-cyano-l-phenylethyl)-3-methyl-2-phenylquinoline-4-carboxamide.}}\)

A further aspect the invention relates to compounds described herein wherein one or more of the atoms is a radioisotope of the same element. In a particular form of this aspect of the invention the compound is labeled with tritium. Such radio-labeled compounds are synthesized either by incorporating radio-labeled starting materials or, in the case of tritium, exchange of hydrogen for tritium by known methods. Known methods include (1) electrophilic halogenation, followed by reduction of the halogen in the presence of a tritium source, for example, by hydrogenation with tritium gas in the presence of a palladium catalyst, or (2) exchange of hydrogen for tritium performed in the presence of tritium gas and a suitable organometallic (e.g. palladium) catalyst.
Compounds of the invention labeled with tritium are useful for the discovery of novel medicinal compounds which bind to and modulate the activity, by agonism, partial agonism, or antagonism, of an NK-3 receptor. Such tritium-labeled compounds may be used in assays that measure the displacement of such compounds to assess the binding of ligands that bind to NK-3 receptors.

In a further aspect the invention relates to compounds described herein additionally comprising one or more atoms of a radioisotope. In a particular form of this aspect of the invention the compound comprises a radioactive halogen. Such radio-labeled compounds are synthesized by incorporating radio-labeled starting materials by known methods. Particular embodiments of this aspect of the invention are those in which the radioisotope is selected from $^{18}$F, $^{123}$I, $^{125}$I, $^{131}$I, $^{75}$Br, $^{76}$Br, $^{77}$Br or $^{82}$Br. A most particular embodiment of this aspect of the invention is that in which the radioisotope is $^{18}$F. Such compounds comprising one or more atoms of a radioisotope are useful as positron emission tomography (PET) ligands and for other uses and techniques to determine the location of NK3 receptors.

Therapeutic uses of compounds:

In another aspect the invention relates to compounds in accord with Formula I described herein and the use of such compounds in therapy and in compositions useful for therapy.

In another aspect the invention encompasses the use of compounds described herein for the therapy of diseases mediated through the action of NK-3 receptors. Such an aspect encompasses methods of treatment or prophylaxis of diseases or conditions in which modulation of the NK-3 receptor is beneficial which methods comprise administering a therapeutically-effective amount of an antagonistic compound of the invention to a subject suffering from said disease or condition.

One embodiment of this aspect of the invention is a method of treatment or prophylaxis of disorders, wherein the disorder is depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases including irritable bowel syndrome and inflammatory bowel disorder, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders associated with excessive gonadotrophins and/or androgens including dysmenorrhea, benign prostatic hyperplasia, prostatic cancer, or testicular cancer comprising administering a pharmacologically effective amount of a compound of Formula I to a patient in need thereof.
A further aspect of the invention is the use of a compound according to the invention, an enantiomer thereof or a pharmaceutically-acceptable salt thereof, in the treatment or prophylaxis of a disease or condition in which modulation of the NK-3 receptor is beneficial. Particular diseases and conditions that may be treated are depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases including irritable bowel syndrome and inflammatory bowel disorder, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders associated with excessive gonadotrophins and/or androgens including dysmenorrhea, benign prostatic hyperplasia, prostatic cancer, and testicular cancer. More particular embodiments encompass uses of a compound in the treatment or prophylaxis of anxiety, depression, schizophrenia and obesity.

A further aspect of the invention is the use of a compound according to the invention, an enantiomer thereof or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of the diseases or conditions mentioned herein. A particular embodiment of this aspect of the invention is the use of a compound of the invention in the manufacture of a medicament for treatment or prophylaxis of depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases including irritable bowel syndrome and inflammatory bowel disorder, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders associated with excessive gonadotrophins and/or androgens including dysmenorrhea, benign prostatic hyperplasia, prostatic cancer, and testicular cancer.

PHARMACEUTICAL COMPOSITIONS

Compounds of the invention, enantiomers thereof, and pharmaceutically-acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration. According to a further aspect of the invention, there is provided a pharmaceutical composition including preferably less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture with an inert pharmaceutically-acceptable diluent, lubricant or carrier.

Examples of diluents, lubricants and carriers are:

- for tablets and dragees: lactose, starch, talc, stearic acid;
- for capsules: tartaric acid or lactose;
- for injectable solutions: water, alcohols, glycerin, vegetable oils;
- for suppositories: natural or hardened oils or waxes.
There is also provided a process for the preparation of such a pharmaceutical composition which process comprises mixing or compounding the ingredients together and forming the mixed ingredients into tablets or suppositories, encapsulating the ingredients in capsules or dissolving the ingredients to form injectable solutions.

Pharmaceutically-acceptable derivatives include solvates and salts. For example, the compounds of the invention may form acid addition salts with acids, such as conventional pharmaceutically-acceptable acids including maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulfonic acids.

Acid addition salts of the compounds of Formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts. Acid addition salts of compounds of Formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

For the uses, methods, medicaments and compositions mentioned herein the amount of compound used and the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of about 0.1 mg to about 20 mg/kg of animal body weight. Such doses may be given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carriers, lubricants and diluents.

Some compounds of the invention may exist in tautomeric, enantiomeric, stereoisomeric or geometric isomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallization, or chiral HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemization.
Exemplary compounds of the invention may be prepared by processes analogous to that described in Scheme 1. Those of skill in the art will readily appreciate that many suitable amines and acid chlorides and carboxylic acids may be used to form compounds within the scope of the subject matter described herein as Formula I.

EXEMPLARY COMPOUNDS

The exemplary compounds and processes describe the invention by way of illustration and example for clarity of understanding. However to those skilled in the art, upon contemplation of the teaching of compounds, processes and methods of this invention, modifications and changes will be apparent that may be made thereto without departing from the spirit or scope of the invention.

Exemplary compounds 1 through 15 and other compounds of the invention may be prepared by processes analogous to those described herein and as shown in Scheme 1, by use of alternative suitable amines in place of (R)-2-amine-2-phenyl-ethanol and carboxylic acids in place of 3-methyl-2-phenyl-quinoline-4-carboxylic acid to form compounds within the scope of the subject matter described herein as formula I.

Example 1: N-((S)-2-cyano-1-phenylethyl)-3-hydroxy-2-phenylquinoline-4-carboxamide

This material was prepared as follows.

(a) ((R)-2-Hydroxy-1-phenyl-ethyl)-carbamic acid benzyl ester.

A solution of (R)-2-amino-2-phenyl-ethanol (3.0 g, 21.8 mmol) and triethyl amine (4.5 mL, 32.8 mmol) was dissolved in methylene chloride (60 mL). To this was added benzyl chloroformate (3.4 mL, 24 mmol) and the solution was stirred at room temperature overnight. The solution was then washed with pH 7 buffer, the organic layer was
concentrated (MgSO₄) and purified by flash silica chromatography using a gradient of 1-5% methanol in methylene chloride to afford the product as a white solid (3.2 g).

(b) Toluene-4-sulfonic acid (R)-2-benzyloxy carbonylamino-2-phenyl-ethyl ester.

A solution of ((R)-2-hydroxy-1-phenyl-ethyl)-carbamic acid benzyl ester (1.0 g, 3.7 mmol) and triethylamine (771 µL, 5.5 mmol) was dissolved in methylene chloride. To this was added tosyl chloride (1.05 g, 5.5 mmol) and mixture was allowed to stir overnight at room temperature. The next day the solution was washed with 10% citric acid, dried (MgSO₄), concentrated, and purified by flash silica chromatography using a gradient of 50% hexanes in methylene chloride to 100% methylene chloride to afford the product (1.3 g) as a white solid.

(c) ((S)-2-Cyano-1-phenyl-ethyl)-carbamic acid benzyl ester.

To a solution of toluene-4-sulfonic acid (R)-2-benzyloxy carbonylamino-2-phenyl-ethyl ester (2.8 g, 6.6 mmol) in DMSO (30 mL) was added potassium cyanide (1.28 g, 20 mmol) and the mixture was stirred at 45 °C for 6 h. The mixture was diluted with water and diethyl ether, extracted, dried (MgSO₄) and purified by flash silica chromatography using a solvent gradient mixture starting with 50% methylene chloride/hexanes and ending with 45% methylene chloride, 45% hexanes, and 10% ethyl acetate to afford the product as a white solid (1.6 g).

(d) (S)-3-Amino-3-phenyl-propionitrile.

A mixture of ((S)-2-cyano-1-phenyl-ethyl)-carbamic acid benzyl ester (770 mg), 10% palladium on carbon (DeGussa type) (100 mg) in methanol (10 mL) was stirred under
hydrogen (1 atmosphere) for 2 h. The catalyst was removed by filtration, and the filtrate concentrated to afford the product as a clear oil (514 mg).

(e) N-((S)-2-Cyano-l-phenylethyl)-3-hydroxy-2-phenylquinoline-4-carboxamide.

To solution of 3-hydroxy-2-phenylquinoline-4-carboxylic acid (272 mg, 1.0 mmol) and triethylamine (286 µL, 2.1 mmol) in ethyl acetate (30 mL) was added thionyl chloride (55 µL, 0.75 mol) and the mixture was stirred for 45 min. To the mixture was added (S)-3-amino-3-phenyl-propionitrile (Ia) (100 mg, 0.68 mmol). The temperature was raised to 40°C, and stirring continued for 3 h, then the mixture was allowed to cool to room temperature, and stirring continued for 12 h. The mixture was concentrated under reduced pressure, redissolved in methylene chloride, washed with pH 7 buffer, dried (MgSO₄) and purified by flash silica chromatography using a gradient of 0.5 to 5% methanol in methylene chloride to afford the product as a yellow powder (58 mg). ¹H NMR (300 MHz, DMSO) δ 9.85 (s, 1H), 9.52 (d, J = 7.6 Hz, 1H), 8.00 - 7.95 (m, 3H), 7.72 (d, J = 8.1 Hz, 1H), 7.59 - 7.34 (m, 10H), 5.56 (q, J = 7.5 Hz, 1H), 3.17 - 3.11 (m, 2H); m/z 394.1. HRMS m/z 394.1506, calcd for C₂₅H₁₉N₃O₂ 394.1555.

Example 2: 3-Amino-N-[(S)-2-cyano-l-phenylethyl]-2-(3-fluorophenyl)quinolin-4-carboxamide (2)

The compound of Example 2 was prepared in accord with the following Scheme:

A solution of 3-amino-2-(3-fluorophenyl)quinoline-4-carboxylic acid (56.4mg, 0.2 mmol), HOBT hydrate (46.3 mg, 0.3 mmol), 4-methylmorpholine (55 µl, 0.3 mmol) in
tetrahydrofuran (11 ml) was added EDC (57.9 mg, 0.3 mmol) at RT under N₂. (>S)-3-amino-3-phenylpropanenitrile (Ia) (29.2 mg, 0.2 mmol) was then added and the reaction mixture stirred at RT for 3.0 h. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and 10% aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over sodium sulfate and then concentrated in vacuo. The residue was purified by chromatography eluting with 15-25% ethyl acetate / hexane to give the title compound (35 mg, 43%) as a solid. ¹H NMR (300MHz, CDCl₃) δ 3.05 (d, 1H), 3.31 (d, 1H), 4.9 (b, 2H), 5.6 (q, 1H), 6.99 (m, 1H), 7.08 (m, 1H), 7.12 (m, 2H), 7.21 (m, 2H), 7.33 (m, 1H), 7.52 (m, 1H), 7.57 (m, 1H), 7.70 (m, 1H), 7.76 (m, 1H), 7.99 (m, 1H), 8.0 (m, 1H), 8.97 (m, 1H). MS APCI, m/z = 411 (M+1). LCMS: 2.12 min.

Example 3. N-r(l S)-2-cyano-1-phenylethyl-3-methyl-2-phenylquinoline-4-carboxamide (3)

![Chemical structure of compound 3]

The compound of Example 3 was prepared in accord with the following Scheme:

This compound was prepared according to the procedure described for N-[(1S)-2-cyano-1-phenylethyl]-3-hydroxy-2-phenylquinoline-4-carboxamide (1) by reacting (S)-3-amino-3-phenyl-propionitrile (Ia) with 3-methyl-2-phenyl-quinoline-4-carboxylic acid (in place of 3-hydroxy-2-phenyl-quinoline-4-carboxylic acid). ¹H NMR (300 MHz, DMSO) δ 9.67 (d, J = 8.6 Hz, IH), 8.05 (d, J = 8.4 Hz, IH), 7.77 (s, IH), 7.58 - 7.37 (m, 14H), 5.61 (s, IH), 3.20 - 3.01 (m, 2H), 2.16 (s, 3H). HRMS m/z 392.1733, calcd for C₂₆H₂₁N₃O₂ 392.1763.
<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>N-((S)-2-cyano-l-phenylethyl)-3-hydroxy-2-phenylquinoline-4-carboxamide</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>3-amino-N-[(S)-2-cyano-1-1-phenylethyl]-2-(3-fluorophenyl)quinolm-4-carboxamide</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>N-((S)-2-cyano-l-phenylethyl)-3-methyl-2-phenylquinoline-4-carboxamide</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>N-((S)-2-cyano-l-phenylethyl)-3-methoxy-2-phenylquinoline-4-carboxamide</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>N-((S)-2-cyano-l-phenylethyl)-2-phenylquinoline-4-carboxamide</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
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<td>-------------------</td>
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</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>N-((S)-2-cyano-1-phenylethyl)-3-(methylsulfonamido)-2-phenylquinoline-4-carboxamide</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Chemical Structure" /></td>
<td>1-(4-((S)-2-cyano-1-phenylethylcarbamoyl)-2-phenylquinolin-3-yl)-N,N-dimethylmethanamine oxide</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8.png" alt="Chemical Structure" /></td>
<td>N-((S)-2-cyano-1-phenylethyl)-3-(methylsulfonamidomethyl)-2-phenylquinoline-4-carboxamide</td>
</tr>
<tr>
<td>10</td>
<td><img src="image10.png" alt="Chemical Structure" /></td>
<td>N-((S)-2-cyano-1-phenylethyl)-3-(cyanomethyl)-2-phenylquinoline-4-carboxamide</td>
</tr>
<tr>
<td>11</td>
<td><img src="image11.png" alt="Chemical Structure" /></td>
<td>3-amino-N-((S)-2-cyano-1-phenylethyl)-2-phenylquinoline-4-carboxamide</td>
</tr>
</tbody>
</table>
BIOLOGICAL TESTS

NK-3 Receptor Binding Activity:

Generally, NK-3r binding activity may be assessed using assays performed as described in Krause et al., (Proc. Natl. Acad. Sci. USA 94: 310-315, 1997). NK-3r complementary DNA is cloned from human hypothalamic RNA using standard procedures. The receptor cDNA is inserted into a suitable expression vector transfected into a Chinese hamster ovary cell line, and a stably-expressing clonal cell line may be isolated, characterized and used for experiments.

Cells may be grown in tissue culture medium by techniques known to those of skill in the art and recovered by low speed centrifugation. Cell pellets may be homogenized, total cellular membranes isolated by high speed centrifugation and suspended in buffered saline. Generally, receptor binding assays may be performed by incubating suitable amounts of purified membrane preparations with 125I-methylPhe7-neurokinin B3 in the presence or absence of test compounds. Membrane proteins may be harvested by rapid filtration and radioactivity may be quantitated in a β-plate scintillation counter. Nonspecific binding may be distinguished from specific binding by use of suitable controls and the affinity of compounds for the expressed receptor may be determined by using different concentrations of compounds.

Preparation of membranes from CHO cells transfected with cloned NK-3 receptors:

A human NK-3 receptor gene was cloned using methods similar to those described for other human NK receptors (Aharony et al, Mol. Pharmacol. 45:9-19, 1994; Caccese et al, Neuropeptides 33, 239-243, 1999). The DNA sequence of the cloned NK-3 receptor differed from the published sequence (Buell et al, FEBS Letts. 299,90-95, 1992; Huang et al, Biochem. Biophys. Res. Commun. 184,966-972, 1992) having a silent single T>C base change at nucleotide 1320 of the coding sequence. Since the change is silent, the cloned gene provides a primary amino acid sequence for the encoded NK-3 receptor protein identical to the published sequence. The receptor cDNA was used to transfect CHO-K1 cells using standard methods and a clone stably-expressing the receptor was isolated and characterized. Plasma membranes from these cells were prepared as published (Aharony et al, 1994).

Cells were harvested and centrifuged to remove medium. The pelleted cells were homogenized (Brinkman Polytron, three 15 sec bursts on ice) in a buffer consisting of 50 mM Tris-HCl (pH 7.4), 120 mM NaCl, 5 mM KCl, 10 mM EDTA and protease inhibitors (0.1 mg/ml soybean trypsin inhibitor, and 1 mM iodoacetamide). The homogenate was
centrifuged at 1000xg for 10 min at 4 °C to remove cell debris. Pellets were washed once with homogenizing buffer. Supernatants were combined and centrifuged at 40,000xg for 20 min at 4 °C. The membrane-containing pellet was homogenized with a Polytron as before. The suspension was centrifuged at 40,000xg for 20 min at 4 °C, the pellet suspended in buffer (20 mM HEPES, pH 7.4 containing 3 mM MgCl₂, 30 mM KCl, and 100 μM thiorphan) and the protein concentration determined. The membrane suspension was then diluted to 3 mg/ml with buffer containing 0.02% BSA, and flash frozen. Samples were stored at -80 °C until used.

**Assay for NK-3 Receptor Binding Activity:**


Competition experiments were carried out in 0.2 mL assay buffer (50 mM Tris-HCl, 4 mM MnCl₂, 10 μM thiorphan, pH 7.4) containing membranes (2 μg protein/reaction), tested competitors, and [¹²⁵I]-MePhe⁷NKB (0.2 nM). Unlabeled homologue ligand (0.5 μM) was used to define nonspecific binding. Incubations were carried out at 25 °C for 90 min. Receptor-bound ligand was isolated by vacuum filtration in a Packard Harvester onto GF/C plates presoaked in 0.5% BSA. Plates were washed with 0.02 M Tris, pH 7.4. Computation of equilibrium binding constants (Kᵰ and Ki), receptor density (Bmax), and statistical analysis was carried out as published previously (Aharony *et al.*, 1995) using GraphPad Prism or IDBS XL/it software.

**NK-3 Functional Activity:**

Generally, NK-3 functional activity may be assessed by using calcium mobilization assays in stable NK-3r-expressing cell lines. Calcium mobilization induced by the methylPhe⁷-neurokinin B agonist may be monitored using a FLIPR (Molecular Devices) instrument in the manner described by the manufacturer. Agonists may be added to the cells and fluorescence responses continuously recorded for up to 5 min. The actions of antagonists may be assessed by preincubating cells prior to administration of the methylPhe⁷-neurokinin B agonist. The action of agonists may be assessed by observing their intrinsic activity in such a system.

**Assay for NK-3 Functional Activity:**

NK-3 receptor expressing CHO cells were maintained in growth media (Ham's F12 medium, 10% FBS, 2mM L-glutamine, and 50 mg/mL Hygromycin B). One day prior to the assay cells were dispensed into 384-well plates in Ultraculture media (Cambrex Bio Science)
with 2 mM L-glutamine to achieve 70-90% confluency. To quantify NK-3 receptor-induced calcium mobilization, cells were first washed with assay buffer consisting of Hanks' Balanced Salt Solution, 15 mM HEPES, and 2.5 mM probenecid, pH 7.4. The cells were then loaded with Fluo4/AM dye (4.4 μM) in assay buffer. Cells were incubated for one hour and then washed with assay buffer, exposed to 0.02 - 300 nM senktide and the fluorescence response recorded using a FLIPR instrument (Molecular Devices Corporation). To quantify antagonism of the agonist response, cells were preincubated with varying concentrations of test compound for 2-20 min and then exposed to 2 nM senktide, a concentration that alone elicits about an 70% maximal calcium response. The resulting data was analyzed using XLfit software (IDBS manufacturer) to determine EC50 and IC50 values.
Claim 1. A compound in accord with Formula I.

wherein:

- $R^1$ is cyanomethyl;
- $A$ is phenyl or $C_{3-7}$cycloalkyl-;
- $R^2$ at each occurrence is independently selected from H, -OH, -NH$_2$, -CN, halogen, $d$-alkyl-, $C_{3-7}$cycloalkyl-, $C_{1-6}$alkoxy- and $C_{1-6}$alkyl-;
- $n$ is 1, 2 or 3;
- $R^3$ at each occurrence is independently selected from H, -OH, -NH$_2$, -NO$_2$, -CN, halogen, $C_{1-6}$alkyl-, $C_{1-6}$alkoxy- and $C^alkoxyd-ealkyl-$;
- $m$ is 1, 2 or 3;
- $R^4$ is selected from H, -OH, -OSO$_2$R$^6$, $C_{i-6}$alkyl-, $C_{1-6}$alkoxy-, $C_{1-6}$alkoxy$C_{1-6}$alkyl-,
  and E-(CH$_2$)$_p$-, where E is selected from -NR$^6$R$^7$, -NR$^6$SO$_2$R$^7$, -N$^+$($O$)R$^6$R$^7$, aryl and an N- or C-linked 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 nitrogen atoms or an N-oxide thereof, and $p$ is 0, 1, 2, 3, 4 or 5;
- $R^5$ at each occurrence is independently selected from H, -OH, -CN, halogen, -R$^6$, -OR$^6$, -NR$^6$R$^7$, -SR$^6$, -SOR$^6$ and -SO$_2$R$^6$;
- $q$ is 1, 2 or 3;

wherein:

- $R^6$ and $R^7$ at each occurrence are independently selected from H, a $C_{1-6}$ straight or branched alkyl group, a $C_{2-6}$ straight or branched alkenyl or alkynyl group and a $C_{3-7}$carbocyclic group having zero, one or two double- or triple-bonds, wherein said groups are either unsubstituted or substituted with one or more moieties selected from -OH, =0, -NH$_2$, -CN, halogen, aryl and $C_{1-3}$alkoxy-;

and,
when \( R^2, R^3 \) or \( R^4 \) is a \( \text{C}_{2-6} \) alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NBb, -CN, phenyl and halogen;

or a stereoisomer, enantiomer, in vvo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 2. A compound according to Claim 1, wherein:

- \( A \) is phenyl;
- \( R^2 \) is selected from \( H \), halogen and unsubstituted \( \text{C}_{1-6} \) alkoxy-;
- \( R^3 \) is \( H \) or halogen;
- \( n \) and \( m \) are both 1, and

when \( R^4 \) is a \( \text{C}_{2-6} \) alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH\(_2\), -CN and halogen;

or a stereoisomer, enantiomer, in vvo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 3. A compound according to Claim 1, wherein:

- \( A \) is phenyl;
- \( R^2 \) is selected from \( H \), halogen and unsubstituted \( \text{C}_{1-6} \) alkoxy-;
- \( R^3 \) is \( H \) or halogen;
- \( n \) and \( m \) are both 1, and
- \( R^5 \) is \( H \);

or a stereoisomer, enantiomer, in vvo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 4. A compound according to Claim 1, wherein:

- \( A \) is phenyl;
- \( R^2 \) is selected from \( H \), \( F \) and -OCH\(_3\);
- \( R^3 \) is \( H \) or \( F \);
n, m and q are each 1;
R^5 at each occurrence is independently selected from H, -OH and halogen;

or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 5. A compound according to Claim 1, selected from:
N-((S)-2-cyano-l-phenylethyl)-3-hydroxy-2-phenylquinoline-4-carboxamide;
3-amino-N-((S)-2-cyano-l-phenylethyl)-2-phenylquinoline-4-carboxamide;
N-((S)-2-cyano-l-phenylethyl)-3-methyl-2-phenylquinoline-4-carboxamide;
N-((S)-2-cyano-l-phenylethyl)-3-methoxy-2-phenylquinoline-4-carboxamide;
N-((S)-2-cyano-l-phenylethyl)-2-phenylquinoline-4-carboxamide;
N-((S)-2-cyano-l-phenylethyl)-3-(methylsulfonamido)-2-phenylquinoline-4-carboxamide;
1-(4-((S)-2-cyano-1-phenylethylcarbamoyl)-2-phenylquinolin-3-yl)-N,N-dimethylmethanamine oxide;
N-((S)-2-cyano-1-phenylethyl)-3-(methylsulfonamidomethyl)-2-phenylquinoline-4-carboxamide, and
N-((S)-2-cyano-1-phenylethyl)-3-(cyanomethyl)-2-phenylquinoline-4-carboxamide;

or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 6. A compound according to Claim 1, in accord with Formula II,

\[
\begin{array}{c}
\text{II} \\
\begin{array}{cc}
\text{R}^1 & \text{A} \\
\text{O} & \text{NH} \\
\text{R}^4 & \text{R}^5 \\
\end{array}
\end{array}
\]

wherein R^1, A, R^2, n, R^3, m, R^4, R^5 and q are as defined for Formula I;

or a stereoisomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.
Claim 7. A process for preparing a compound of Formula I,

\[
\begin{align*}
R^1 & \quad A \quad (R^2)_n \\
\text{O} & \quad \text{NH} \\
\text{R}^4 & \\
(R^5)_q \\
(\text{R}^6)_m
\end{align*}
\]

wherein:

- \( R^1 \) is cyanomethyl;
- \( A \) is phenyl or \( \text{C}_3\text{-7C}_{\text{3-7}}\text{C}_{\text{3-7}}\text{OaIlC}_{\text{3-7}}\text{y} \);
- \( R^2 \) at each occurrence is independently selected from \( \text{H}, \text{-OH}, \text{-NH}_2, \text{-CN}, \text{halogen}, \text{Ci-alkyl}, \text{C}_3\text{cycoalkyl}, \text{C}_1\text{-6alkoxy} \) and \( \text{Q-alkoxyQ} \text{ealkyl} \);
- \( n \) is 1, 2 or 3;
- \( R^3 \) at each occurrence is independently selected from \( \text{H}, \text{-OH}, \text{-NH}_2, \text{-NO}_2, \text{-CN}, \text{halogen}, \text{C}_1\text{-6alkyl}, \text{C}_1\text{-6alkoxy} \) and \( \text{C}_1\text{-6alkoxyC} \text{ealkyl} \);
- \( m \) is 1, 2 or 3;
- \( R^4 \) is selected from \( \text{H}, \text{-OH}, \text{-OSO}_2\text{R}^6, \text{C}_1\text{-6alkyl}, \text{C}_1\text{-6alkoxy}, \text{C}_1\text{-6alkoxyC} \text{ealkyl} \), and \( E-(\text{CH}_2)_V \), where \( E \) is selected from \( \text{-NR}^6\text{R}^7, \text{-NR}^6\text{SO}_2\text{R}^7, \text{-N}^+\text{(OOR}^6\text{R}^7, \text{aryl and an N- or C-linked 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 nitrogen atoms or an N-oxide thereof, and p is 0, 1, 2, 3, 4 or 5;}
- \( R^5 \) at each occurrence is independently selected from \( \text{H}, \text{-OH}, \text{-CN}, \text{halogen}, \text{-R}^6, \text{-OR}^6, \text{-NR}^6\text{R}^7, \text{-SR}^6, \text{-SOR}^6 \) and \( \text{-SO}_2\text{R}^6; \)
- \( q \) is 1, 2 or 3;

wherein:

\( \text{R}^6 \) and \( \text{R}^7 \) at each occurrence are independently selected from \( \text{H}, \text{a C}_1\text{-6 straight or branched alkyl group, a C}_2\text{-6 straight or branched alkenyl or alkynyl group and a C}_3\text{-7carbocyclic group having zero, one or two double- or triple-bonds, wherein said groups are either unsubstituted or substituted with one or more moieties selected from \text{-OH, =0, -NH}_2, \text{-CN, halogen, aryl and C}_1\text{-3alkoxy};} \)

and,
when \( R^2, R^3 \) or \( R^4 \) is a \( C_{2-6} \) alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH\(_2\), -CN, phenyl and halogen; said process comprising:
reacting a amino alcohol with benzyl chloroformate to afford a carbobenzyloxy alcohol;
reacting said carbobenzyloxy alcohol with toluenesulfonyl chloride to afford a toluene sulfonate;
reacting said toluene sulfonate with potassium cyanide to afford an N-protected amine nitrile;
deprotecting said N-protected amine nitrile with hydrogen in the presence of palladium catalyst to afford an amine nitrile;
coupling said amine nitrile with a quinoline-carboxylic acid by first reacting said quinoline-carboxylic acid with thionyl chloride to afford a corresponding acid chloride, and then reacting said acid chloride with said amine nitrile to afford a compound of Formula I.

Claim 8. A method of treatment or prophylaxis of a disease or condition in which modulation of the NK-3 receptor is beneficial which method comprises administering to a subject suffering from said disease or condition a therapeutically-effective amount of a compound in accord with Formula I:

\[
\begin{align*}
&\text{R}^1 \text{ is cyanomethyl}; \\
&\text{A is phenyl or } C^\text{cycloalkyl}; \\
&\text{R}^2 \text{ at each occurrence is independently selected from } H, -\text{OH}, -\text{NH}_2, -\text{CN}, \text{halogen, } C_{1-6}\text{alkyl, } C_{3-7}\text{CyClOaIlCyI, } C_{1-6}\text{alkoxy- and } C_{1-6}\text{alkoxyC}_{1-6}\text{alkyl}; \\
&\text{n is 1, 2 or 3}; \\
\end{align*}
\]

wherein:

\[
R^1 \text{ is cyanomethyl;}
\]

\[
A \text{ is phenyl or } C^\text{cycloalkyl};
\]

\[
R^2 \text{ at each occurrence is independently selected from } H, -\text{OH}, -\text{NH}_2, -\text{CN}, \text{halogen, } C_{1-6}\text{alkyl, } C_{3-7}\text{CyClOaIlCyI, } C_{1-6}\text{alkoxy- and } C_{1-6}\text{alkoxyC}_{1-6}\text{alkyl};
\]

\[
n \text{ is 1, 2 or 3};
\]
R³ at each occurrence is independently selected from H, -OH, -NH₂, -NO₂, -CN, halogen, C₁₋₆alkyl-, C₁₋₆alkoxy- and C₁₋₆alkoxyC₁₋₆alkyl-;

m is 1, 2 or 3;

R⁴ is selected from H, -OH, -OSO₂R⁶, Ci₆alkyl-, Ci₆alkoxy-, C₁₋₆alkoxyC₁₋₆alkyl-, and E-(CH₂)p-, where E is selected from -NR⁶R⁷, -NR⁶SO₂R⁷, -N⁺(O)R⁶R⁷, aryl and an N- or C-linked 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 nitrogen atoms or an N-oxide thereof, and p is 0, 1, 2, 3, 4 or 5;

R⁵ at each occurrence is independently selected from H, -OH, -CN, halogen, -R⁶, -OR⁶, -NR⁶R⁷, -SR⁶, -SOR⁶ and -SO₂R⁶;

q is 1, 2 or 3;

wherein:

R⁶ and R⁷ at each occurrence are independently selected from H, a C₁₋₆ straight or branched alkyl group, a C₂₋₆ straight or branched alkenyl or alkynyl group and a C₃₋₇carbocyclic group having zero, one or two double- or triple-bonds, wherein said groups are either unsubstituted or substituted with one or more moieties selected from -OH, =O, -NH₂, -CN, halogen, aryl and C₁₋₃alkoxy-;

and,

when R², R³ or R⁴ is a C₂₋₆alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -CN, phenyl and halogen;

or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 9. The method of Claim 8, wherein said disease or condition is selected from depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases, irritable bowel syndrome, inflammatory bowel disorder, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders associated with excessive gonadotrophins and/or androgens including dysmenorrhea, benign prostatic hyperplasia, prostatic cancer, and testicular cancer.
Claim 10. A pharmaceutical composition comprising a pharmaceutically-acceptable diluent, lubricant or carrier and a compound in accord with Formula I:

\[ \text{I} \]

wherein:

- \( R^1 \) is cyanomethyl;
- \( A \) is phenyl or C\(_{3-7}\)cycloalkyl-;
- \( R^2 \) at each occurrence is independently selected from H, -OH, -NH\(_2\), -CN, halogen, C\(_{1-6}\)alkyl-, C\(_{3-7}\)cycloalkyl-, C\(_{1-6}\)alkoxy- and C\(_{1-6}\)alkoxyC\(_{1-6}\)alkyl-;
- \( n \) is 1, 2 or 3;
- \( R^3 \) at each occurrence is independently selected from H, -OH, -NH\(_2\), -NO\(_2\), -CN, halogen, C\(_{1-6}\)alkyl-, C\(_{1-6}\)alkoxy- and C\(_{1-6}\)alkoxyC\(_{1-6}\)alkyl-;
- \( m \) is 1, 2 or 3;
- \( R^4 \) is selected from H, -OH, -OSO\(_2\)R\(_6\), C\(_{1-6}\)alkyl-, C\(_{1-6}\)alkoxy-, C\(_{1-6}\)alkoxyC\(_{1-6}\)alkyl-, and E-(CH\(_2\))\(p\), where E is selected from -NR\(_6\)R\(_7\), -NR\(_6\)SO\(_2\)R\(_7\), -N\(4(\text{O'})\)R\(_6\)R\(_7\), aryl and an N-, or C-linked 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 nitrogen atoms or an N-oxide thereof, and \( p \) is 0, 1, 2, 3, 4 or 5;
- \( R^5 \) at each occurrence is independently selected from H, -OH, -CN, halogen, -R\(_6\), -OR\(_6\), -NR\(_6\)R\(_7\), -SR\(_6\), -SOR\(_6\) and -SO\(_2\)R\(_6\);
- \( q \) is 1, 2 or 3;

wherein:

- \( R^6 \) and \( R^7 \) at each occurrence are independently selected from H, a C\(_{1-6}\) straight or branched alkyl group, a C\(_{2-6}\) straight or branched alkenyl or alkynyl group and a C\(_{3-7}\)carbocyclic group having zero, one or two double- or triple-bonds, wherein said groups are either unsubstituted or substituted with one or more moieties selected from -OH, =0, -NH\(_2\), -CN, halogen, aryl and C\(_{1-3}\)alkoxy-; and,
when R², R³ or R⁴ is a C₂₋₆ alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -CN, phenyl and halogen;

or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 11. A method of treatment or prophylaxis of a disease or condition in which modulation of the NK-3 receptor is beneficial which method comprises administering a therapeutically-effective amount of a pharmaceutical composition according to Claim 10 to a subject suffering from said disease or condition.

Claim 12. The method of Claim 11, wherein said disease or condition is selected from depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases, irritable bowel syndrome, inflammatory bowel disorder, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders associated with excessive gonadotrophins and/or androgens including dysmenorrhea, benign prostatic hyperplasia, prostatic cancer, and testicular cancer.

Claim 13. A compound in accord with Formula I:

![Chemical Structure]

wherein:

- R¹ is cyanomethyl;
- A is phenyl or C₃₋₇ cycloalkyl-;
R² at each occurrence is independently selected from H, -OH, -NH₂, -CN, halogen, C₁₋₆ alkyl-, C₃₋₇ cycloalkyl-, C₁₋₆ alkoxy- and C₁₋₆ alkoyC₁₋₆ alkyl-;

n is 1, 2 or 3;

R³ at each occurrence is independently selected from H, -OH, -NH₂, -NO₂, -CN, halogen, C₁₋₆ alkyl-, C₁₋₆ alkoxy- and C₁₋₆ alkoxyC₁₋₆ alkyl-;

m is 1, 2 or 3;

R⁴ is selected from H, -OH, -OSO₂R⁶, C₁₋₆ alkyl-, C₃₋₇ alkoxy-, C₅ alkoxyd-alkyl-, and E-(CH₂)ₚ-, where E is selected from -NR⁶R⁷, -NR⁶SO₂R⁷, -N⁺(O⁻)R⁶R⁷, aryl and an N- or C-linked 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 nitrogen atoms or an N-oxide thereof, and p is o, 1, 2, 3, 4 or 5;

R⁵ at each occurrence is independently selected from H, -OH, -CN, halogen, -R⁵, -OR⁶, -NR⁶R⁷, -SR⁶, -SOR⁶ and -SO₂R⁶;

q is 1, 2 or 3;

wherein:

R⁵ and R⁷ at each occurrence are independently selected from H, a C₁₋₆ straight or branched alkyl group, a C₂₋₆ straight or branched alkenyl or alkynyl group and a C₃₋₇ carbocyclic group having zero, one or two double- or triple-bonds, wherein said groups are either unsubstituted or substituted with one or more moieties selected from -OH, =0, -NH₂, -CN, halogen, aryl and C₁₋₆ alkoxy-;

and,

when R², R³ or R⁴ is a C₂₋₆ alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -CN, phenyl and halogen;

or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof,

for use in the treatment or prophylaxis of a disease or condition in which modulation of the NK-3 receptor is beneficial.

Claim 14. The use according to Claim 13, wherein said disease or condition is selected from depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases, irritable bowel syndrome, inflammatory bowel disorder, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders associated with excessive
gonadotrophins and/or androgens including dysmenorrhea, benign prostatic hyperplasia, prostatic cancer, and testicular cancer.

Claim 15. The use in the manufacture of a medicament for the treatment or prophylaxis of a disease or condition in which modulation of the NK-3 receptor is beneficial of a compound in accord with Formula I:

![Chemical Structure](image)

wherein:

- $R^1$ is cyanomethyl;
- $A$ is phenyl or C$_{3-7}$cycloalkyl;
- $R^2$ at each occurrence is independently selected from H, -OH, -NH$_2$, -CN, halogen, C$_{1-6}$alkyl-, C$_{3-7}$cycloalkyl-, C$_{1-6}$alkoxy- and C$_{1-6}$alkoxyC$_{1-6}$alkyl-;
- $n$ is 1, 2 or 3;
- $R^3$ at each occurrence is independently selected from H, -OH, -NH$_2$, -NO$_2$, -CN, halogen, C$_{1-6}$alkyl-, C$_{1-6}$alkoxy- and Q$^a$alkoxyd-alkyl-;
- $m$ is 1, 2 or 3;
- $R^4$ is selected from H, -OH, -OSO$_2$R$^6$, C$_{1-6}$alkyl-, C$_{1-6}$alkoxy-, C$_{1-6}$alkoxyC$_{1-6}$alkyl- and E-(CH$_2$)$_p$-, where E is selected from -NR$^6$R$^7$, -NR$^6$SO$_2$R$^7$, -N$^+$(OOR$^6$R$^7$, aryl and an N- or C-linked 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 nitrogen atoms or an N-oxide thereof, and $p$ is 0, 1, 2, 3, 4 or 5;
- $R^5$ at each occurrence is independently selected from H, -OH, -CN, halogen, -R$^6$, -OR$^6$, -NR$^6$R$^7$, -SR$^6$, -SOR$^6$ and -SO$_2$R$^6$;
- $q$ is 1, 2 or 3;

wherein:

- $R^6$ and $R^7$ at each occurrence are independently selected from H, a C$_{1-6}$ straight or branched alkyl group, a C$_{2-6}$ straight or branched alkenyl or alkynyl group and a
C₃₋₇ carbocyclic group having zero, one or two double- or triple-bonds, wherein said groups are either unsubstituted or substituted with one or more moieties selected from -OH, =O, -NH₂, -CN, halogen, aryl and C₁₋₃ alkoxy-;

and,

when R², R³ or R⁴ is a C₂₋₆ alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said moieties are unsubstituted or have 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -CN, phenyl and halogen;

or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 16. The use according to Claim 15, wherein said disease or condition is selected from depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases, irritable bowel syndrome, inflammatory bowel disorder, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders associated with excessive gonadotrophins and/or androgens including dysmenorrhea, benign prostatic hyperplasia, prostatic cancer, and testicular cancer.
INTERNATIONAL SEARCH REPORT

International application No. PCT/SE2006/001067

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC: C07D, A61K, A61P

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

SE, DK, FI, NO classes as above

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

EPO-INTERNATIONAL, WPI DATA, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>WO 9719926 A1 (SMITHKLINE BEECHAM S.P.A.), 5 June 1997 (05.06.1997)</td>
<td>1-16</td>
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</table>

D. 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 application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) 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

"T" 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

"&" document member of the same patent family

Date of the actual completion of the international search 28 December 2006

Date of mailing of the international search report 1 January 2007

Name and mailing address of the ISA/Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer Anna S 8lund/Els
Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2005)
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**INTERNATIONAL SEARCH REPORT**

**Bos No. π**  Observations where certain claims were found unsearchable (Continuation of item 2 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. ☒ Claims Nos.: 8 - 9, 11 - 12  
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   Claims 8-9,11-12 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic
   
   ... / ...

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).

**Bos No. III**  Observations where unity of invention is lacking (Continuation of item 3 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**

P-j  The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐  The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐  No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.
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