

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 December 2006 (28.12.2006)

PCT

(10) International Publication Number
WO 2006/137789 A1

(51) International Patent Classification:

C07D 215/52 (2006.01) **A61P 25/22** (2006.01)
A61K 31/47 (2006.01) **A61P 25/24** (2006.01)
A61P 11/06 (2006.01) **A61P 25/28** (2006.01)
A61P 25/00 (2006.01) **A61P 3/04** (2006.01)
A61P 25/18 (2006.01) **A61P 35/00** (2006.01)

15437, Wilmington, DE 19850-5437 (US). **WOODS, James** [US/US]; AstraZeneca Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **LI, Yan** [US/US]; AstraZeneca Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437 (US).

(21) International Application Number:

PCT/SE2006/000758

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Södertälje (SE).

(22) International Filing Date: 21 June 2006 (21.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/693,281 23 June 2005 (23.06.2005) US

(71) Applicant (for all designated States except US): **ASTRAZENECA** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SIMPSON, R. Thomas** [US/US]; AstraZeneca Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **KANG, James** [US/US]; AstraZeneca Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **ALBERT, S., Jeffrey** [US/US]; AstraZeneca Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **ALHAMBRA, Christobal** [US/US]; AstraZeneca Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **KOETHER, M., Gerard** [US/US]; AstraZeneca Wilmington, 1800 Concord Pike, P.O. Box

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

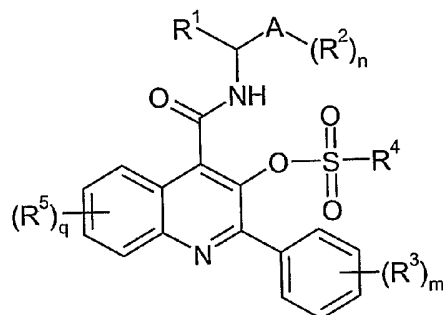
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

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.

(54) Title: Quinoline 3 -sulfonate esters as NK3 receptor modulators



(I)

(57) Abstract: Compounds of Formula I wherein R¹, A, R², R³, R⁴, R⁵, 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.

QUINOLINE 3-SULFONATE ESTERS

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). Tachykinins are synthesized in the central nervous system (CNS), as well as in peripheral tissues, where they exert a variety of biological activities. Three tachykinin receptors are known which are named neurokinin-1 (NK-1), neurokinin-2 (NK-2) and neurokinin-3 (NK-3) receptors. NK-1 and NK-2 receptors are expressed in a wide variety of peripheral tissues and NK-1 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 and 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.

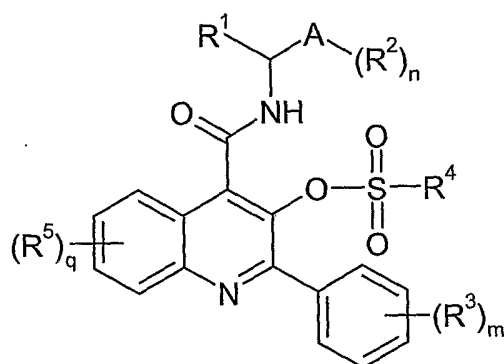
Non-peptide ligands have been developed for each of the tachykinin receptors, however known non-peptide NK-3 receptor antagonists suffer from a number of problems such as species selectivity which limits the potential to evaluate these compounds in many appropriate disease models. New non-peptide NK-3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

for use as therapeutic agents and as tools to investigate the biological consequences of NK-3 receptor modulation.

Description of the Invention

Disclosed are compounds, particularly sulfonate ester derivatives with affinity for neurokinin receptors. 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 conditions, 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 NK3 receptors is beneficial.

Compounds disclosed are ligands for neurokinin receptors, particularly NK-3 receptors (NK3r), and encompasses stereoisomers, enantiomers, in vivo-hydrolysable precursors and pharmaceutically-acceptable salts of compounds of Formula I,



I

wherein:

R^1 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-6}$ cycloalkyl and $-(CH_2)_p-C(O)OC_{1-4}$ alkyl where p is 0, 1, 2 or 3;

A is phenyl or $-C_{3-7}$ cycloalkyl;

R^2 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

n is selected from 1, 2, 3, 4 or 5;

R^3 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-NO_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

m is selected from 1, 2, 3, 4 and 5;

R^4 is selected from $-C_{1-6}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{3-7}$ cycloalkyl and E , where E is selected from $-NR^6R^7$, phenyl, or a 5- or 6-membered aromatic or non-aromatic heterocyclic ring

having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, or E is naphthyl or an 8-, 9- or 10-membered fused aromatic or non-aromatic heterocyclic ring system having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms,

5 R^5 at each occurrence is independently selected from H, -OH, -CN, halogen, $-R^6$, $-OR^6$, $-NR^6R^7$, $-SR^6$, $-SOR^6$ and $-SO_2R^6$;

 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
10 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-;

wherein:

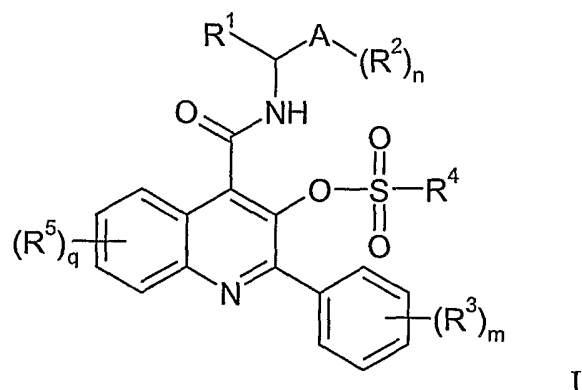
15 when R^1 , R^2 or R^3 is an alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said alkyl, cycloalkyl, alkoxy or alkoxyalkyl is unsubstituted or has 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, $-NH_2$, $-NO_2$, -CN and halogen;

 when R^4 is alkyl or cycloalkyl, said alkyl or cycloalkyl is unsubstituted or has 1, 2 or
20 3 substituents independently selected from -OH, $-NH_2$, $-NO_2$, -CN, phenyl, naphthyl, halogen, a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, -NHR and -NRR, where R at each occurrence is independently selected from C_{1-6} alkyl, and

 when R^4 is E, E is unsubstituted or has 1, 2 or 3 substituents independently selected
from -CN, $-NO_2$, $-CF_3$, -NHR, -NRR, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{2-6}$ alkenyl and $-C_{2-6}$ alkynyl.

25 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
30 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 NK3 receptors are considered to have a role.

Compounds of the invention are compounds of Formula I.



wherein:

R^1 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-6}$ cycloalkyl and $-(CH_2)_p-C(O)OC_{1-4}$ alkyl

5 where p is 0, 1, 2 or 3;

A is phenyl or $-C_{3-7}$ cycloalkyl;

R^2 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

n is selected from 1, 2, 3, 4 or 5;

10 R^3 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-NO_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

m is selected from 1, 2, 3, 4 and 5;

R^4 is selected from $-C_{1-6}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{3-7}$ cycloalkyl and E , where E is selected from $-NR^6R^7$, phenyl, or a 5- or 6-membered aromatic or non-aromatic heterocyclic ring
15 having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, or E is naphthyl or an 8-, 9- or 10-membered fused aromatic or non-aromatic heterocyclic ring system having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms,

R^5 at each occurrence is independently selected from H , $-OH$, $-CN$, halogen, $-R^6$,
20 $-OR^6$, $-NR^6R^7$, $-SR^6$, $-SOR^6$ and $-SO_2R^6$;

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

25 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-;

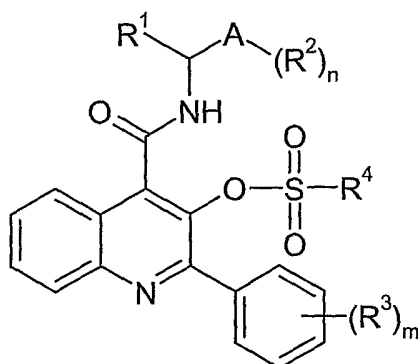
wherein:

when R^1 , R^2 or R^3 is an alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said alkyl, cycloalkyl, alkoxy or alkoxyalkyl is unsubstituted or has 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -NO₂, -CN and halogen;

when R^4 is alkyl or cycloalkyl, said alkyl or cycloalkyl is unsubstituted or has 1, 2 or 3 substituents independently selected from -OH, -NH₂, -NO₂, -CN, phenyl, naphthyl, halogen, a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, -NHR and -NRR, where R at each occurrence is independently selected from C₁₋₆alkyl, and

when R^4 is E, E is unsubstituted or has 1, 2 or 3 substituents independently selected from -CN, -NO₂, -CF₃, -NHR, -NRR, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₂₋₆alkenyl and -C₂₋₆alkynyl, stereoisomers, enantiomers, in vivo-hydrolysable precursors and pharmaceutically-acceptable salts thereof.

Particular compounds are those of Formula Ia



Ia.

wherein R^1 , A, R^2 , n, R^3 , M, and R^4 are as defined for Formula I.

Other particular compounds are those of Formula Ia wherein:

R^1 is selected from -C₁₋₄alkyl, -C₃₋₆cycloalkyl and -C(O)OC₁₋₄alkyl;

R^2 and R^3 at each occurrence are independently selected from halogen and

unsubstituted -C₁₋₆alkoxy;

n and m are both 1;

R^4 is selected from -C₁₋₆alkyl, and

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

More particular compounds are those of Formula Ia wherein:

R^1 is selected from -C₁₋₄alkyl and -C₃₋₆cycloalkyl;

R^2 and R^3 at each occurrence are independently selected from halogen and unsubstituted $-C_{1-6}$ alkoxy;

n and m are both 1, and

R^4 is selected from $-C_{1-6}$ alkyl,

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

Still more particular compounds are those of Formula Ia wherein:

R^1 is selected from ethyl or cyclopropyl;

R^2 and R^3 at each occurrence are independently selected from fluoro and methoxy;

10 n and m are both 1, and

R^4 is selected from methyl or ethyl,

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

Particular compounds are selected from:

15 Methanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Ethanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Trifluoro-methanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

2,2,2-Trifluoro-ethanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

20 Propane-1-sulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

3,3,3-Trifluoro-propane-1-sulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Cyclopropanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Methanesulfonic acid 4-[(cyclopropyl-phenyl-methyl)-carbamoyl]-2-phenyl-quinolin-3-yl

25 ester;

Methanesulfonic acid 4-[1-(3-fluoro-phenyl)-propylcarbamoyl]-2-phenyl-quinolin-3-yl ester;

Methanesulfonic acid 4-{[cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-phenyl-quinolin-3-yl ester;

Methanesulfonic acid 2-(3-fluoro-phenyl)-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

30 Methanesulfonic acid 4-[(cyclopropyl-phenyl-methyl)-carbamoyl]-2-(3-fluoro-phenyl)-quinolin-3-yl ester;

Methanesulfonic acid 2-(3-fluoro-phenyl)-4-[1-(3-fluoro-phenyl)-propylcarbamoyl]-quinolin-3-yl ester;

Methanesulfonic acid 4-{{cyclopropyl-(3-fluoro-phenyl)-methyl}-carbamoyl}-2-(3-fluoro-phenyl)-quinolin-3-yl ester;

Methanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Ethanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

5 Trifluoro-methanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

2,2,2-Trifluoro-ethanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Propane-1-sulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

10 3,3,3-Trifluoro-propane-1-sulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Cyclopropanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Methanesulfonic acid 4-(((S)-cyclopropyl-phenyl-methyl)-carbamoyl]-2-phenyl-quinolin-3-yl ester;

15 Methanesulfonic acid 4-[(S)-1-(3-fluoro-phenyl)-propylcarbamoyl]-2-phenyl-quinolin-3-yl ester;

Methanesulfonic acid 4-{{[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-phenyl-quinolin-3-yl ester;

20 Methanesulfonic acid 2-(3-fluoro-phenyl)-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

Methanesulfonic acid 4-(((S)-cyclopropyl-phenyl-methyl)-carbamoyl]-2-(3-fluoro-phenyl)-quinolin-3-yl ester;

Methanesulfonic acid 2-(3-fluoro-phenyl)-4-[(S)-1-(3-fluoro-phenyl)-propylcarbamoyl]-quinolin-3-yl ester, and

25 Methanesulfonic acid 4-{{[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-(3-fluoro-phenyl)-quinolin-3-yl ester;

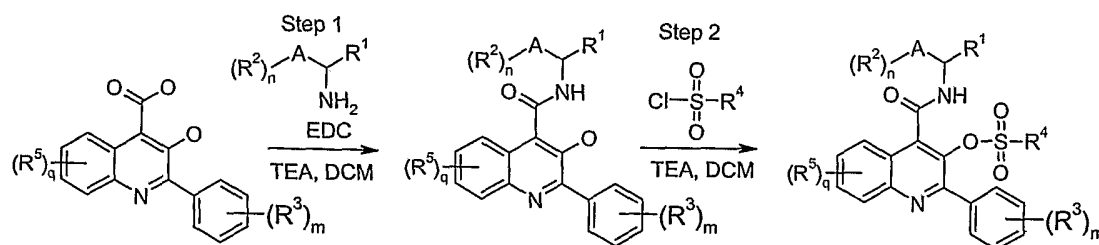
stereoisomers, enantiomers, in vivo-hydrolysable precursors and pharmaceutically-acceptable salts thereof.

30 Compounds of the present invention have the advantage that they may be more potent, more selective, more efficacious in vivo, be less toxic, be longer acting, produce fewer side effects, be more easily absorbed, 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,

many compounds of the invention will be found to have IC₅₀'s of less than 100 nM for NK3 receptors.

Compounds of formula I may be made by the method illustrated in Scheme 1.

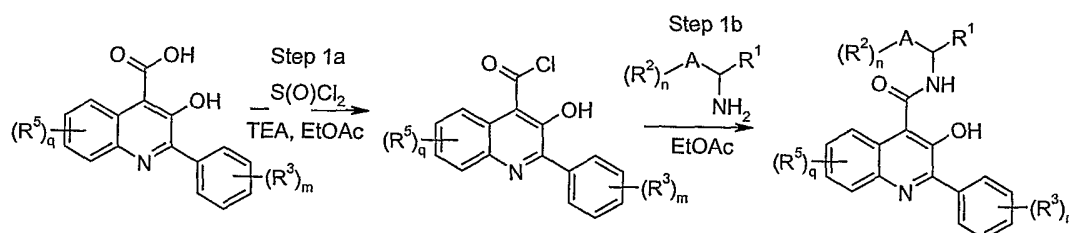
Scheme 1.



Synthesis of an amide product of Step 1 can be accomplished by coupling an appropriately substituted quinoline acid with an appropriately substituted amine by reacting with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) and triethylamine (TEA) in a dichloromethane (CH₂Cl₂ or DCM) solution. The intermediate resulting from Step 1 can then be converted to a sulfonate ester as shown in Step 2 by reacting with an appropriate sulfonyl chloride and TEA in a DCM solution.

Alternatively, synthesis of an amide product of Step 1 can be accomplished as illustrated in Scheme 2. Synthesis of an acid chloride can be accomplished according to Step 1a by reacting an appropriately substituted quinoline acid with S(O)Cl₂ (thionyl chloride) and TEA in (ethyl acetate) (EtOAc). A formed acid chloride can then be reacted with an appropriately substituted amine in EtOAc according to Step 1b to provide an intermediate amide.

Scheme 2.



In 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 NK3 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 NK3 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 .

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 NK3 receptors. Such an aspect encompasses methods of treatment or prophylaxis of diseases or conditions in which modulation of the NK3 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 conditions, 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 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, for the treatment or

prophylaxis of a disease or condition in which modulation of the NK3 receptor is beneficial. Particular diseases and conditions that may be treated are depression, anxiety, schizophrenia, cognitive disorders, psychoses, obesity, inflammatory diseases including irritable bowel conditions, emesis, pre-eclampsia, chronic obstructive pulmonary disease, disorders
5 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 for 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
10 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
15 including irritable bowel conditions, 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
20 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.

25 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.

30 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.

5 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
10 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.

15 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
20 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,
25 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.

30 Exemplary compounds of the invention may be prepared by processes analogous to that described in Schemes 1 or 2. 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.

Abbreviations and Definitions:

As used herein, unless otherwise indicated, C₁₋₆alkyl includes but is not limited to methyl, ethyl, n-propyl, n-butyl, i-propyl, i-butyl, t-butyl, s-butyl moieties, whether alone or part of another group and alkyl groups may be straight-chained or branched.

5 As used herein, unless otherwise indicated, C₁₋₆alkoxy includes but is not limited to -O-methyl, -O-ethyl, -O-n-propyl, -O-n-butyl, -O-i-propyl, -O-i-butyl, -O-t-butyl, -O-s-butyl moieties, whether alone or part of another group and alkoxy groups may be straight-chained or branched.

10 As used herein C₃₋₆cycloalkyl groups include but are not limited to the cyclic alkyl moieties cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, unless otherwise indicated, C₂₋₆alkenyl includes but is not limited to 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl and 3-butenyl.

As used herein, unless otherwise indicated, C₂₋₆alkynyl includes but is not limited to ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl and 3-butylnyl.

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

DCM refers to dichloromethane;

EtOAc refers to ethyl acetate;

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

20 EDTA refers to ethylenediaminetetraacetic acid;

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

TEA refers to triethylamine.

25 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", 3rd 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).

30 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

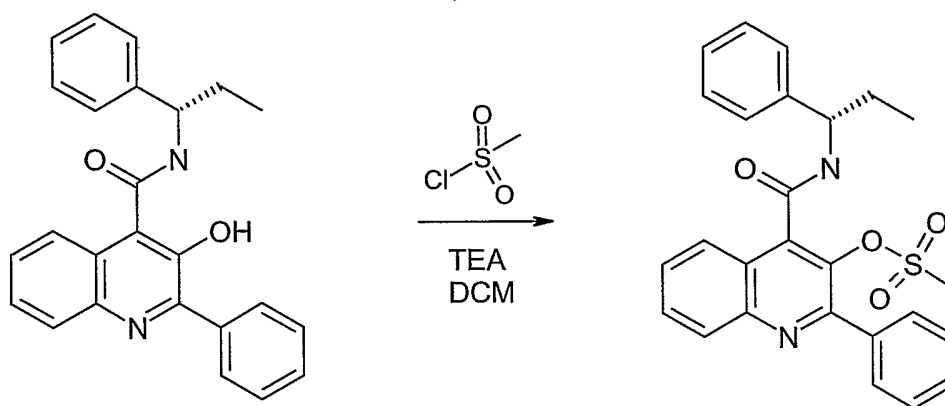
formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts.

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.

Example 1

2-Phenyl-4-([(1S)-1-phenylpropyl]amino}carbonyl)quinolin-3-yl methanesulfonate:

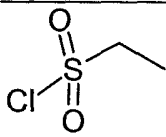
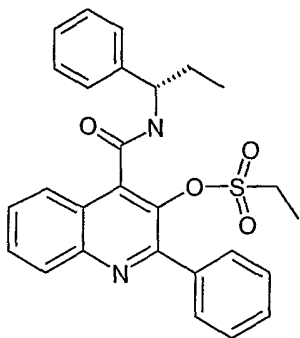


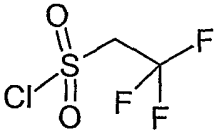
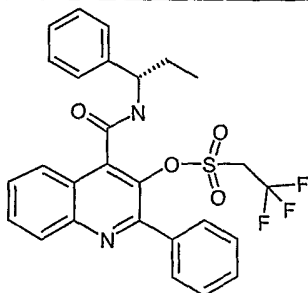
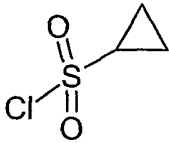
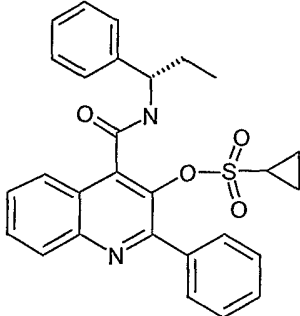
To a solution of the 3-hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]quinoline-4-carboxamide (20 mg, 0.052 mmol) in dichloromethane (0.5 mL) at room temperature under N₂ triethylamine was added (14 μ L, 0.104 mmol). The reaction mixture was cooled to 0 $^{\circ}$ C and methanesulfonyl chloride (5 μ L, 0.062 mmol) was added. The reaction mixture was stirred for 1 h at 0 $^{\circ}$ C, then diluted with dichloromethane and washed with an aqueous solution of citric acid (5%), aqueous saturated NaHCO₃ and brine. The organic layer was dried (Na₂SO₄), filtered and concentrated to provide the title compound (1) as a solid (19 mg, 79% yield). ¹H NMR (300 MHz, CDCl₃) δ 0.98 (t, J = 7.5 Hz, 3H), 1.91 - 2.00 (m, 1H), 2.10

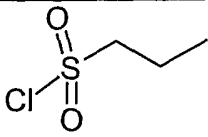
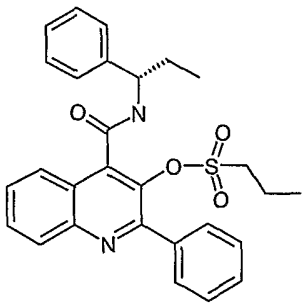
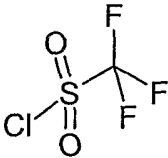
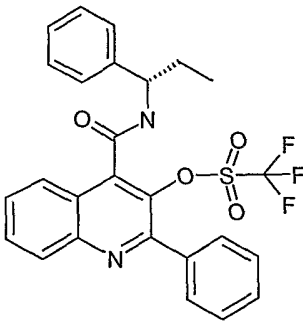
- 2.19 (m, 1H), 2.48 (s, 3H), 5.20 (dt, J = 8.0, 8.0 Hz, 1H), 6.75 (bd, J= 8.0 Hz, 1H), 7.30 - 7.44 (m, 5H), 7.49- 7.59 (m, 4H), 7.76 (dd, J= 8.4, 8.4 Hz, 1H), 7.81 (d, J= 8.4 Hz, 1H), 7.87 (d, J= 7.8 Hz, 2H), 8.16 (d, J= 8.4 Hz, 1H). MS ES+, m/z = 461(M+1).

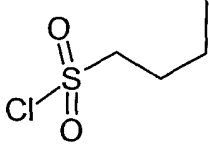
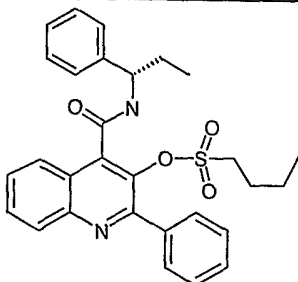
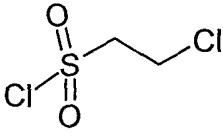
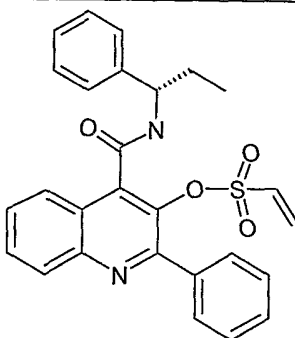
Examples 2-11

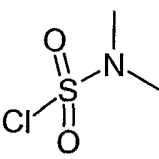
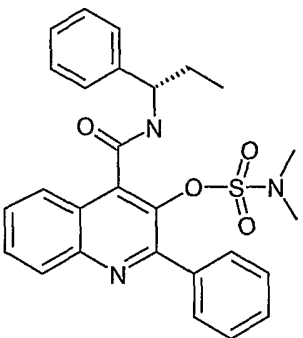
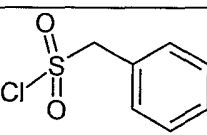
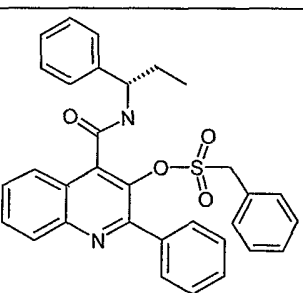
5 Examples 2 through 11 in the following table were prepared using a procedure analogous to that of Example 1 using the indicated sulfonyl chloride such as to provide the desired compound.

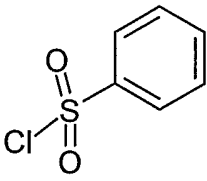
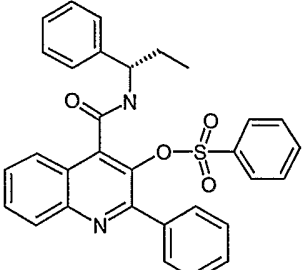
Ex. No.	Sulfonyl chloride	Compound structure	Yield (%)	MS ES+	¹ H NMR (300 MHz, CDCl ₃)
2			90	m/z = 475(M+1)	0.97 (t, J = 7.5 Hz, 3H), 1.16 (t, J = 7.5, 3H) 1.90 - 2.00 (m, 1H), 2.10 - 2.21 (m, 1H), 2.49 - 2.64 (m, 2H), 5.20 (dt, J = 8.0, 8.0 Hz, 1H), 6.78 (bd, J= 7.5 Hz, 1H), 7.32 - 7.44 (m, 5H) 7.48 - 7.58 (m, 4H), 7.72 - 7.85 (m, 4H), 8.16 (d, J= 8.4 Hz, 1H).

Ex. No.	Sulfonyl chloride	Compound structure	Yield (%)	MS ES+	¹ H NMR (300 MHz, CDCl ₃)
3			53	m/z = 529(M+1)	0.97 (t, J = 7.5 Hz, 3H), 1.90 - 2.00 (m, 1H), 2.10 - 2.15 (m, 1H), 3.06-3.17 (m, 1H), 3.48 -3.56 (m, 1H), 5.16 (dt, J = 8.0, 8.0 Hz, 1H), 6.53 (bd, J= 7.4 Hz , 1H), 7.33 - 7.43 (m, 5H) 7.52 - 7.61 (m, 4H), 7.75 - 7.84 (m, 4H), 8.18 (d, J= 8.4 Hz, 1H).
4			69	m/z = 487(M+1)	0.61-0.76 (m, 2H), 0.92 - 1.07 (m, 5H), 1.66 - 2.00 (m, 1H), 2.11 - 2.20 (m, 1H), 5.21 (dt, J = 8.0, 8.0 Hz, 1H), 6.85 (bd, J= 7.2 Hz , 1H), 7.30 - 7.60 (m, 9H) 7.71 - 7.77 (m, 1H), 7.83 (d, J= 8.10, 1H), 7.92 -7.95 (m, 2H) 8.15 (d, J= 8.4 Hz, 1H).

Ex. No.	Sulfonyl chloride	Compound structure	Yield (%)	MS ES+	¹ H NMR (300 MHz, CDCl ₃)
5			71	m/z = 489(M+1)	0.80 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.3 , 3H), 1.6 -1.67 (m, 2H), 1.88 - 1.98 (m, 1H), 2.07 - 2.19 (m, 1H), 2.37 -2.58 (m, 2H), 5.20 (dt, J = 8.0, 8.0 Hz, 1H), 6.84 (bd, J= 7.9 Hz , 1H), 7.31 - 7.44 (m, 5H) 7.48 - 7.56 (m, 4H), 7.71 - 7.85 (m, 4H), 8.13 (d, J= 8.3 Hz, 1H).
6			37	m/z = 515(M+1)	0.96 (t, J = 7.3 Hz, 3H), 1.90 - 2.03 (m, 1H), 2.14 - 2.23 (m, 1H), 5.19 (dt, J = 8.0, 8.0 Hz, 1H), 6.45 (bd, J= 7.5 Hz , 1H), 7.32 - 7.42 (m, 5H) 7.50 - 7.59 (m, 4H), 7.70 - 7.82 (m, 4H), 8.18 (d, J= 8.5 Hz, 1H).

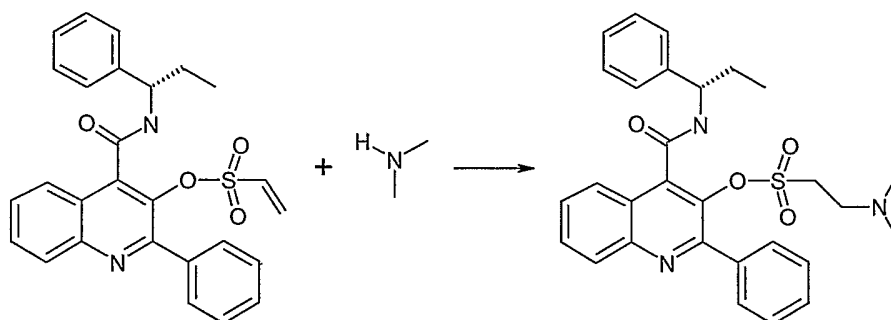
Ex. No.	Sulfonyl chloride	Compound structure	Yield (%)	MS ES+	¹ H NMR (300 MHz, CDCl ₃)
7			95	m/z = 503(M+1)	0.81 (t, J = 7.3 Hz, 3H), 0.97 (t, J = 7.3, 3H), 1.21 - 1.24 (m, 2H), 1.54 - 1.60 (m, 2H) 1.90 - 1.99 (m, 1H), 2.11 - 2.21 (m, 1H), 2.40 - 2.62 (m, 2H), 5.20 (dt, J = 8.0, 8.0 Hz, 1H), 6.82 (bd, J = 7.5 Hz, 1H), 7.29 - 7.34 (m, 1H) 7.37 - 7.44 (m, 4H), 7.48 - 7.58 (m, 4H) 7.72 - 7.86 (m, 4H), 8.15 (d, J = 8.3 Hz, 1H).
8			59	m/z = 473(M+1)	0.99 (t, J = 7.3 Hz, 3H), 1.92 - 2.04 (m, 1H), 2.13 - 2.22 (m, 1H), 5.23 (dt, J = 8.0, 7.7 Hz, 1H), 5.58 - 5.71 (m, 2H), 5.98 (d, J = 15.4 Hz, 1H), 6.82 (bd, J = 7.7 Hz, 1H), 7.3 - 7.35 (m, 1H) 7.37 - 7.60 (m, 8H), 7.73 - 7.78 (m, 1H), 7.82 - 7.84 (m, 3H), 8.14 (d, J = 8.5 Hz, 1H).

Ex. No.	Sulfonyl chloride	Compound structure	Yield (%)	MS ES+	¹ H NMR (300 MHz, CDCl ₃)
9			69	m/z = 490(M+1)	0.98 (t, J = 7.3 Hz, 3H), 1.92 - 2.01 (m, 1H), 2.13 - 2.22 (m, 1H), 2.43 (s, 6H), 5.23 (dt, J = 8.0, 8.0 Hz, 1H), 6.95 (bd, J = 7.5 Hz, 1H), 7.28 - 7.57 (m, 9H), 7.70 - 7.76 (m, 1H), 7.85 - 7.93 (m, 3H), 8.13 (d, J = 8.3 Hz, 1H).
10			69	m/z = 537(M+1)	0.95 (t, J = 7.3 Hz, 3H), 1.87 - 1.96 (m, 1H), 2.04 - 2.11 (m, 1H), 3.56 (d, J = 13.56 Hz, 1H), 3.89 (d, J = 13.5 Hz), 5.20 (dt, J = 8.1, 8.1 Hz, 1H), 6.77 (bd, J = 7.5 Hz, 1H), 7.12 - 7.15 (m, 2H), 7.30 - 7.49 (m, 11H), 7.54 - 7.59 (m, 1H), 7.76 - 7.85 (m, 4H), 8.17 (d, J = 8.5 Hz, 1H).

Ex. No.	Sulfonyl chloride	Compound structure	Yield (%)	MS ES+	¹ H NMR (300 MHz, CDCl ₃)
11			78	m/z = 523(M+1)	1.01 (t, J = 7.3 Hz, 3H), 1.97 - 2.09 (m, 1H), 2.19 - 2.28 (m, 1H), 5.25 (dt, J = 8.1, 8.1 Hz, 1H), 6.97 (bd, J = 7.5 Hz, 1H), 7.18 - 7.23 (m, 4H), 7.30 - 7.36 (m, 4H), 7.39 - 7.49 (m, 5H), 7.55 - 7.60 (m, 3H), 7.70 - 7.76 (m, 1H), 7.89 (d, J = 8.3 Hz, 1H) 8.10 (d, J = 8.3 Hz, 1H).

Example 12

2-phenyl-4-({[(1S)-1-phenylpropyl]amino}carbonyl)quinolin-3-yl 2-(dimethylamino)ethanesulfonate:



5

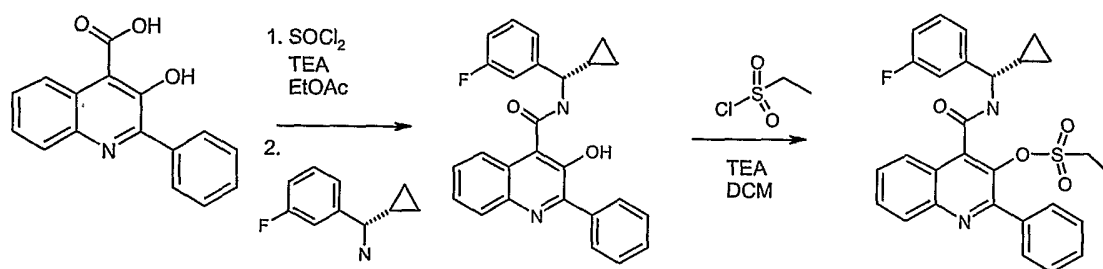
To 2-phenyl-4-({[(1S)-1-phenylpropyl]amino}carbonyl)quinolin-3-yl ethylenesulfonate (example 10) (30 mg, 0.063 mmol) was added dimethylamine (1.0 mmol) in methanol (0.5 mL). The reaction mixture was stirred at room temperature for 4 hr, concentrated, then directly purified via column chromatography (SiO₂) using a gradient of 0-4% MeOH in DCM. The title compound was isolated as a solid (18 mg, 56% yield). ¹H NMR (300 MHz, CDCl₃) δ 0.97 (t, J = 7.3 Hz, 3H), 1.89 - 1.99 (m, 1H), 2.03- 2.19 (m, 1H), 2.08 (s, 6H), 2.58-2.68 (m, 3H), 2.78 - 2.85 (m, 1H), 5.19 (dt, J = 8.0, 8.0 Hz, 1H), 6.79 (bd, J = 7.7

10

Hz, 1H), 7.31 - 7.42 (m, 5H) 7.46 - 7.56 (m, 4H), 7.71 - 7.79 (m, 2H) 7.84 - 7.87 (m, 2H), 8.14 (d, J = 8.3 Hz, 1H). MS ES⁺, m/z = 518 (M+1).

Example 13

4-({[(S)-cyclopropyl(3-fluorophenyl)methyl]amino}carbonyl)-2-phenylquinolin-3-yl ethanesulfonate:



(a) 4-({[(S)-cyclopropyl(3-fluorophenyl)methyl]amino}carbonyl)-2-phenylquinolin-3-yl ethanesulfonate was prepared using a procedure analogous to that for Example 1. The title compound was isolated as a solid (49 mg, 89% yield). ¹H NMR (300 MHz, CDCl₃) δ 0.41 - 0.47 (m, 1H), 0.63 - 0.74 (m, 3H), 1.20 (t, J = 7.3 Hz, 3H), 1.28 - 1.35 (m, 1H) 2.62 (q, J = 7.5 Hz, 2H), 4.71 (dd, J = 8.0, 8.0 Hz, 1H), 6.99 - 7.05 (m, 2H), 7.22 - 7.28 (m, 2H) 7.34 - 7.41 (m, 1H), 7.49 - 7.63 (m, 4H), 7.74 - 7.80 (m, 1H), 7.83 - 7.87 (m, 3H) 8.17 (d, J = 8.3 Hz, 1H). MS ES⁺, m/z = 505 (M+1).

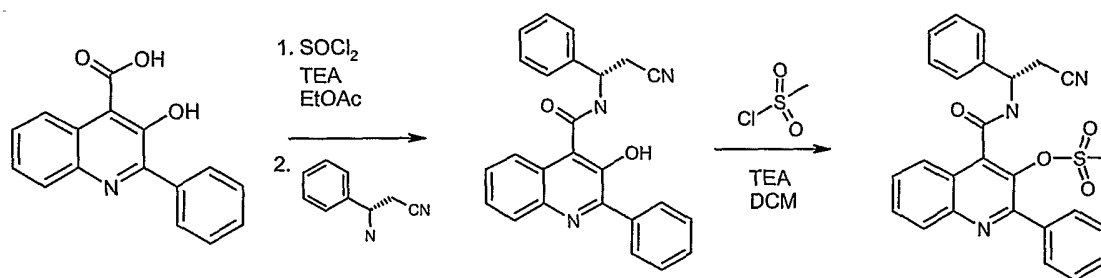
(b) N-[(S)-cyclopropyl(3-fluorophenyl)methyl]-3-hydroxy-2-phenylquinoline-4-carboxamide:

To a suspension of 3-hydroxy-2-phenylcinchoninic acid (300 mg, 1.13 mmol) in EtOAc (4 mL) at room temperature was added TEA (0.63 mL, 4.52 mmol) to give a clear solution. The reaction mixture was cooled to -3 °C under N₂ and the thionyl chloride (0.086 mL, 1.19 mmol) in EtOAc (1 mL) was added dropwise via an addition funnel over a 20 minute period. The reaction mixture was then allowed to warm to room temperature and was stirred an additional hour. The (S)-1-cyclopropyl-1-(3-fluoro-phenyl)-methylamine hydrochloride (250 mg, 1.24 mmol) in EtOAc (3 mL) was then added and the reaction mixture was heated at 70 °C for 3 hr. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with an aqueous solution of citric acid (10%), aqueous saturated NaHCO₃ and brine. The organic layer was dried (Na₂SO₄), filtered and concentrated. The resulting material was purified using column chromatography (SiO₂, gradient of 0-50% EtOAc/Hex) to give the title compound (193 mg, 42% yield). ¹H NMR (300 MHz, CDCl₃) δ 0.53 - 0.66 (m, 2H), 0.75 - 0.80 (m, 2H) 1.28 - 1.37 (m, 1H), 4.72 (dd, J

= 8.0, 8.0 Hz, 1H), 6.92 (d, $J = 7.7$, 1H), 6.99 - 7.05 (m, 1H), 7.18 - 7.24 (m, 2H) 7.33 - 7.40 (m, 2H), 7.46 - 7.51 (m, 3H), 7.57 - 7.62 (m, 2H), 8.06-8.08 (m, 3H) 8.15 - 8.20 (m, 1H). MS ES⁺, $m/z = 413$ (M+1).

Example 14

5 4-({[(1S)-2-cyano-1-phenylethyl]amino}carbonyl)-2-phenylquinolin-3-yl methanesulfonate:

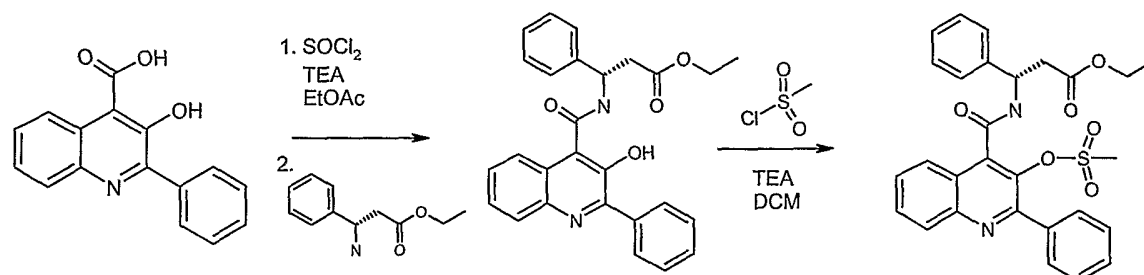


(a) 4-({[(1S)-2-cyano-1-phenylethyl]amino}carbonyl)-2-phenylquinolin-3-yl methanesulfonate was prepared using a procedure analogous to that for Example 1. The title compound was isolated as a solid (41 mg, 79% yield). ¹H NMR (300 MHz, CDCl₃) δ 2.51 (s, 3H), 3.28 (dd, $J = 7.0$ Hz, 5.5 Hz, 2H), 6.7 (dt, $J = 5.6$, 5.6 Hz, 1H) 6.92 (bd, $J = 7.5$ Hz, 1H), 7.37 - 7.58 (m, 8H) 7.61 - 7.66 (m, 1H), 7.76 - 7.87 (m, 3H), 7.94 (d, $J = 7.9$, 1H), 8.18 (d, $J = 8.5$ Hz, 1H). MS ES⁺, $m/z = 472$ (M+1).

(b) N-[(1S)-2-cyano-1-phenylethyl]-3-hydroxy-2-phenylquinolin-4-carboxamide was prepared using a procedure analogous to that of Example 13, step (b). ¹H NMR (300 MHz, CDCl₃) δ 3.09 (dd, $J = 4.7$, 17.0 Hz), 3.3 (dd, $J = 6.4$, 17 Hz, 1H), 5.6 (dt, $J = 6.7$, 6.8 Hz, 1H) 6.97 (bs, 1H), 7.43 - 7.49 (m, 8H), 7.58 - 7.61 (m, 2H), 8.03 - 8.07 (m, 2H), 8.11 - 8.18 (m, 2H). MS ES⁺, $m/z = 394$ (M+1).

Example 15

20 Ethyl (3S)-3-[(3-[(methanesulfonyl)oxy]-2-phenylquinolin-4-yl)carbonyl]amino]-3-phenylpropanoate



(a) Ethyl (3S)-3-[(3-[(methanesulfonyl)oxy]-2-phenylquinolin-4-yl)carbonyl]amino]-3-phenylpropanoate was prepared using a procedure analogous to that for Example 1. The title

compound was isolated as a solid (27 mg, 78% yield). ^1H NMR (300 MHz, CDCl_3) δ 1.15 (t, $J = 7.2$ Hz, 3H), 2.49 (s, 3H), 3.10 - 3.13 (m, 2H), 4.07 (q, $J = 7.2$, 2H), 5.79 (dt, $J = 6.03$, 6.03 Hz, 1H), 7.29 - 7.62 (m, 10H) 7.74 - 7.80 (m, 1H), 7.85 - 7.90 (m, 3H), 8.18 (d, $J = 8.5$ Hz, 1H). MS ES+, $m/z = 519$ (M+1).

- 5 (b) Ethyl (3S)-3-{[(3-hydroxy-2-phenylquinolin-4-yl)carbonyl]amino}-3-phenylpropanoate was prepared using a procedure analogous to that of Example 13, step (b). ^1H NMR (300 MHz, CDCl_3) δ 1.19 (t, $J = 7.2$ Hz, 3H), 3.05 - 3.07 (m, 2H), 4.13 (q, $J = 7.2$, 2H), 5.76 - 5.83 (m, 1H), 7.31 - 7.36 (m, 1H), 7.39 - 7.40 (m, 3H), 7.45 - 7.52 (m, 3H), 7.57 - 7.60 (m, 2H), 7.75 (bd, $J = 8.5$, 1H), 8.05 - 8.08 (m, 2H), 8.13 - 8.17 (m, 2H), 11.37 (bs, 1H). MS ES+, $m/z = 441$ (M+1).

NK3r Binding Activity:

Generally, NK3r binding activity may be assessed using assays performed as described in Krause et al (Proc. Natl. Acad. Sci. USA 94: 310-315, 1997). NK3r complementary DNA is cloned from human hypothalamic RNA using standard procedures.

- 15 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
20 cellular membranes isolated by high speed centrifugation and resuspended in buffered saline. Generally, receptor binding assays may be performed by incubating suitable amounts of purified membrane preparations with ^{125}I -methylPhe⁷-neurokinin B, 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
25 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
30 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.

5 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

10 centrifuged at 1000xg for 10 min at 4 °C to remove cell debris. Pellets were washed 1x 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 and resuspended in buffer (20 mM HEPES, pH 7.4 containing 3 mM MgCl₂, 30 mM KCl, and 100 µM thiorphan) and the
15 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:

A receptor binding assay method with [¹²⁵I]-MePhe⁷-NKB was modified from that
20 described by Aharony et al., J. Pharmacol. Exper. Ther., 274:1216-1221, 1995.

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.

25 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 (K_D and K_i), receptor density (B_{max}), and statistical analysis was carried out as published previously (Aharony et al., 1995) using GraphPad Prism or IDBS XLfit software.

NK-3 Functional Activity:

Generally, NK-3 functional activity may be assessed by using calcium mobilization assays in stable NK3r-expressing cell lines. Calcium mobilization induced by the methylPhe⁷-neurokinin B agonist may be monitored using a FLIPR (Molecular Devices)

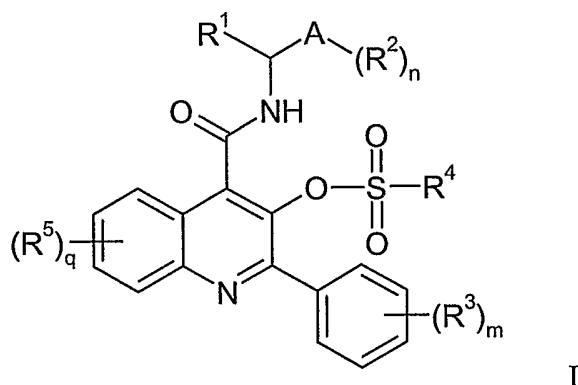
instrument in the manner described by the manufacturer. Agonists may be added to the cells and fluorescence responses continuously recorded for up to 5 min. The actions of antagonists may be assessed by preincubating cells prior to administration of the methylPhe⁷-neurokinin B agonist. The action of 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 μ M) 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.

CLAIMS

Claim 1. A compound in accord with Formula I.



wherein:

R^1 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-6}$ cycloalkyl and $-(CH_2)_p-C(O)OC_{1-4}$ alkyl where p is 0, 1, 2 or 3;

A is phenyl or $-C_{3-7}$ cycloalkyl;

R^2 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

n is selected from 1, 2, 3, 4 or 5;

R^3 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-NO_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

m is selected from 1, 2, 3, 4 and 5;

R^4 is selected from $-C_{1-6}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{3-7}$ cycloalkyl and E , where E is selected from $-NR^6R^7$, phenyl, or a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, or E is naphthyl or an 8-, 9- or 10-membered fused aromatic or non-aromatic heterocyclic ring system having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms,

R^5 at each occurrence is independently selected from H , $-OH$, $-CN$, halogen, $-R^6$, $-OR^6$, $-NR^6R^7$, $-SR^6$, $-SOR^6$ and $-SO_2R^6$;

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, -NH₂, -CN, halogen, aryl and C₁₋₃alkoxy-;

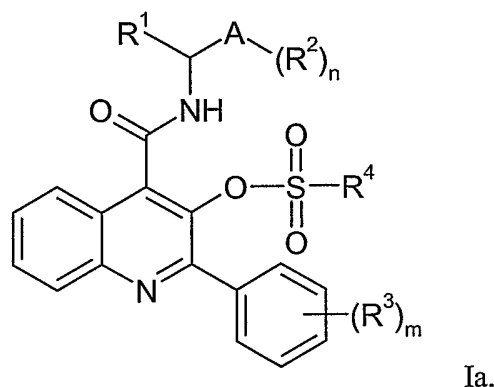
wherein:

when R¹, R² or R³ is an alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said alkyl, cycloalkyl, alkoxy or alkoxyalkyl is unsubstituted or has 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -NO₂, -CN and halogen;

when R⁴ is alkyl or cycloalkyl, said alkyl or cycloalkyl is unsubstituted or has 1, 2 or 3 substituents independently selected from -OH, -NH₂, -NO₂, -CN, phenyl, naphthyl, halogen, a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, -NHR and -NRR, where R at each occurrence is independently selected from C₁₋₆alkyl, and

when R⁴ is E, E is unsubstituted or has 1, 2 or 3 substituents independently selected from -CN, -NO₂, -CF₃, -NHR, -NRR, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₂₋₆alkenyl and -C₂₋₆alkynyl, or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 2. A compound according to Claim 1, in accord with Formula Ia



wherein R¹, A, R², n, R³, M, and R⁴ are as defined for Formula I.

Claim 3. A compound according to Claim 2, wherein:

R¹ is selected from -C₁₋₄alkyl, -C₃₋₆cycloalkyl and -C(O)OC₁₋₄alkyl;

R² and R³ at each occurrence are independently selected from halogen and unsubstituted -C₁₋₆alkoxy;

n and m are both 1;

R^4 is selected from $-C_{1-6}$ alkyl, and
or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 4. A compound according to Claim 2, wherein:

R^1 is selected from $-C_{1-4}$ alkyl and $-C_{3-6}$ cycloalkyl;
 R^2 and R^3 at each occurrence are independently selected from halogen and unsubstituted $-C_{1-6}$ alkoxy;
 n and m are both 1;
 R^4 is selected from $-C_{1-6}$ alkyl,
or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 5. A compound according to Claim 2, wherein:

R^1 is selected from ethyl or cyclopropyl;
 R^2 and R^3 at each occurrence are independently selected from fluoro and methoxy;
 n and m are both 1;
 R^4 is selected from methyl or ethyl,
or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof.

Claim 6. A compound according to Claim 1, selected from:

Methanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Ethanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Trifluoro-methanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
2,2,2-Trifluoro-ethanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Propane-1-sulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
3,3,3-Trifluoro-propane-1-sulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;

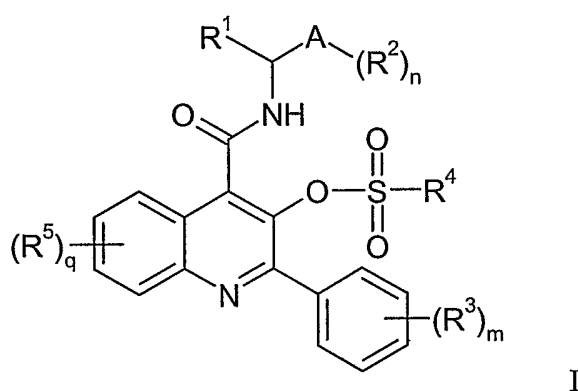
Cyclopropanesulfonic acid 2-phenyl-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Methanesulfonic acid 4-[(cyclopropyl-phenyl-methyl)-carbamoyl]-2-phenyl-quinolin-3-yl ester;
Methanesulfonic acid 4-[1-(3-fluoro-phenyl)-propylcarbamoyl]-2-phenyl-quinolin-3-yl ester;
Methanesulfonic acid 4-{[cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-phenyl-quinolin-3-yl ester;
Methanesulfonic acid 2-(3-fluoro-phenyl)-4-(1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Methanesulfonic acid 4-[(cyclopropyl-phenyl-methyl)-carbamoyl]-2-(3-fluoro-phenyl)-quinolin-3-yl ester;
Methanesulfonic acid 2-(3-fluoro-phenyl)-4-[1-(3-fluoro-phenyl)-propylcarbamoyl]-quinolin-3-yl ester;
Methanesulfonic acid 4-{[cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-(3-fluoro-phenyl)-quinolin-3-yl ester;
Methanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Ethanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Trifluoro-methanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
2,2,2-Trifluoro-ethanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Propane-1-sulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
3,3,3-Trifluoro-propane-1-sulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Cyclopropanesulfonic acid 2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Methanesulfonic acid 4-[[((S)-cyclopropyl-phenyl-methyl)-carbamoyl]-2-phenyl-quinolin-3-yl ester;
Methanesulfonic acid 4-[(S)-1-(3-fluoro-phenyl)-propylcarbamoyl]-2-phenyl-quinolin-3-yl ester;
Methanesulfonic acid 4-{[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-phenyl-quinolin-3-yl ester;
Methanesulfonic acid 2-(3-fluoro-phenyl)-4-((S)-1-phenyl-propylcarbamoyl)-quinolin-3-yl ester;
Methanesulfonic acid 4-[[((S)-cyclopropyl-phenyl-methyl)-carbamoyl]-2-(3-fluoro-phenyl)-quinolin-3-yl ester;

Methanesulfonic acid 2-(3-fluoro-phenyl)-4-[(S)-1-(3-fluoro-phenyl)-propylcarbamoyl]-quinolin-3-yl ester, and

Methanesulfonic acid 4-{[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-(3-fluoro-phenyl)-quinolin-3-yl ester;

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

Claim 7. A process for preparing a compound of Formula I,



wherein:

R^1 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-6}$ cycloalkyl and $-(CH_2)_p-C(O)OC_{1-4}$ alkyl where p is 0, 1, 2 or 3;

A is phenyl or $-C_{3-7}$ cycloalkyl;

R^2 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

n is selected from 1, 2, 3, 4 or 5;

R^3 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-NO_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

m is selected from 1, 2, 3, 4 and 5;

R^4 is selected from $-C_{1-6}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{3-7}$ cycloalkyl and E, where E is selected from $-NR^6R^7$, phenyl, or a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, or E is naphthyl or an 8-, 9- or 10-membered fused aromatic or non-aromatic heterocyclic ring system having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms,

R^5 at each occurrence is independently selected from H, -OH, -CN, halogen, $-R^6$, $-OR^6$, $-NR^6R^7$, $-SR^6$, $-SOR^6$ and $-SO_2R^6$;

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-;

wherein:

when R^1 , R^2 or R^3 is an alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said alkyl, cycloalkyl, alkoxy or alkoxyalkyl is unsubstituted or has 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, $-NH_2$, $-NO_2$, -CN and halogen;

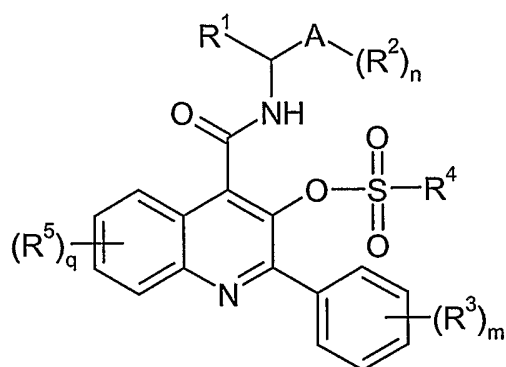
when R^4 is alkyl or cycloalkyl, said alkyl or cycloalkyl is unsubstituted or has 1, 2 or 3 substituents independently selected from -OH, $-NH_2$, $-NO_2$, -CN, phenyl, naphthyl, halogen, a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, -NHR and -NRR, where R at each occurrence is independently selected from C_{1-6} alkyl, and

when R^4 is E, E is unsubstituted or has 1, 2 or 3 substituents independently selected from -CN, $-NO_2$, $-CF_3$, -NHR, -NRR, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{2-6}$ alkenyl and $-C_{2-6}$ alkynyl, said process comprising:

coupling a substituted quinoline acid with a substituted amine by reacting with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide and triethylamine in a CH_2Cl_2 solution to form an amide;

converting said amide to a sulfonate ester by reacting with a sulfonyl chloride and TEA in a DCM solution to form said compound of Formula I.

Claim 8. A method of treatment or prophylaxis of a disease or condition in which modulation of the NK3 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:



I

wherein:

R^1 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-6}$ cycloalkyl and $-(CH_2)_p-C(O)OC_{1-4}$ alkyl where p is 0, 1, 2 or 3;

A is phenyl or $-C_{3-7}$ cycloalkyl;

R^2 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

n is selected from 1, 2, 3, 4 or 5;

R^3 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-NO_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

m is selected from 1, 2, 3, 4 and 5;

R^4 is selected from $-C_{1-6}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{3-7}$ cycloalkyl and E , where E is selected from $-NR^6R^7$, phenyl, or a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, or E is naphthyl or an 8-, 9- or 10-membered fused aromatic or non-aromatic heterocyclic ring system having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms,

R^5 at each occurrence is independently selected from H , $-OH$, $-CN$, halogen, $-R^6$, $-OR^6$, $-NR^6R^7$, $-SR^6$, $-SOR^6$ and $-SO_2R^6$;

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-;

wherein:

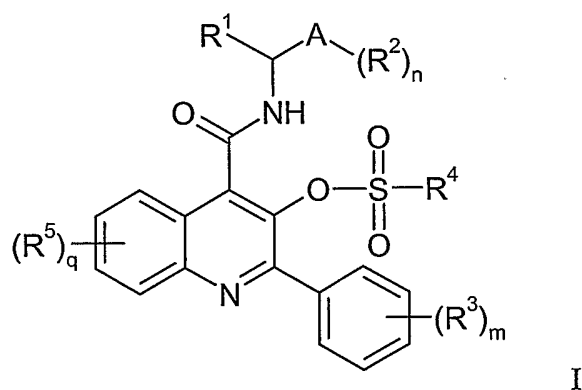
when R^1 , R^2 or R^3 is an alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said alkyl, cycloalkyl, alkoxy or alkoxyalkyl is unsubstituted or has 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -NO₂, -CN and halogen;

when R^4 is alkyl or cycloalkyl, said alkyl or cycloalkyl is unsubstituted or has 1, 2 or 3 substituents independently selected from -OH, -NH₂, -NO₂, -CN, phenyl, naphthyl, halogen, a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, -NHR and -NRR, where R at each occurrence is independently selected from C₁₋₆alkyl, and

when R^4 is E, E is unsubstituted or has 1, 2 or 3 substituents independently selected from -CN, -NO₂, -CF₃, -NHR, -NRR, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₂₋₆alkenyl and -C₂₋₆alkynyl, 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 including irritable bowel conditions, 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:



wherein:

R^1 is selected from hydrogen, -C₁₋₄alkyl, -C₃₋₆cycloalkyl and -(CH₂)_p-C(O)OC₁₋₄alkyl where p is 0, 1, 2 or 3;

A is phenyl or -C₃₋₇cycloalkyl;

R² at each occurrence is independently selected from hydrogen, -OH, -NH₂, -CN, halogen, -C₁₋₆alkyl, -C₃₋₇cycloalkyl, -C₁₋₆alkoxy and -C₁₋₆alkoxyC₁₋₆alkyl;

n is selected from 1, 2, 3, 4 or 5;

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

m is selected from 1, 2, 3, 4 and 5;

R⁴ is selected from -C₁₋₆alkyl, -C₂₋₄alkenyl, -C₃₋₇cycloalkyl and E, where E is selected from -NR⁶R⁷, phenyl, or a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, or E is naphthyl or an 8-, 9- or 10-membered fused aromatic or non-aromatic heterocyclic ring system having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms,

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-;

wherein:

when R¹, R² or R³ is an alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said alkyl, cycloalkyl, alkoxy or alkoxyalkyl is unsubstituted or has 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -NO₂, -CN and halogen;

when R⁴ is alkyl or cycloalkyl, said alkyl or cycloalkyl is unsubstituted or has 1, 2 or 3 substituents independently selected from -OH, -NH₂, -NO₂, -CN, phenyl, naphthyl, halogen, a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, -NHR and -NRR, where R at each occurrence is independently selected from C₁₋₆alkyl, and

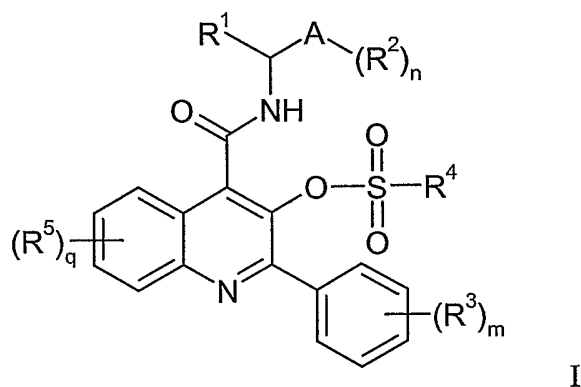
when R⁴ is E, E is unsubstituted or has 1, 2 or 3 substituents independently selected from -CN, -NO₂, -CF₃, -NHR, -NRR, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₂₋₆alkenyl and -C₂₋₆alkynyl,

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 NK3 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 including irritable bowel conditions, 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. The use of a compound in accord with Formula I:



wherein:

R^1 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-6}$ cycloalkyl and $-(CH_2)_p-C(O)OC_{1-4}$ alkyl where p is 0, 1, 2 or 3;

A is phenyl or $-C_{3-7}$ cycloalkyl;

R^2 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

n is selected from 1, 2, 3, 4 or 5;

R^3 at each occurrence is independently selected from hydrogen, -OH, -NH₂, -NO₂, -CN, halogen, -C₁₋₆alkyl, -C₁₋₆alkoxy and -C₁₋₆alkoxyC₁₋₆alkyl;

m is selected from 1, 2, 3, 4 and 5;

R^4 is selected from -C₁₋₆alkyl, -C₂₋₄alkenyl, -C₃₋₇cycloalkyl and E, where E is selected from -NR⁶R⁷, phenyl, or a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, or E is naphthyl or an 8-, 9- or 10-membered fused aromatic or non-aromatic heterocyclic ring system having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms,

R^5 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:

R^6 and R^7 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-;

wherein:

when R^1 , R^2 or R^3 is an alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said alkyl, cycloalkyl, alkoxy or alkoxyalkyl is unsubstituted or has 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, -NH₂, -NO₂, -CN and halogen;

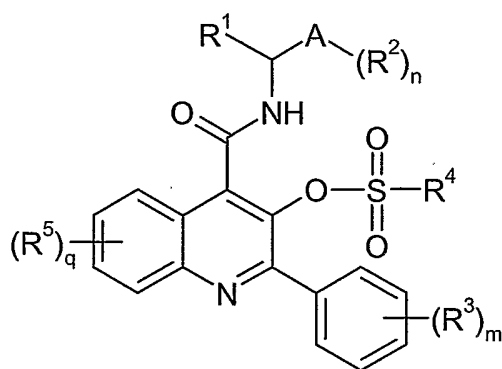
when R^4 is alkyl or cycloalkyl, said alkyl or cycloalkyl is unsubstituted or has 1, 2 or 3 substituents independently selected from -OH, -NH₂, -NO₂, -CN, phenyl, naphthyl, halogen, a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, -NHR and -NRR, where R at each occurrence is independently selected from C₁₋₆alkyl, and

when R^4 is E, E is unsubstituted or has 1, 2 or 3 substituents independently selected from -CN, -NO₂, -CF₃, -NHR, -NRR, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₂₋₆alkenyl and -C₂₋₆alkynyl, or a stereoisomer, enantiomer, in vivo-hydrolysable precursor or pharmaceutically-acceptable salt thereof,

for the treatment or prophylaxis of a disease or condition in which modulation of the NK3 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 including irritable bowel conditions, 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 NK3 receptor is beneficial of a compound in accord with Formula I:



I

wherein:

R^1 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-6}$ cycloalkyl and $-(CH_2)_p-C(O)OC_{1-4}$ alkyl where p is 0, 1, 2 or 3;

A is phenyl or $-C_{3-7}$ cycloalkyl;

R^2 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

n is selected from 1, 2, 3, 4 or 5;

R^3 at each occurrence is independently selected from hydrogen, $-OH$, $-NH_2$, $-NO_2$, $-CN$, halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy and $-C_{1-6}$ alkoxy C_{1-6} alkyl;

m is selected from 1, 2, 3, 4 and 5;

R^4 is selected from $-C_{1-6}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{3-7}$ cycloalkyl and E, where E is selected from $-NR^6R^7$, phenyl, or a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4

nitrogen atoms, or E is naphthyl or an 8-, 9- or 10-membered fused aromatic or non-aromatic heterocyclic ring system having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms,

R^5 at each occurrence is independently selected from H, -OH, -CN, halogen, $-R^6$, $-OR^6$, $-NR^6R^7$, $-SR^6$, $-SOR^6$ and $-SO_2R^6$;

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-;

wherein:

when R^1 , R^2 or R^3 is an alkyl, cycloalkyl, alkoxy or alkoxyalkyl moiety, said alkyl, cycloalkyl, alkoxy or alkoxyalkyl is unsubstituted or has 1, 2, 3, 4 or 5 substituents independently selected at each occurrence from -OH, $-NH_2$, $-NO_2$, -CN and halogen;

when R^4 is alkyl or cycloalkyl, said alkyl or cycloalkyl is unsubstituted or has 1, 2 or 3 substituents independently selected from -OH, $-NH_2$, $-NO_2$, -CN, phenyl, naphthyl, halogen, a 5- or 6-membered aromatic or non-aromatic heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from an oxygen atom, a sulfur atom and up to 4 nitrogen atoms, -NHR and -NRR, where R at each occurrence is independently selected from C_{1-6} alkyl, and

when R^4 is E, E is unsubstituted or has 1, 2 or 3 substituents independently selected from -CN, $-NO_2$, $-CF_3$, -NHR, -NRR, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{2-6}$ alkenyl and $-C_{2-6}$ alkynyl,

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 including irritable bowel conditions, 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/SE2006/000758

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

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9532948 A1 (SMITHKLINE BEECHAM FARMACEUTICI S.P.A.), 7 December 1995 (07.12.1995) --	1-16
A	WO 9719926 A1 (SMITHKLINE BEECHAM S.P.A.), 5 June 1997 (05.06.1997) --	1-16
A	WO 0238548 A1 (GLAXOSMITHKLINE S.P.A.), 16 May 2002 (16.05.2002) --	1-16
A	WO 2005014575 A1 (SMITHKLINE BEECHAM CORPORATION), 17 February 2005 (17.02.2005) --	1-16

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* 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

20 Sept 2006

Date of mailing of the international search report

04-10-2006

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

Renzo C. Verboom/Eö
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000758

Box No. II 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, 11-14
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 8-9, 11-14 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as
.../...
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 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

- ☐ 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000758

Box II.1

diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000758

International patent classification (IPC)

C07D 215/52 (2006.01)
A61K 31/47 (2006.01)
A61P 11/06 (2006.01)
A61P 25/00 (2006.01)
A61P 25/18 (2006.01)
A61P 25/22 (2006.01)
A61P 25/24 (2006.01)
A61P 25/28 (2006.01)
A61P 3/04 (2006.01)
A61P 35/00 (2006.01)

Download your patent documents at www.prv.se

The cited patent documents can be downloaded at www.prv.se by following the links:

- In English/Searches and advisory services/Cited documents (service in English) or
- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.

The password is **DUKYGALLFU**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2006/000758**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02083664 A1 (GLAXOSMITHKLINE S.P.A.), 24 October 2002 (24.10.2002) -- -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/2006

International application No.

PCT/SE2006/000758

WO	9532948	A1	07/12/1995	AP	578 A	26/03/1997
				AP	9500745 D	00/00/0000
				AT	246677 T	15/08/2003
				AT	273959 T	15/09/2004
				AU	699319 B	03/12/1998
				AU	1216299 A	25/03/1999
				AU	2616495 A	21/12/1995
				BG	64004 B	30/09/2003
				BG	101008 A	29/08/1997
				BG	103181 A	30/09/1999
				BR	9507788 A	23/09/1997
				CA	2191352 A,C	07/12/1995
				CA	2257662 A,C	07/12/1995
				CN	1092642 B,C	16/10/2002
				CN	1156451 A	06/08/1997
				CN	1276211 A	13/12/2000
				CN	1428145 A	09/07/2003
				CZ	291476 B	12/03/2003
				CZ	9603470 A	15/10/1997
				DE	69531458 D,T	05/08/2004
				DE	69533408 D,T	08/09/2005
				DK	804419 T	24/11/2003
				DZ	1889 A	17/02/2002
				EP	0804419 A,B	05/11/1997
				SE	0804419 T3	
				EP	0940391 A,B	08/09/1999
				SE	0940391 T3	
				ES	2204952 T	01/05/2004
				ES	2227769 T	01/04/2005
				FI	115052 B	28/02/2005
				FI	964712 A	23/01/1997
				FI	990268 A	10/02/1999
				HK	1003884 A	00/00/0000
				HK	1024469 A	06/05/2005
				HU	76286 A	28/07/1997
				HU	9603262 D	00/00/0000
				HU	9900343 D	00/00/0000
				IL	113844 A	17/05/2005
				IL	126806 D	00/00/0000
				IL	128220 D	00/00/0000
				IL	139301 D	00/00/0000
				IT	MI941099 A	27/11/1995
				JP	3664492 B	29/06/2005
				JP	10500697 T	20/01/1998
				JP	2000026314 A	25/01/2000
				JP	2002179594 A	26/06/2002
				JP	2005068155 A	17/03/2005
				MA	23560 A	00/00/0000
				NO	307783 B	29/05/2000
				NO	965036 A	24/01/1997
				NO	991813 A	24/01/1997
				NZ	287442 A	27/05/1998
				NZ	329979 A	28/07/2000
				OA	10592 A	27/08/2002
				PL	186075 B	31/10/2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/2006

International application No.

PCT/SE2006/000758

WO	9532948	A1	07/12/1995	PL	186665	B	27/02/2004
				PL	317381	A	01/04/1997
				PT	804419	T	31/12/2003
				PT	940391	T	31/12/2004
				RO	114445	A,B	30/04/1999
				RU	2155754	C	10/09/2000
				SI	804419	T	29/02/2004
				SI	940391	T	31/12/2004
				SK	4799	A	11/06/1999
				SK	151496	A	09/07/1997
				SK	282721	B	06/11/2002
				SK	282722	B	06/11/2002
				TW	427977	B	00/00/0000
				TW	533199	B	00/00/0000
				US	5811553	A	22/09/1998
				US	6608083	B	19/08/2003
				US	20030236281	A	25/12/2003
				US	20050096316	A	05/05/2005
				US	20060160846	A	20/07/2006
				ZA	9504269	A	14/05/1996
				IT	237026	Y	31/08/2000
				IT	1293558	B	01/03/1999
				IT	MI950494	A,U,V	16/09/1996

WO	9719926	A1	05/06/1997	AP	9801238	D	00/00/0000
				AU	1031897	A	19/06/1997
				BG	102557	A	31/03/1999
				BR	9611757	A	06/04/1999
				CA	2238328	A	05/06/1997
				CN	1207729	A	10/02/1999
				CZ	9801580	A	14/10/1998
				DZ	2128	A	26/10/2002
				EA	1771	B	00/00/0000
				EP	1019377	A	19/07/2000
				HU	9901016	A	28/03/2000
				IL	124418	D	00/00/0000
				IT	1276171	B	27/10/1997
				IT	MI952462	A	26/05/1997
				JP	2000513325	T	10/10/2000
				MA	24011	A	00/00/0000
				NO	311213	B	29/10/2001
				NO	982333	A	22/07/1998
				OA	11011	A	06/03/2003
				PL	326928	A	09/11/1998
				SK	66898	A	02/12/1998
				TR	9800883	T	00/00/0000
				TW	409123	B	00/00/0000
				US	20020068827	A	06/06/2002
				ZA	9609811	A	22/05/1998
				ID	16747	A	00/00/0000
				IT	1307330	B	30/10/2001
				IT	MI961688	A	02/02/1998
				NZ	323388	A	28/01/2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/2006

International application No.

PCT/SE2006/000758

WO	0238548	A1	16/05/2002	AU	1504302	A	21/05/2002
				EP	1334088	A	13/08/2003
				GB	0027701	D	00/00/0000
				US	20040077658	A	22/04/2004

WO	2005014575	A1	17/02/2005	EP	1651632	A	03/05/2006
				GB	0318727	D	00/00/0000

WO	02083664	A1	24/10/2002	AT	313539	T	15/01/2006
				AT	318266	T	15/03/2006
				DE	60208178	D,T	24/08/2006
				DE	60209362	D	00/00/0000
				EP	1377567	A,B	07/01/2004
				EP	1385839	A,B	04/02/2004
				EP	1659120	A	24/05/2006
				ES	2254688	T	16/06/2006
				GB	0109123	D	00/00/0000
				JP	2004525183	T	19/08/2004
				JP	2004525184	T	19/08/2004
				US	20040152726	A	05/08/2004
				US	20040180902	A	16/09/2004
				US	20050176762	A	11/08/2005
				WO	02083663	A	24/10/2002
				AU	2002350956	A	30/06/2003
				GB	0205649	D	00/00/0000