CYCLIC QUATERNARY AMMONIUM COMPOUNDS

BACKGROUND OF THE INVENTION

Conventional cough preparations containing an effective anti-tussive agent such as codeine have long been used for the symptomatic relief of coughs. However, codeine has various side effects which are undesirable.

Accordingly, the present invention relates to compounds and pharmaceutical compositions having anti-tussive activity, and a method of treating and/or preventing coughs in warm-blooded animals in need thereof by administering an effective amount of the compounds or the pharmaceutical compositions of the invention.

SUMMARY OF THE INVENTION

The problems of the prior art have been overcome by the present invention, which provides compounds and pharmaceutical compositions possessing anti-tussive activity, and a method of administering the same to warm-blooded animals, including humans. The present invention is related to cyclic quaternary ammonium compounds that have been found to be useful in the treatment and/or prevention of cough.

In one aspect, the present invention concerns the use of certain cyclic quaternary ammonium compounds as active ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in warm-blooded animals, including humans.

Another aspect of the present invention provides a method for the treatment and/or prevention of cough in warm-blooded animals, including humans, which method comprises administering to a warm-blooded animal in need thereof certain cyclic quaternary ammonium compounds.

Another aspect of the present invention is directed to certain novel cyclic quaternary ammonium compounds that are useful for the treatment and/or prevention of cough in warm-blooded animals, including humans.

In another aspect, the present invention provides a pharmaceutical composition for the treatment and/or prevention of cough, comprising an effective amount of certain novel cyclic quaternary ammonium compounds and a pharmaceutically acceptable carrier, diluent or excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow diagram showing the layout of the experimental apparatus used for cough determination; and

Figures 2A and 2B are expanded scale recordings of pressure changes derived from the differential pressure transducer during characteristic responses exhibited by a guinea-pig during exposure to an aerosol of citric acid.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms have the following meaning:

"Alkyl" refers to a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having one point of attachment. Examples include *n*-propyl (a C_3 alkyl), *iso*propyl (also a C_3 alkyl) and *t*-butyl (a C_4 alkyl).

"Alkoxyalkyl" refers to an alkylene group substituted with an alkoxy group. For example, methyoxyethyl ($CH_3OCH_2CH_2$-) and ethoxymethyl ($CH_3CH_2OCH_2$-) are both C_3 alkoxyalkyl groups.

"Alkylene" refers to a divalent radical which is a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having two points of attachment. An example is propylene (-$CH_2CH_2CH_2$-), a C_3 alkylene.

"Aralkyl" refers to an alkylene group wherein one of the points of attachment is to an aryl group. An example is the benzyl group ($C_6H_5CH_2$-), a C_7 aralkyl group.

"Alkanoyloxy" refers to an ester substituent wherein the ether oxygen is the point of attachment to the molecule. Examples include propanoyloxy ($CH_3CH_2C(O)$-O-), a C_3 alkanoyloxy and ethanoyloxy ($CH_3C(O)$-O), a C_2 alkanoyloxy.

"Alkoxy" refers to an O-atom substituted by an alkyl group, for example methoxy (-OCH_3), a C_1 alkoxy.

"Alkoxycarbonyl" refers to an ester substituent wherein the carbonyl carbon is the point of attachment to the molecule. Examples include ethoxycarbonyl (CH_3CH_2OC=O), a C_3 alkoxycarbonyl, and methoxycarbonyl ($CH_3OC(O)$-), a C_2 alkoxycarbonyl.

"Aryl" refers to aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl (also known as heteroaryl groups) and biaryl groups, all of which may be optionally substituted. Carbocyclic aryl groups are generally preferred in the compounds of the present invention, wherein phenyl and naphthyl groups are preferred carbocyclic aryl groups.

"Cycloalkyl" refers to a ring, which may be saturated or unsaturated and monocyclic, bicyclic or tricyclic formed entirely from carbon atoms. An example is the cyclopentenyl group (C_5H_7-), which is a five carbon unsaturated cycloalkyl group.

"Carbocyclic" refers to a ring which may be either an aryl ring or a cycloalkyl ring, both as defined above.

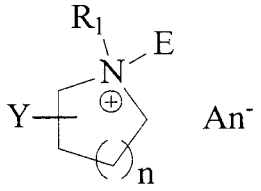
"Thioalkyl" refers to a sulfur atom substituted by an alkyl group, for example thiomethyl (CH_3S-), a C_1 thioalkyl.

The origin of the cough to be treated by the present invention is not particularly limited, and can include virtually any respiratory disorder, such as chronic obstructive pulmonary disease, tuberculosis, bronchitis, respiratory malignancies, asthma, allergy, pulmonary fibrosis,

respiratory tract inflammation, emphysema, pneumonia, lung cancer, presence of foreign bodies, soar throat, common cold, influenza, respiratory tract infection, bronchoconstriction, inhalation of irritants, smoker's cough, chronic non-productive cough, neoplastic cough, cough due to angiotension converting enzyme (ACE) inhibitor therapy, etc. Cough may also occur without a known cause.

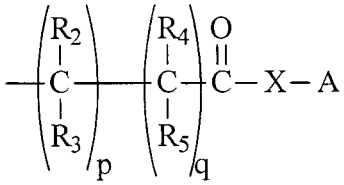
This invention describes certain cyclic quaternary ammonium compounds and their utility as anti-tussive agents. The invention relates to the discovery that cyclic quaternary ammonium compounds of the following formula (I), and pharmaceutically acceptable salts, esters, amides, complexes, chelates, solvates, stereoisomers, stereoisomeric mixtures, geometric isomers, crystalline or amorphous forms, metabolites, metabolic precursors or prodrugs thereof, are useful in the treatment and/or prevention of cough in warm-blooded animals, including humans.

Thus in a first aspect, the present invention is directed to a method for the treatment and/or prevention of cough in a warm-blooded animal, which method comprises administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



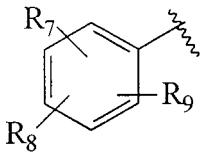
(I)

wherein n is an integer of from 0 to 4; R_1 and E are independently selected from $-CH_2-R_{16}$ and a group represented by the following formula (II):

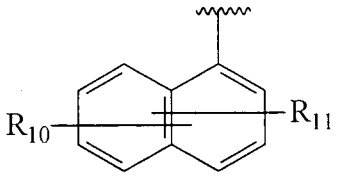


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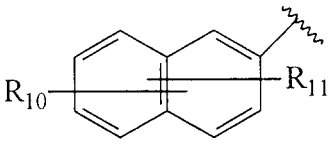
wherein R_2, R_3, R_4, R_5, R_6 and R_{16} are independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; p is an integer of from 0 to 8 and q is an integer of from 0 to 8; A is selected from C_5-C_{12} alkyl, a C_3-C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X):



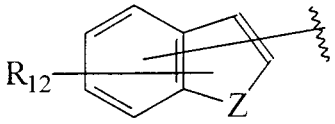
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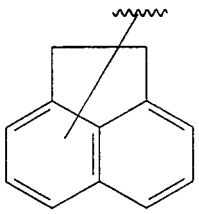
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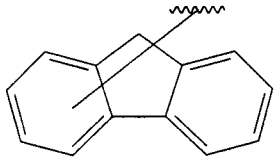
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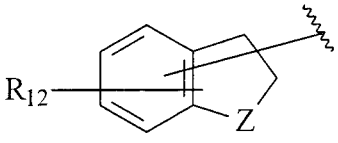
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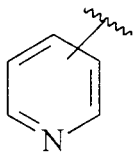
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(VIII)



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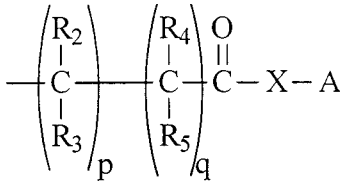


(X)

where R_7, R_8, R_9 R_{10}, R_{11} and R_{12} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl, C_1-C_6

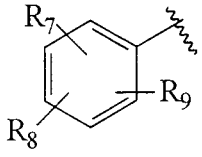
thioalkyl, aryl and $N(R_{13},R_{14})$ where R_{13} and R_{14} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6 alkyl, and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to X when Z is CH, or X may be a direct bond to Z when Z is N, or Z may be directly bonded to R_{15} when Z is N and X is not a direct bond to Z, R_{15} is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and benzyl; and X is N-R_6 except when Z in A is nitrogen and X is a direct bond to Z;

Y is a group on any one of the carbon atoms of the nitrogen heterocyclic ring of formula (I) and is independently selected from hydrogen, -CH_2-R_{16} and a group represented by the following formula (II):

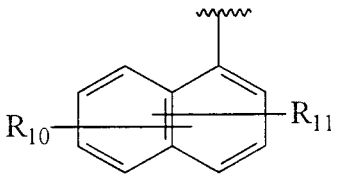


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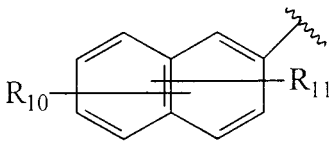
wherein R_2, R_3, R_4, R_5, R_6 and R_{16} are independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; p is an integer of from 0 to 8 and q is an integer of from 0 to 8; A is selected from C_5-C_{12} alkyl, a C_3-C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X):



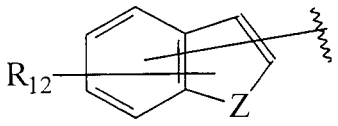
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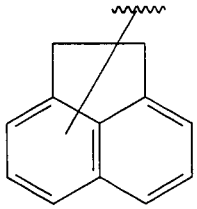
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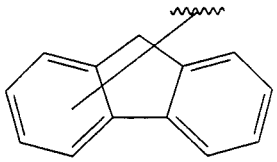
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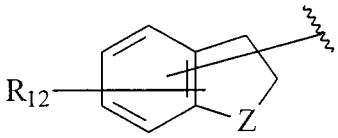
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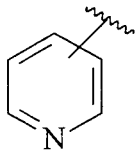
(VII)



(VIII)



(IX)



(X)

where R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl, C_1-C_6 thioalkyl, aryl and $N(R_{13},R_{14})$ where R_{13} and R_{14} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6 alkyl, and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to X when Z is CH, or X may be a direct bond to Z when Z is N, or Z may be directly bonded to R_{15} when Z is N and X is not a direct bond to Z, R_{15} is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and benzyl; and X is N-R_6 except when Z in A is nitrogen and X is a direct bond to Z; An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt, with the proviso that when Y is not represented by formula (II) then R_1 and E cannot both be

-CH_2-R_{16}.

In one preferred aspect, the present invention concerns a method as described above in the first aspect, wherein n is 1 or 2 in formula (I).

In another preferred aspect, the present invention concerns a method as described above in the first aspect, wherein Y is represented by formula (II).

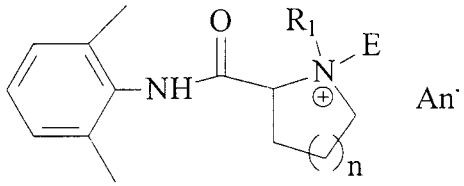
In another preferred aspect, the present invention concerns a method as described above in the first aspect, wherein p is 0 and q is 0.

In yet another preferred aspect, the present invention concerns a method as described above in the first aspect, wherein A is selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X).

In another preferred aspect, the present invention concerns a method as described above in the first aspect, wherein R_1 and E both are $-CH_2-R_{16}$.

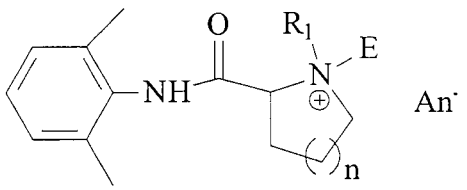
In yet another preferred aspect, the present invention concerns a method as described above in the first aspect or any one of the preceding preferred aspects, wherein A is selected from formulae (III), (IV) and (V).

The present invention also provides a method for the treatment and/or prevention of cough in a warm-blooded animal, which method comprises administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound having the following formula, or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



wherein n is 2; R_1 and E are each $-CH_2-R_{16}$, where R_{16} is independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; and An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt.

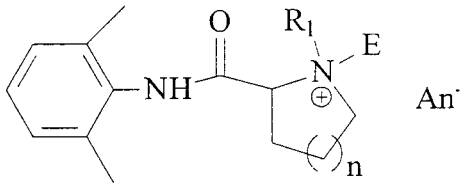
The present invention further provides a method for the treatment and/or prevention of cough in a warm-blooded animal, which method comprises administering to a warm-blooded



animal in need thereof, a therapeutically effective amount of a compound of formula (I) which is N-methyl-bupivacaine chloride having the following structure, or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:

wherein n is 2; R_1 is CH_3; E is n-C_4H_9 and An^- is chloride anion.

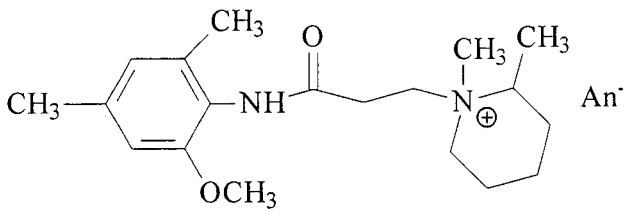
The present invention further provides a method for the treatment and/or prevention of cough in a warm-blooded animal, which method comprises administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound of formula (I) which is N-methyl-mepivacaine chloride having the following structure, or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



wherein n is 2; R_1 is CH_3; E is CH_3 and An^- is chloride anion.

The present invention further provides a method for the treatment and/or prevention of cough in a warm-blooded animal, which method comprises administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound of formula (I) which is N-methyl-vadocaine chloride having the following structure, or a pharmaceutically

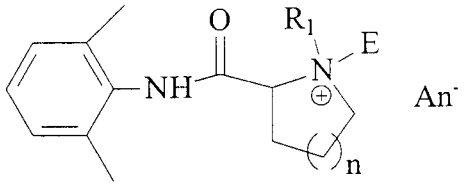
acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



wherein An^- is chloride anion.

The present invention also provides for the use of a compound of formula (I) as defined in the first aspect as active ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in a warm-blooded animal.

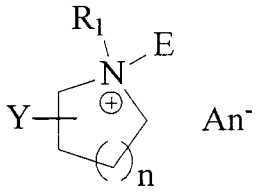
The present invention further provides for the use of a compound having the following formula, or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



wherein n is 2; R_1 and E are each $-CH_2-R_{16}$, where R_{16} is independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; and An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt, as active ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in a warm-blooded animal.

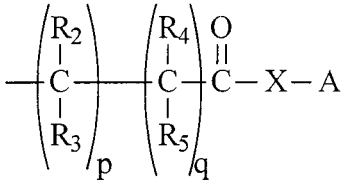
The present invention further provides for the use of a compound selected from N-methyl-bupivacaine chloride, N-methyl-mepivacaine chloride and N-methyl-vadocaine chloride, or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, as active ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in a warm-blooded animal.

In another aspect, the present invention is directed to novel cyclic quaternary ammonium compounds of the following formula (I), and pharmaceutically acceptable salts, esters, amides, complexes, chelates, solvates, stereoisomers, stereoisomeric mixtures, geometric isomers, crystalline or amorphous forms, metabolites, metabolic precursors or prodrugs thereof:



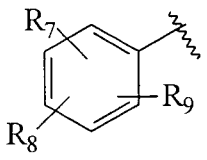
(I)

wherein n is an integer of from 0 to 4; R_1 and E are independently selected from $-CH_2-R_{16}$ and a group represented by the following formula (II):

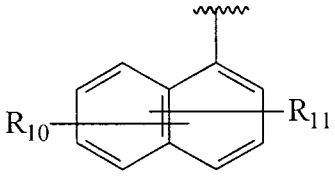


(II)

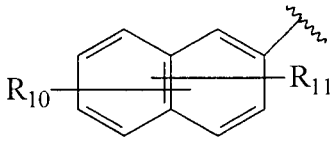
wherein R_2, R_3, R_4, R_5, R_6 and R_{16} are independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; p is an integer of from 0 to 8 and q is an integer of from 0 to 8; A is selected from C_5-C_{12} alkyl, a C_3-C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X):



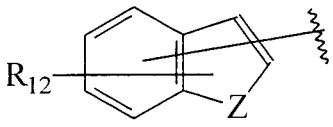
(III)



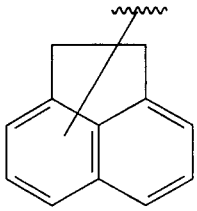
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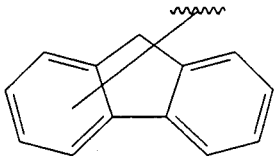
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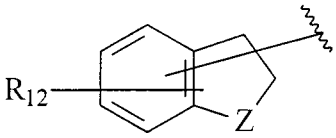
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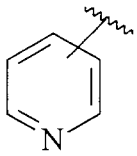
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(VIII)



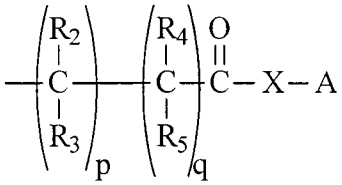
(IX)



(X)

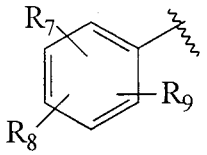
where R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl, C_1-C_6 thioalkyl, aryl and $N(R_{13},R_{14})$ where R_{13} and R_{14} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6 alkyl, and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to X when Z is CH, or X may be a direct bond to Z when Z is N, or Z may be directly bonded to R_{15} when Z is N and X is not a direct bond to Z, R_{15} is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and benzyl; and X is N-R_6 except when Z in A is nitrogen and X is a direct bond to Z;

Y is a group on any one of the carbon atoms of the nitrogen heterocyclic ring of formula (I) and is independently selected from hydrogen, -CH_2-R_{16} and a group represented by the following formula (II):

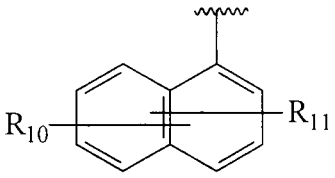


(II)

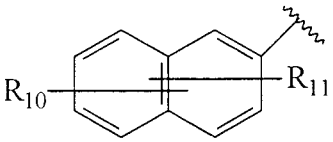
wherein R_2, R_3, R_4, R_5, R_6 and R_{16} are independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; p is an integer of from 0 to 8 and q is an integer of from 0 to 8; A is selected from C_5-C_{12} alkyl, a C_3-C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X):



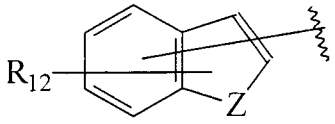
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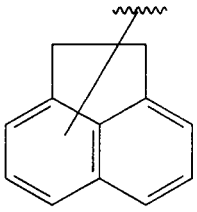
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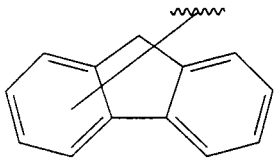
(V)



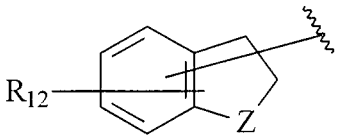
(VI)



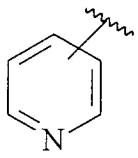
(VII)



(VIII)



(IX)



(X)

where R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl, C_1-C_6

thioalkyl, aryl and $N(R_{13},R_{14})$ where R_{13} and R_{14} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6 alkyl, and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to X when Z is CH, or X may be a direct bond to Z when Z is N, or Z may be directly bonded to R_{15} when Z is N and X is not a direct bond to Z, R_{15} is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and benzyl; and X is N-R_6 except when Z in A is nitrogen and X is a direct bond to Z; An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt, with the provisos that (a) when Y is not represented by formula (II) then R_1 and E cannot both be $-CH_2-R_{16}$; and (b) when n is 0, 1 or 2, and p is 0 or 1, and q is 0 or 1 then A is selected from formulae (VI), (VII), (VIII) and (IX).

The present invention further provides for a pharmaceutical composition for the treatment and/or prevention of cough, comprising an effective amount of a compound of formula (I) as defined in the preceding paragraph, or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof and a pharmaceutically acceptable carrier, diluent or excipient.

The compounds of the present invention may be prepared by direct quaternisation of the corresponding amino precursors with an appropriate alkyl halide. For example, N-methyl-bupivacaine chloride can be synthesized by treatment of bupivacaine (commercially available from e.g. Sigma-Aldrich) with methyl chloride. Similarly N-methyl-bupivacaine iodide can be synthesized by treatment of bupivacaine (commercially available from e.g. Sigma-Aldrich) with methyl iodide. Quaternary mepivacaine such as N-methyl-mepivacaine chloride and N-methyl-mepivacaine iodide can be similarly prepared from mepivacaine and methyl chloride

or methyl iodide respectively. In an analogous approach, quaternary vadocaine can be synthesized by treatment of vadocaine (methods for the preparation of this compound and other closely related analogs are described in U.S. 4,353,914) with an appropriate alkyl halide. N-methyl-vadocaine chloride can thus be synthesized by reaction of vadocaine with methyl chloride.

Alternatively, the compounds of the present invention may be prepared by analogy with known synthetic methodology (see, e.g., Belgian Patent 614,154, which follows from Swedish Patent 1779/71, the disclosures of which are herein incorporated by reference). A conventional route of synthesis involves three steps and can be described (as in the aforementioned patent, see also T. Takahashi, J. Okada, M. Hori, A. Kato, K. Kanematsu, and Y. Yamamoto, *J. Pharm. Soc. Japan* 76, 1180-6 (1956)) as follows.

In a first step an aromatic amine is reacted with chloracetyl chloride in a suitable solvent such as dichloromethane and in the presence of triethylamine. The reaction is conducted at low temperature (-15°C) and the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and if necessary, can be purified by chromatography techniques. In a second step, the above chlorinated derivative can be reacted with an appropriate cyclic tertiary amine in a solvent such as methanol with a catalyst (e.g., potassium iodide) to form a quaternary ammonium salt. The chlorinated intermediate can react as well with a secondary amine to provide the corresponding tertiary amine, which is then further reacted with a chlorinated derivative to form a quaternary ammonium salt.

The synthetic procedures described herein, especially when taken with the general knowledge in the art, provide sufficient guidance to those of ordinary skill in the art to perform the synthesis, isolation, and purification of the compounds of the present invention.

It is recognized that there is at least one chiral center in the compounds used within the scope of the present invention and thus such compounds will exist as various stereoisomeric

forms. Applicants intend to include all the various stereoisomers within the scope of the invention. Though the compounds may be prepared as racemates and can conveniently be used as such, individual enantiomers also can be isolated or preferentially synthesized by known techniques if desired. Such racemates and individual enantiomers and mixtures thereof are intended to be included within the scope of the present invention. Pure enantiomeric forms if produced may be isolated by preparative chiral HPLC. The free base may be converted if desired, to the monohydrochloride salt by known methodologies, and subsequently, if desired, to other acid addition salts by reaction with inorganic or organic salts. Acid addition salts can also be prepared metathetically by reacting one acid addition salt with an acid that is stronger than that of the anion of the initial salt.

The present invention also encompasses the pharmaceutically acceptable salts, esters, amides, complexes, chelates, solvates, crystalline or amorphous forms, metabolites, metabolic precursors or prodrugs of the compounds of formulae (I). Pharmaceutically acceptable esters and amides can be prepared by reacting, respectively, a hydroxy or amino functional group with a pharmaceutically acceptable organic acid, such as identified below. A prodrug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which is degraded or modified by one or more enzymatic or other in vivo processes to the parent bioactive form. Generally, a prodrug has a different pharmakokinetic profile than the parent drug such that, for example, it is more easily absorbed across the mucosal epithelium, it has better salt formation or solubility and/or it has better systemic stability (e. g., an increased plasma half-life).

Those skilled in the art recognize that chemical modifications of a parent drug to yield a prodrug include: (1) terminal ester or amide derivatives which are susceptible to being cleaved by esterases or lipases; (2) terminal peptides which may be recognized by specific or nonspecific proteases; or (3) a derivative that causes the prodrug to accumulate at a site of action through

membrane selection, and combinations of the above techniques. Conventional procedures for the selection and preparation of prodrug derivatives are described in H. Bundgaard, Design of Prodrugs, (1985). Those skilled in the art are well-versed in the preparation of prodrugs and are well-aware of its meaning.

In another embodiment, the present invention provides compositions which include a compound of the present invention as described above in admixture or otherwise in association with one or more inert carriers, excipients and diluents, as well as optional ingredients if desired. Inert carriers include any material which does not degrade or otherwise covalently react with a compound of the invention. Thus, the present invention provides a pharmaceutical or veterinary composition (hereinafter, simply referred to as a pharmaceutical composition) containing a compound of the present invention as described above, in admixture with a pharmaceutically acceptable carrier, excipient or diluent. The invention further provides a pharmaceutical composition containing an effective amount of a compound of the present invention as described above, in association with a pharmaceutically acceptable carrier.

The pharmaceutical compositions of the present invention may be in any form which allows for the composition to be administered to a patient. For example, the composition may be in the form of a solid, liquid or gas (aerosol). Typical routes of administration include, without limitation, oral, topical, parenteral, sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, epidural, intrasternal injection or infusion techniques. Pharmaceutical composition of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a patient take the form of one or more dosage units, where for example, a tablet, capsule or cachet may be a single dosage unit, and a container of a compound of the present invention in aerosol form may hold a plurality of dosage units.

Materials used in preparing the pharmaceutical compositions should be pharmaceutically pure and non-toxic in the amounts used. The inventive compositions may include one or more compounds (active ingredients) known for a particularly desirable effect. It will be evident to those of ordinary skill in the art that the optimal dosage of the active ingredient(s) in the pharmaceutical composition will depend on a variety of factors. Relevant factors include, without limitation, the type of subject (*e.g.*, human), the particular form of the active ingredient, the manner of administration and the composition employed.

In general, the pharmaceutical composition includes a compound of the present invention as described herein, in admixture with one or more carriers. The carrier(s) may be particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup or injectable liquid. In addition, the carrier(s) may be gaseous, so as to provide an aerosol composition useful in, *e.g.*, inhalatory administration.

When intended for oral administration, the composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the composition may be formulated into a powder, granule, compressed tablet, pill, capsule, cachet, chewing gum, wafer, lozenges, or the like form. Such a solid composition will typically contain one or more inert diluents or edible carriers. In addition, one or more of the following adjuvants may be present: binders such as syrups, acacia, sorbitol, polyvinylpyrrolidone, carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, gum tragacanth or gelatin, and mixtures thereof; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; fillers such as lactose, mannitols, starch, calcium phosphate, sorbitol, methylcellulose, and mixtures thereof; lubricants

such as magnesium stearate, high molecular weight polymers such as polyethylene glycol, high molecular weight fatty acids such as stearic acid, silica, wetting agents such as sodium lauryl sulfate, glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin, a flavoring agent such as peppermint, methyl salicylate or orange flavoring, and a coloring agent.

When the composition is in the form of a capsule, *e.g.*, a gelatin capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil.

The composition may be in the form of a liquid, *e.g.*, an elixir, syrup, solution, aqueous or oily emulsion or suspension, or even dry powders which may be reconstituted with water and/or other liquid media prior to use. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred compositions contain, in addition to the present compounds, one or more of a sweetening agent, thickening agent, preservative (*e.g.*, alkyl *p*-hydoxybenzoate), dye/colorant and flavor enhancer (flavorant). In a composition intended to be administered by injection, one or more of a surfactant, preservative (*e.g.*, alkyl *p*-hydroxybenzoate), wetting agent, dispersing agent, suspending agent (*e.g.*, sorbitol, glucose, or other sugar syrups), buffer, stabilizer and isotonic agent may be included. The emulsifying agent may be selected from lecithin or sorbitol monooleate.

The liquid pharmaceutical compositions of the invention, whether they be solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or digylcerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as

sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

A liquid compositions intended for either parenteral or oral administration should contain an amount of the inventive compound such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. Preferred oral compositions contain between about 4% and about 50% of the active compound of the present invention. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01 to 10% by weight of active compound.

The pharmaceutical composition may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment, cream or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the inventive compound of from about 0.1 to about 25% w/v (weight per unit volume).

The composition may be intended for rectal administration, in the form, *e.g.*, of a suppository which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol. Low-melting waxes are preferred for the preparation of a suppository, where mixtures of fatty acid glycerides and/or cocoa butter are suitable waxes. The waxes may be melted, and the compound of the present

invention is dispersed homogeneously therein by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

The composition may include various materials which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials which form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule or cachet.

The composition in solid or liquid form may include an agent which binds to the compound of the present invention and thereby assists in the delivery of the active components. Suitable agents which may act in this capacity include a monoclonal or polyclonal antibody, a protein or a liposome.

The pharmaceutical composition of the present invention may consist of gaseous dosage units, *e.g.*, it may be in the form of an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system which dispenses the active ingredients. Aerosols of compounds of the invention may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, and the like, which together may form a kit. Preferred aerosols may be determined by one skilled in the art, without undue experimentation. The pharmaceutical compositions may be prepared by methodology well known in the pharmaceutical art. The compounds of the present invention may be in the form of a solvate in a pharmaceutically acceptable solvent such as water or physiological saline.

Suitable pharmaceutically acceptable salts include acid addition salts of acids such as hydrochloric, hydrobromic, benzenesulfonic (besylate), benzoic, camphorsulfonic,

ethanesulfonic, fumaric, gluconic, glutamic, isethionic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, succinic, p-toluenesulfonic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid, although the preferred acid addition salt is the hydrochloride salt.

As indicated above the magnitude of the therapeutic or prophylactic dose of the compounds of the present invention in the treatment and/or prevention of cough will depend upon the severity and nature of the condition being treated and the route of administration. The dose and the frequency of the dosing will also vary according to age, body weight and response of the individual patient. In general, the total daily dose range for the compounds of the present invention for the treatment or prevention of cough is from about 0.1 to about 800 mg in single or repeated doses.

Any suitable route of administration as described above may be employed to provide an effective dosage of the compounds of the present invention, although administration by inhalation is preferred, most preferably in aerosol form. Suitable forms of administration include, but are not limited to, inhalation (delivered by, e.g., metered-dose inhaler, jet nebulizer, ultrasonic nebulizer, dry powder inhaler, etc.), nasal sprays, nebulization, oral administration such as via tablets, capsules, lozenges, syrups, sprays, suspensions, elixirs, gargles, and other liquid preparations, aerosol foams, parental administration, and sublingal administration.

The compounds of the present invention can include pharmaceutically acceptable carriers and other conventional additives, including aqueous based carriers, co-solvents such as ethyl alcohol, propylene glycol and glycerin, fillers, lubricants, wetting agents, flavoring agents, coloring agents, emulsifying, suspending or dispersing agents, suspending agents, etc. For aerosol delivery of the compounds of the present invention, pharmaceutically acceptable diluents, carriers, and/or propellants may be included in the formulations for use in appropriate devices. These are prepared by procedures well known to

those skilled in the art (see e.g., Medication Teaching Manual, 5th Ed., Bethesda, MD, American Society of Hospital Pharmacists, 1991).

The compositions of the present invention may optionally include other known therapeutic agents, including decongestants such as pseudoephedrine HCl, phenylephrine HCl and ephedrine HCl, non-steroidal anti-inflammatory drugs such as acetaminophen, aspirin, phenacetin, ibuprofen and ketoprofen, expectorants such as glyceryl guaiacolate, terpin hydrate and ammonium chloride, antihistamines such as chlorpheniramine maleate, doxylamine succinate, brompheniramine maleate and diphenhydramine hydrochloride, and anesthetic compounds such as phenol.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1

Synthesis of 2-{[(2,6-Dimethylphenyl)amino]carbonyl}-1-methyl-1-pentylpiperidinium iodide

(N-methyl-bupivacaine iodide)

Bupivacaine hydrochloride was dissolved in H_2O (15 mL), saturated aqueous $NaHCO_3$ (30 mL), and extracted with dichloromethane (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to 60 mL. Methyl iodide (1.0 mL, 16.12 mmol) was then added to the filtrate and the reaction mixture was stirred at room temperature for 48 hours. The solvent was evaporated and the resultant solid dissolved in water (50 mL). The resulting solution was extracted with ether (2 x 50 mL) and then with CH_2Cl_2 (2 x 50 mL). The combined dichloromethane layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the product (2.62 g, 79% yield) as yellow crystals. ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4 (CH_3), 18.7 (CH_3), 19.6 (CH_2), 19.7 (CH_2), 19.8 (CH_2), 23.9 (CH_2), 24.8

(CH_3), 43.9 (CH_3), 61.1 (CH_2), 65.1 (CH_3), 69.1 (CH), 127.6 (CH), 128.1 (CH), 132.3 (C), 134.9 (C), 165.1(C).

EXAMPLE 2

Synthesis of 2-{[(2,6-Dimethylphenyl)amino]carbonyl}-1,1-dimethylpiperidinium iodide (N-methyl-mepivacaine iodide)

Mepivacaine hydrochloride (2.92 g, 10.32 mmol) was dissolved in H_2O (15 mL), saturated aqueous $NaHCO_3$ (30 mL), and extracted with dichloromethane (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* (50 mL). Methyl iodide (1.3 mL, 20.64 mmol) was then added to the filtrate and the reaction mixture was stirred at room temperature for 48 hours. The solvent was evaporated, and the resultant solid dissolved in water (200 mL). The aqueous solution was extracted with ether (2 x 200 mL) and then with CH_2Cl_2 (2 x 200 mL). The combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the product (3.19 g, 80% yield) as yellow crystals. ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9 (CH_3), 19.6 (CH_2), 20.2 (CH_2), 24.5 (CH_2), 46.4 (CH_3), 53.6 (CH_3), 65.0 (CH_2), 69.9 (CH), 127.8 (CH), 128.2 (CH), 132.4 (C). 134.9 (C), 164.7 (C).]

EXAMPLE 3

The following method is one of the general methods available to determine the antitussive activity of the compounds of the present invention.

Male albino Dunkin-Hartley strain guinea-pigs (weight 300-400g) can be obtained from various commercial suppliers.

The method is a modification of that described by Adcock J.J.., Schneider C. and Smith T.W., "Effects of Morphine and a Novel Opioid Pentapeptide BW443C, on Cough, Nociception

and Ventilation in the Unanaesthetized Guinea-pig", *Br. J. Pharmacol.*, **93**, 93-100 (1988). Individual conscious guinea-pigs are placed unrestrained into a sealed purpose built perspex exposure chamber (3,000 cm^3 volume) and allowed to acclimatize prior to aerosol administration. The layout of the experimental apparatus used is shown in Figure 1.

Cylinder air is introduced into the exposure chamber at a flow rate of 1 liter/min, maintained by a needle valve and monitored by a rotameter. From the rotameter the air passes through the cup of an ultrasonic nebulizer (DeVilbis UltraNeb 2000) which is used to generate aerosols of drug or citric acid at 0.15 ml/min. A Fleisch pneumotachograph, connected to a differential pressure transducer (Grass model PT5) is attached to the outflow from the exposure chamber and provides a measurement of airflow from the chamber. The differential pressure transducer is connected to a Grass polygraph from which a hard copy record can be produced. The output from the polygraph is directed to a computerized data acquisition system (Poh-Ne-Mah) for real time recording of data. A tie-clip microphone is placed in the exposure chamber and connected via a pre-amplifier to a loudspeaker output to provide the observer with an audio monitor of responses.

Cough responses are induced by exposure to an aerosol of citric acid (1M) for 10 minutes. Animals are continuously monitored by trained observer, and the number of coughs are counted during a 15 minute period from commencement of the citric acid aerosol administration. Three characteristic responses can be produced by exposure to citric acid: cough, sneeze and "wet dog" shake.

The three types of response are differentiated primarily by sound and visual observation. Confirmation of the numbers of multiple coughs is determined by reference to the change in flow rate displayed by the Poh-Ne-Mah system monitor. Printouts demonstrating the pressure changes characteristic of the different response to irritant are shown in Figures 2A and 2B. Data records for individual guinea-pigs on the Poh-Ne-Mah system are stored on an optical disk. Each cough

is marked on the Grass polygraph paper trace, and from these record numbers, frequency and time of onset of coughs are determined. The cough response is defined by a characteristic coughing sound and behavior, associated with a marked biphasic pressure change. The biphasic pressure changes associated with a sneeze are not of as great a magnitude as those associated with a cough, the secondary rise in pressure also being far less than during a cough (Figure 2B). The sound of a sneeze differed from that of a cough, and sneezing is associated with nose rubbing activity. The third response, a "wet dog" shake, produces a rise in pressure only (Figure 2A) and lacked the definitive sound of a cough or sneeze.

Quantities of drugs are weighed out and dissolved in a vehicle. Equal volumes are aliquotted into sample tubes before being passed, together with another sample tube containing the same volume of vehicle, to an independent observer for coding. Pre-treatments are matched by concentration together with a vehicle control group. Two to five guinea-pigs are randomly allocated to each treatment group. Animals are pre-treated with either vehicle (e.g. distilled water, 0.9% sterile saline, Tween or 1 to 25% ethanol depending on the solubility of the compound), reference compound (e.g. lidocaine, bupivacaine or mepivacaine) or test drugs for 5 minutes immediately prior to citric acid aerosol exposure. Test drugs and reference compound are administered as aerosols at concentrations selected from 0.1, 1.0, 2.0, 5.0 and 10.0 mg/ml. The sequence of pre-treatment administration is determined according to a 4x4 Latin Square design.

Data can be presented as the mean ±SEM number of coughs produced by individual guinea-pigs within each group during the 15 minute observation period or mean±SEM latency of cough and are analyzed using one way analysis of variance to compare mean responses between matched groups of animals (doses) and between unmatched groups (treatments) followed by the Tukey-Kramer multiple comparison test where appropriate.

In one set of experiments using the general protocol described above, the antitussive activity of N-methyl-bupivacaine iodide was tested. Results showed that pre-treatment of guinea pigs with aerosols of N-methyl-bupivacaine iodide at 5.0 mg/ml immediately before exposure to citric acid (1M) inhibited cough responses by >90% compared with vehicle (25% ethanol) pre-treated guinea pigs over the 15 minute observation period. Similarly, other cyclic quaternary ammonium compounds of the present invention can be evaluated by this method.

EXAMPLE 4

In another experiment similar to that described above in Example 3, the duration of the antitussive effects of the compounds of the present invention against citric acid-induced cough responses can be investigated in conscious guinea pigs. Cyclic quaternary ammonium compounds of the present invention, reference compounds or vehicle are tested by administering as aerosol pre-treatments (0.1, 1.0, 2.0, 5.0 or 10.0 mg/ml, 5 minute duration) at 5 minutes, 30 minutes, 1 hour, 2 hours and 4 hours prior to induction of cough responses by citric acid aerosol. Data and results are analyzed as described in Example 3.

EXAMPLE 5

The antitussive effects of a 5 minute pre-treatment with aerosolized compounds of the present invention and reference compound (e.g. lidocaine, bupivacaine or mepivacaine) on capsaicin aerosol-induced cough can be investigated in conscious guinea-pigs using a method similar to that described in Example 1. Data and results are analyzed as described in Example 3.

EXAMPLE 6

Therapeutic treatment with the compounds of the present invention can also be determined by a similar method as described in Example 3. The antitussive effects of

compounds of the present invention and reference compound (e.g. lidocaine, bupivacaine or mepivacaine) that are administered after induction of cough responses by exposure to citric acid aerosol are investigated in conscious guinea pigs. Vehicle or test agents are administered as aerosols (10, 5, 2, 1.0 or 0.1mg/ml; 5 minute duration) 2 minutes after exposure to citric acid aerosol began. Cough responses are recorded during a 15 minute observation period (t=0 to t=15 minutes) from initiation of the citric acid exposure. Data and results are analyzed as described in Example 3.

EXAMPLE 7

Investigation of antitussive activity of aerosolized test compound on citric acid-induced cough responses in conscious rabbits

Protocol

Twenty-two male New Zealand white rabbits are randomly allocated to either of two groups of 11 rabbits.

Pairs of rabbits (control versus test) are placed in individual exposure chambers with an airflow of 5 liter/min through the chambers.

Each rabbit is exposed to ozone (3 ppm) for 1 hour.

The rabbits are then immediately exposed to aerosols of either vehicle (chamber 1) or test compound (10 mg/ml, chamber 2) at a nebulization rate of 0.9 ml/min.

Cough responses are induced with citric acid aerosol (1.6 M).

Coughs are counted during the 10 minute exposure to citric acid.

All rabbits are exposed to ozone before vehicle or test drug pre-treatment.

Data and results are analyzed as described in Example 3.

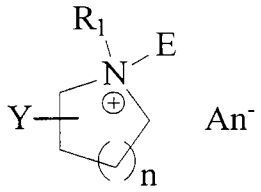
All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually incorporated by reference.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

The invention includes all embodiments and variations substantially as hereinbefore described and with reference to the examples and drawings. From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited by the disclosed embodiments or examples. Many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. In the specification, the word "comprising" is used as an open-ended term, substantially equivalent to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. Citation of references herein shall not be construed as an admission that such references are prior art to the present invention.

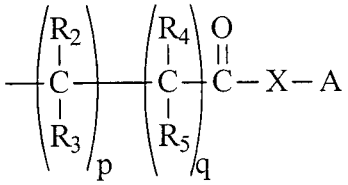
What is claimed is:

1. A method for the treatment and/or prevention of cough in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



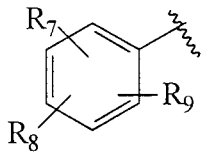
(I)

wherein n is an integer of from 0 to 4; R_1 and E are independently selected from $-CH_2-R_{16}$ and a group represented by the following formula (II):

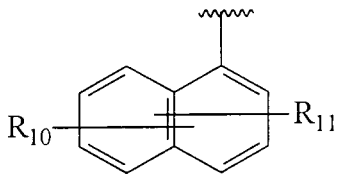


(II)

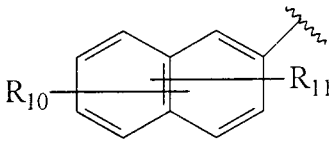
wherein R_2, R_3, R_4, R_5, R_6 and R_{16} are independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; p is an integer of from 0 to 8 and q is an integer of from 0 to 8; A is selected from C_5-C_{12} alkyl, a C_3-C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X):



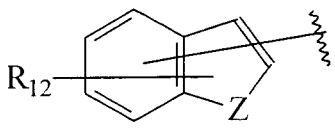
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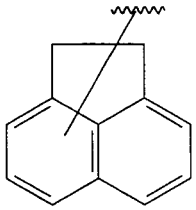
(IV)



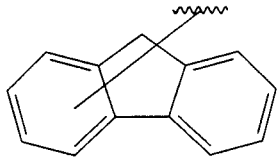
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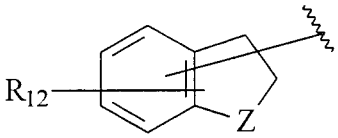
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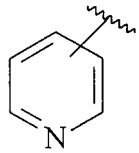
(VII)



(VIII)



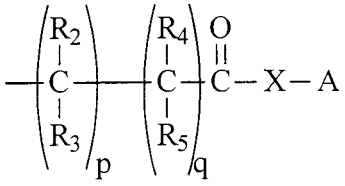
(IX)



(X)

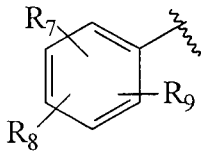
where R_7, R_8, R_9 R_{10}, R_{11} and R_{12} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl, C_1-C_6 thioalkyl, aryl and N(R_{13},R_{14}) where R_{13} and R_{14} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6 alkyl, and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to X when Z is CH, or X may be a direct bond to Z when Z is N, or Z may be directly bonded to R_{15} when Z is N and X is not a direct bond to Z, R_{15} is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and benzyl; and X is N-R_6 except when Z in A is nitrogen and X is a direct bond to Z;

Y is a group on any one of the carbon atoms of the nitrogen heterocyclic ring of formula (I) and is independently selected from hydrogen, -CH_2-R_{16} and a group represented by the following formula (II):

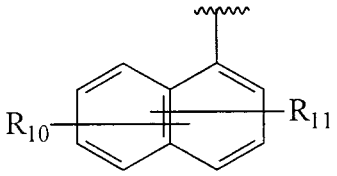


(II)

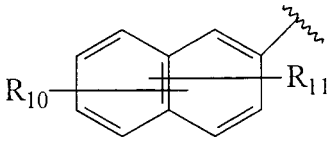
wherein R_2, R_3, R_4, R_5, R_6 and R_{16} are independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; p is an integer of from 0 to 8 and q is an integer of from 0 to 8; A is selected from C_5-C_{12} alkyl, a C_3-C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X):



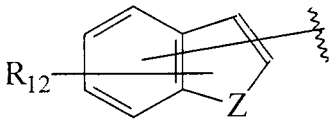
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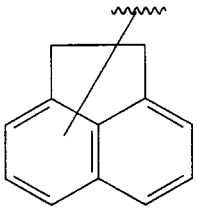
(IV)



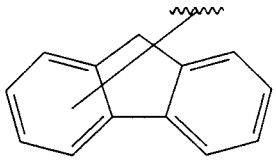
(V)



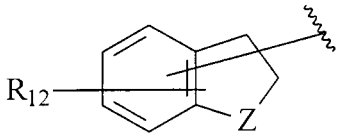
(VI)



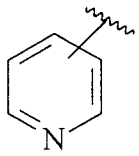
(VII)



(VIII)



(IX)



(X)

where R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl, C_1-C_6 thioalkyl, aryl and $N(R_{13},R_{14})$ where R_{13} and R_{14} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6 alkyl, and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to X when Z is CH, or X may be a direct bond to Z when Z is N, or Z may be directly bonded to R_{15} when Z is N and X is not a direct bond to Z, R_{15} is selected from

hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and benzyl; and X is N-R_6 except when Z in A is nitrogen and X is a direct bond to Z; An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt,

with the proviso that when Y is not represented by formula (II) then R_1 and E cannot both be -CH_2-R_{16}.

2. The method of claim 1 wherein n is 1 or 2.

3. The method of claim 1 wherein Y is represented by formula (II).

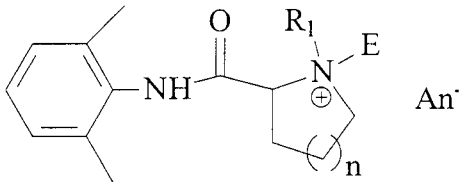
4. The method of claim 1 wherein p is 0 and q is 0.

5. The method of claim 1 wherein A is selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X).

6. The method of claim 1 wherein R_1 and E both are -CH_2-R_{16}.

7. A method according to any one of claims 1-6 wherein A is selected from formulae (III), (IV) and (V).

8. A method for the treatment and/or prevention of cough in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound having the following formula, or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



wherein n is 2; R_1 and E are each -CH_2-R_{16}, where R_{16} is independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl;

and An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt.

9. A method according to any one of claims 1-8 wherein An^- is the anion from a pharmaceutically acceptable salt.

10. A method according to any one of claims 1-8 wherein An^- is a chloride anion.

11. A method for the treatment and/or prevention of cough in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound which is N-methyl-bupivacaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof.

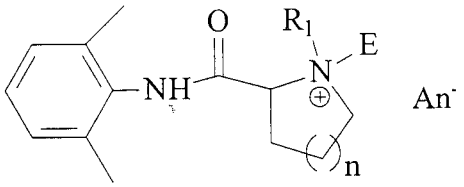
12. A method for the treatment and/or prevention of cough in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound which is N-methyl-mepivacaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof.

13. A method for the treatment and/or prevention of cough in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, a therapeutically effective amount of a compound which is N-methyl-vadocaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof.

14. The use of a compound of formula (I) as defined in claim 1 as active ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in a warm-blooded animal.

15. The use of a compound having the following formula, or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture,

crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, as active ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in a warm-blooded animal:



wherein n is 2; R_1 and E are each $-CH_2-R_{16}$, where R_{16} is independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; and An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt.

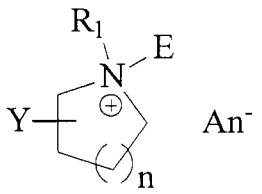
16. The use of a compound which is N-methyl-bupivacaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, as active ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in a warm-blooded animal.

17. The use of a compound which is N-methyl-mepivacaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, as active ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in a warm-blooded animal.

18. The use of a compound which is N-methyl-vadocaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, as active

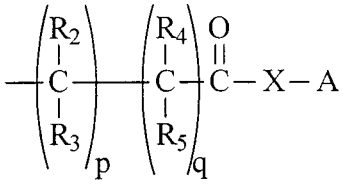
ingredient in the manufacture of a medicament for use in the treatment and/or prevention of cough in a warm-blooded animal.

19. A compound of the following formula (I), or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



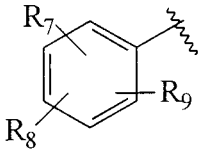
(I)

wherein n is an integer of from 0 to 4; R_1 and E are independently selected from $-CH_2-R_{16}$ and a group represented by the following formula (II):

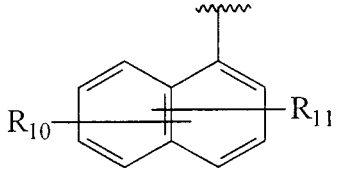


(II)

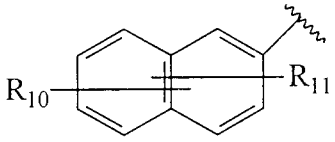
wherein R_2, R_3, R_4, R_5, R_6 and R_{16} are independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; p is an integer of from 0 to 8 and q is an integer of from 0 to 8; A is selected from C_5-C_{12} alkyl, a C_3-C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X):



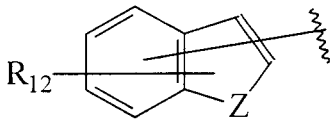
(III)



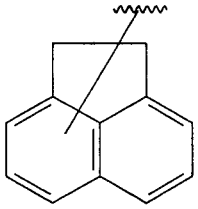
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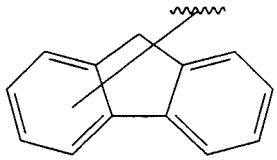
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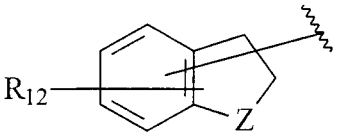
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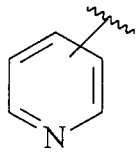
(VII)



(VIII)



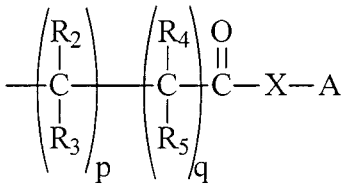
(IX)



(X)

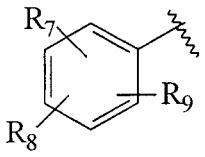
where R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl, C_1-C_6 thioalkyl, aryl and $N(R_{13},R_{14})$ where R_{13} and R_{14} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6 alkyl, and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to X when Z is CH, or X may be a direct bond to Z when Z is N, or Z may be directly bonded to R_{15} when Z is N and X is not a direct bond to Z, R_{15} is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and benzyl; and X is N-R_6 except when Z in A is nitrogen and X is a direct bond to Z;

Y is a group on any one of the carbon atoms of the nitrogen heterocyclic ring of formula (I) and is independently selected from hydrogen, -CH_2-R_{16} and a group represented by the following formula (II):

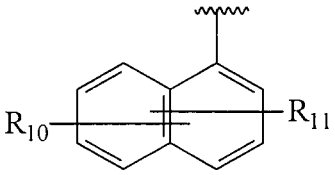


(II)

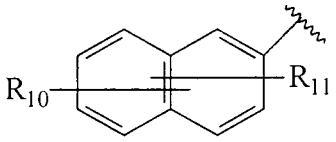
wherein R_2, R_3, R_4, R_5, R_6 and R_{16} are independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; p is an integer of from 0 to 8 and q is an integer of from 0 to 8; A is selected from C_5-C_{12} alkyl, a C_3-C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X):



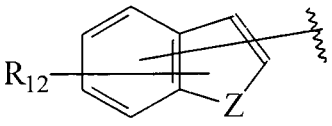
(III)



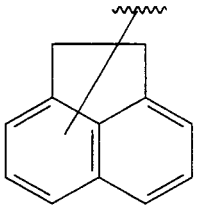
(IV)



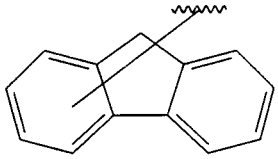
(V)



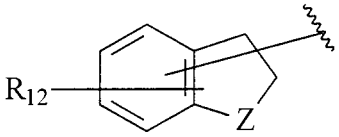
(VI)



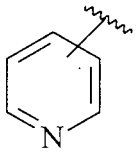
(VII)



(VIII)



(IX)



(X)

where R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl, C_1-C_6 thioalkyl, aryl and $N(R_{13},R_{14})$ where R_{13} and R_{14} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6 alkyl, and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to X when Z is CH, or X may be a direct bond to Z when Z is N, or Z may be directly bonded to R_{15} when Z is N and X is not a direct bond to Z, R_{15} is selected from

hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl and benzyl; and X is N-R_6 except when Z in A is nitrogen and X is a direct bond to Z; An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt,

with the provisos that (a) when Y is not represented by formula (II) then R_1 and E cannot both be -CH_2-R_{16}; and (b) when n is 0, 1 or 2, and p is 0 or 1, and q is 0 or 1 then A is selected from formulae (VI), (VII), (VIII) and (IX).

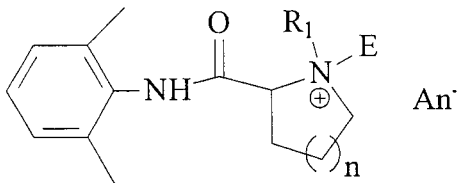
20. A pharmaceutical composition for the treatment and/or prevention of cough, comprising an effective amount of a compound of claim 19 or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof and a pharmaceutically acceptable carrier, diluent or excipient.

21. The use of the compound of claim 19 to formulate a medicament.

22. A pharmaceutical composition comprising an effective amount of a compound of claim 19 or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof and a pharmaceutically acceptable carrier, diluent or excipient.

23. The use of a compound of formula (I) as defined in claim 1 for the treatment and/or prevention of cough in a warm-blooded animal.

24. The use of a compound having the following formula, or a pharmaceutically acceptable salt, ester, amide, complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, for the treatment and/or prevention of cough in a warm-blooded animal:



wherein n is 2; R_1 and E are each $-CH_2-R_{16}$, where R_{16} is independently selected from hydrogen, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl and C_7-C_{12} aralkyl; and An^- is the acid addition salt of a pharmaceutically acceptable acid or the anion from a pharmaceutically acceptable salt.

25. The use of a compound which is N-methyl-bupivacaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, for the treatment and/or prevention of cough in a warm-blooded animal.

26. The use of a compound which is N-methyl-mepivacaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, for the treatment and/or prevention of cough in a warm-blooded animal.

27. The use of a compound which is N-methyl-vadocaine chloride or a pharmaceutically acceptable complex, chelate, solvate, stereoisomer, stereoisomeric mixture, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, for the treatment and/or prevention of cough in a warm-blooded animal.