METHOD AND COMPOSITION

FIELD OF THE INVENTION

The present invention relates to a formulation of a quinuclidinone derivative and to a method of preparing such formulation, as well as to the use of such formulation.

BACKGROUND OF THE INVENTION

3-quinuclidinone derivatives for use in the treatment of various disorders, e.g. hyperproliferative diseases, autoimmune diseases and heart diseases are described in WO05/090341. Similarly, 3-quinuclidinone derivatives for use especially in the treatment of tumor diseases are disclosed in WO04/084893, WO02/024692 and WO03/070250.

In WO05/090341 it is mentioned that a composition of the quinuclidinones disclosed therein may be prepared for any route of administration, e.g. oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, or intraperitoneal and that the precise nature of the carrier or other material will depend on the route of administration. It also is noted that for a parenteral administration, a parenterally acceptable aqueous solution is employed, which is pyrogen free and has requisite pH, isotonicity and stability.

However, the present inventors found that in a liquid aqueous solution, such as one useful for parenteral administration (i.e. generally having a pH of 6.5-7.5) or the corresponding stock solution for preparing a parenterally administrable solution, the inventive compounds had an unacceptably low stability, forming degradation products within only a few hours after solubilization. This lack of chemical stability in a liquid solution was quite unexpected for the compounds described in the above-mentioned prior art documents.

SUMMARY ~~OF THE INVENTION~~

One object according to the present disclosure~~invention~~ is to provide a formulation of 3-quinuclidinone derivatives as defined herein, having an improved shelf life, in particular compared to prior art formulations.

Another object according to the present disclosure~~invention~~ is to provide a formulation of improved shelf life comprising 3-quinuclidinone derivatives as defined herein, that are useful in therapy; e.g. in the treatment of a disorder selected from hyperproliferative diseases, e.g. cancer, autoimmune dis-

eases and heart diseases, said formulation having an improved shelf life, in particular compared to prior art formulations.

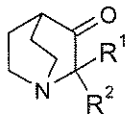
Still another object is to provide a liquid formulation containing a 3-quinuclidinone derivative as defined herein, wherein the 3-quinuclidinone derivative has a reduced degradation rate.

A further object of the present disclosure~~invention~~ is to provide a pharmaceutical formulation for the treatment of hyperproliferative diseases, autoimmune diseases and heart diseases, said formulation containing a 3-quinuclidinone derivative as defined herein below and having an improved shelf life, in particular compared to prior art formulations.

A further object of the present disclosure~~invention~~ is to provide a formulation allowing for prolonged storage of a 3-quinuclidinone derivative as defined herein.

Another object of the present disclosure~~invention~~ is to provide a method for preparing a formulation according to the present disclosure~~invention~~.

In one particular embodiment, the present disclosure~~invention~~ provides a formulation that is an aqueous solution of a 3-quinuclidinone derivative according to formula (I)



I

wherein:

R^1 is selected from H, $-CH_2-O-R^3$, $-CH_2-S-R^3$, and $-CH_2-NR^3R^4$;

R^2 is selected from $-CH_2-O-R^3$, $-CH_2-S-R^3$, and $-CH_2-NR^3R^4$;

R^3 and R^4 are the same or different and are independently selected from H; substituted or non-substituted, unbranched or branched, saturated or unsaturated C3-C12 cycloalkyl or C1-C10 alkyl; substituted or non-substituted benzyl; substituted or non-substituted mono- or bicyclic aryl; substituted or non-substituted mono-, bi- or tricyclic C2-C10 heteroaryl or non-aromatic C2-C10 heterocyclyl containing one or several heteroatoms independently selected from N, O

and S; or R^3 and R^4 in $-CH_2-NR^3R^4$ are bonded together and form, together with the nitrogen atom to which they are bonded, a substituted or non-substituted non-aromatic C2-C10 mono- or bicyclic heterocyclyl optionally containing one or several further heteroatoms independently selected from N, O and S and optionally comprising one or several cyclic keto groups;

wherein the substituents of the substituted groups are independently selected from unbranched or branched, saturated or unsaturated C3-C12 cycloalkyl or C1-C10 alkyl; halogen; halogen-substituted C1-C10 alkyl, mono- or bicyclic aryl; mono-, bi- or tricyclic C2-C10 heteroaryl or non-aromatic C2-C10 heterocyclyl containing one or several heteroatoms independently selected from N, O and S; C1-C10 alkoxy; amino; and C1-C10 alkylamino;

or a pharmaceutically acceptable salt thereof,

and at least one pH regulating agent in an amount such as to provide a pH in the aqueous solution of from about 3.0 to about 5.0.

In one aspect, there is provided an aqueous solution of 2-(hydroxymethyl)-2-(methoxymethyl)quinuclidin-3-one or a pharmaceutically acceptable salt thereof, and a pH regulating agent; wherein the aqueous solution has a pH from 3.0 to 5.0.

In one embodiment, the formulation is a pharmaceutical formulation. Thus, there is provided a liquid formulation as defined herein for use in therapy. In another aspect, there is provided the aqueous solution as defined herein, for use in therapy.

In one embodiment, the formulation is a stock solution allowing long-term storage of a 3-quinuclidinone derivative of formula (I) dissolved therein.

In one embodiment, the 3-quinuclidinone derivative of formula (I) comprised in the formulation of the invention is useful in the treatment of a disorder selected from hyperproliferative diseases, such as cancer, autoimmune diseases and heart diseases, in particular in the treatment of cancer.

In one further embodiment, there is provided a liquid formulation of a 3-quinuclidinone derivative as defined herein for use in a method for the prevention and/or treatment of a pathophysiological condition, e.g. a hyperproliferative disease, such as cancer, an autoimmune disease or a heart disease.

Another embodiment relates to the use of a liquid formulation of a 3-quinuclidinone as defined herein for the manufacturing of a medicament for the prevention and/or treatment of a patho-

physiological condition, e.g. a hyperproliferative disease, such as cancer, an autoimmune disease or a heart disease. In yet another aspect, there is provided the use of an aqueous solution as defined herein, for the manufacturing of a medicament for the treatment of a disorder selected from hyperproliferative diseases, autoimmune diseases and heart diseases.

In one further embodiment, a method for the prevention and/or treatment of a pathophysiological condition is provided which comprises the administration, preferably the parenteral administration, of an effective amount of a composition of the present disclosure~~invention~~, to a mammal in need thereof.

In one further embodiment, a method for the prevention and/or treatment of a pathophysiological condition is provided which comprises the administration, preferably the parenteral administration, of an effective amount of a composition prepared by use of a liquid formulation according to the present disclosure~~invention~~ to a mammal in need thereof.

Furthermore, a method for the prevention and/or treatment of a pathophysiological condition mediated by abnormal cell growth is provided which comprises administering, parenterally or orally, an effective amount of a composition of the present disclosure~~invention~~ or a composition prepared by use of a liquid formulation according to the present disclosure~~invention~~, to a mammal.

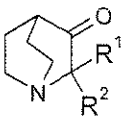
In one particular embodiment, a method for the prevention and/or treatment of a pathophysiological condition mediated by abnormal cell growth is provided which comprises administering, parenterally or orally, an effective amount of a composition of the present disclosure~~invention~~ to a mammal in need of therapeutic intervention to control the pathophysiological condition and wherein abnormal cell growth is controlled.

A method for preparing the liquid formulation of the present disclosure~~invention~~ also is provided, comprising adding to an aqueous phase, a compound of formula (I), or a pharmaceutically acceptable salt thereof, optionally at least one further therapeutically active agent, and a pH regulating agent in an amount so as to provide a pH in the composition of from 3.0 to 5.0.

Further embodiments of the present disclosure~~invention~~ are as described herein below and as defined in the claims.

CLAIMS

1. An aqueous solution of a compound of formula (I)



I

wherein:

R^1 is selected from H, $-CH_2-O-R^3$, $-CH_2-S-R^3$, and $-CH_2-NR^3R^4$;

R^2 is selected from $-CH_2-O-R^3$, $-CH_2-S-R^3$, and $-CH_2-NR^3R^4$;

R^3 and R^4 are the same or different and are independently selected from H; substituted or non-substituted, unbranched or branched, saturated or unsaturated C3-C12 cycloalkyl or C1-C10 alkyl; substituted or non-substituted benzyl; substituted or non-substituted mono- or bicyclic aryl; substituted or non-substituted mono-, bi- or tricyclic C2-C10 heteroaryl or non-aromatic C2-C10 heterocyclyl containing one or several heteroatoms independently selected from N, O and S; or R^3 and R^4 in $-CH_2-NR^3R^4$ are bonded together and form, together with the nitrogen atom to which they are bonded, a substituted or non-substituted non-aromatic C2-C10 mono- or bicyclic heterocyclyl optionally containing one or several further heteroatoms independently selected from N, O and S and optionally comprising one or several cyclic keto groups;

wherein the substituents of the substituted groups are independently selected from unbranched or branched, saturated or unsaturated C3-C12 cycloalkyl or C1-C10 alkyl; halogen; halogen-substituted C1-C10 alkyl, mono- or bicyclic aryl; mono-, bi- or tricyclic C2-C10 heteroaryl or non-aromatic C2-C10 heterocyclyl containing one or several heteroatoms independently selected from N, O and S; C1-C10 alkoxy; amino; C1-C10 alkylamino;

or a pharmaceutically acceptable salt thereof, and

a pH regulating agent;

wherein the aqueous solution has a pH from 3.0 to 5.0, and wherein the compound is 2-(hydroxymethyl)-2-(methoxymethyl)quinuclidin-3-one.

2. The aqueous solution according to claim 1, comprising at least one further therapeutically active agent.

3. The aqueous solution according to any one of the claims 1-2, having a pH between 3.0 and 4.5.

4. The aqueous solution according to any one of the claims 1-3, wherein the compound of formula (I) is present in the aqueous solution at a concentration of from 10 mg/mL to 250 mg/mL.

5. The aqueous solution according to any one of the claims 1-4, wherein the aqueous solution comprises NaCl at a concentration of from 0 to 3% weight by volume.

6. The aqueous solution according to any one of the claims 1-5, for use in therapy.

7. The aqueous solution according to any one of the claims 1-5, for use in the treatment of a disorder selected from hyperproliferative diseases, autoimmune diseases and heart diseases.

8. Use of an aqueous solution according to any one of the claims 1-5, for the manufacturing of a medicament for the treatment of a disorder selected from hyperproliferative diseases, autoimmune diseases and heart diseases.

9. A method for preparing an aqueous solution according to any one of the claims 1-2, by adding, to an aqueous phase, a compound of formula (I), or a pharmaceutically acceptable salt thereof; optionally at least one further therapeutically active agent; and a pH regulating agent in an amount so as to provide a pH in the composition of from 3.0 to 5.0.

10. The method according to claim 9, wherein the pH regulating agent is added in an amount so as to provide a pH in the composition of from 3.0 to 4.5.

11. The method according to claim 9 or claim 10, wherein NaCl is added to the aqueous phase in an amount so as to provide a concentration of NaCl in the liquid composition of from 0 to 3% weight by volume.

12. The method according to any one of the claims 9 to 11, wherein the compound of formula (I), or the pharmaceutically acceptable salt thereof, is added to the aqueous phase in an amount so as to provide a concentration of the compound of formula (I) in the liquid composition of from 10 mg/mL to 250 mg/mL

CLAIMS

1. An aqueous solution of 2-(hydroxymethyl)-2-(methoxymethyl)quinuclidin-3-one or a pharmaceutically acceptable salt thereof, and a pH regulating agent; wherein the aqueous solution has a pH from 3.0 to 5.0.

2. The aqueous solution according to claim 1, comprising at least one further therapeutically active agent.

3. The aqueous solution according to claim 1 or claim 2, having a pH between 3.0 and 4.5.

4. The aqueous solution according to any one of the claims 1-3, wherein 2-(hydroxymethyl)-2-(methoxymethyl)quinuclidin-3-one (I) is present in the aqueous solution at a concentration of from 10 mg/mL to 250 mg/mL.

5. The aqueous solution according to any one of the claims 1-4, wherein the aqueous solution comprises NaCl at a concentration of from 0 to 3% weight by volume.

6. The aqueous solution according to any one of the claims 1-5, for use in therapy.

7. The aqueous solution according to any one of the claims 1-5, for use in the treatment of a disorder selected from hyperproliferative diseases, autoimmune diseases and heart diseases.

8. Use of an aqueous solution according to any one of the claims 1-5, for the manufacturing of a medicament for the treatment of a disorder selected from hyperproliferative diseases, autoimmune diseases and heart diseases.