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(54) Title: DERIVATIVES OF ERYTHROMYCIN, CLARITHROMYCIN, ROXITHROMYCIN OR AZITHROMYCIN WITH ANTIMICROBIAL AND MUCOLYTIC ACTIVITY

(57) Abstract
A pharmaceutical with an enhanced pharmaceutical profile comprises a mucolytic and an antibiotic in which the mucolytic is present in an amount of greater than one molar equivalent of the antibiotic. The antibiotic may be selected from Erythromycin, Roxithromycin, Clarithromycin, Azithromycin, Dirithromycin, and pharmaceutically acceptable salts or esters thereof. The mucolytic is a mucolytically active thiol, especially N-acetylcycteine, mercaptoethanesulfonic acid, tiopronin or methylcysteine. The adducts can be isolated via a simple and efficient process.
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INTRODUCTION

The invention relates to a pharmaceutical including a macrolide antibiotic. The invention also relates to a process for manufacturing the pharmaceutical.

The compounds Erythromycin, Roxithromycin, Clarithromycin, Azithromycin and Dirithromycin are widely used macrolide antibiotics for the treatment of various types of infections. The chemical structures of these macrolides as follows.
It is known that the stability and the pharmacological and immuno-
microbiological profile of these compounds can be improved by derivatisation and
by conversion into various salts.

EP-A-0005789 describes salts of Erythromycin and Erythromycin propionate with
N-acetylcysteine, carboxymethylcysteine, thiazolidin-carboxylic acid and
mercapto-succinic acid. However these salts are sensitive to sunlight, humidity
and heat.

WO-A-96/19489 describes a salt of Roxithromycin with N-acetylcysteine.

There is a need for a pharmaceutical including a macrolide antibiotic which will
have an enhanced pharmaceutical profile.

Statements of the Invention
According to the invention there is provided a pharmaceutical comprising:

a mucolytic and

an antibiotic, pharmaceutically acceptable salts or esters thereof,

wherein the mucolytic is present in an amount of greater than one molar
equivalent of the antibiotic.

In a preferred embodiment of the invention the antibiotic is selected from:

Erythromycin;

Roxithromycin;

Clarithromycin;
Azithromycin;

Dirithromycin; and

pharmaceutically acceptable salts or esters thereof.

Preferably the mucolytic is a mucolytically active thiol. Usually the mucolytically active thiol is selected from:

N-acetylcysteine;

mercaptoethanesulfonic acid;

tiopronin; and

methylcysteine.

Preferably the mucolytic is present in an amount of less than about four molar equivalents of the antibiotic. Most preferably the mucolytic is present in an amount of less than two molar equivalents of the antibiotic.

In a preferred embodiment of the invention the pharmaceutical includes a compound of the formula

\[ [\text{RH}^{+}] [\text{X}^{-}] \]

wherein

R is a radical selected from:
Erythromycin;

Clarithromycin;

5 Roxithromycin;

Azithromycin;

Dirithromycin;

10 pharmaceutically acceptable esters thereof; and

HX is a mucolytically active thiol.

In one embodiment of the invention the pharmaceutical includes a compound of the formula

$$[RH^+][Y^-]$$

wherein

20 $R$ is as defined above and

$HY$ is a pharmaceutically acceptable inorganic or organic acid.

In another embodiment of the invention the pharmaceutical includes a compound of the formula:

$$[RH^+\,(HX^*)_n]\,[X^-]$$

wherein

25 $R$ and $HX$ are as defined above,
HX* is a bound mucolytically active thiol; and

n is a number greater than zero.

For example n may be 1, 2 or 3.

The invention also provides a pharmaceutical including a compound of the formula

\[ [\text{RH}^{\infty}(\text{HX}^*)] [\text{X}^{-}] \]

and compounds of the formulae:

\[ [\text{RH}^{\infty}(\text{HX}^*)_{2}] [\text{X}^{-}] \]

\[ [\text{RH}^{\infty}(\text{HX}^*)_{3}] [\text{X}^{-}] \]

wherein R, HX and HX* are as defined above.

The pharmaceutical may include a compound of the formula:

\[ [\text{RH}^{\infty}(\text{HX}^*)_{n}] [\text{Y}^{\infty}] \]

wherein

R and HX* are as defined above;

HY is a pharmacetically acceptable inorganic or organic acid; and

n is a number greater than zero.

For example n may be 1, 2 or 3.
In a preferred embodiment of the invention the pharmaceutical includes a compound of the formula:

$$[\text{RH}^+ (\text{HX}^*) \ ] [\text{Y}^-]$$

and compounds of the formulae:

$$[\text{RH}^+ (\text{HX}^*)_2 \ ] [\text{Y}^-]$$

$$[\text{RH}^+ (\text{HX}^*)_3 \ ] [\text{Y}^-]$$

wherein R, HX* and HY are as defined above.

The invention also provides a compound of the formula:

$$[\text{RH}^+ (\text{HX}^*)_n \ ] [\text{X}^-]$$

wherein R, HX, HX* and n are as defined above.

The invention further provides a compound of the formula:

$$[\text{RH}^+ (\text{HX}^*) \ ] [\text{X}^-]$$

wherein R, HX and HX* are as defined above.

In addition, the invention provides compounds of the formulae:

$$[\text{RH}^- \ (\text{HX}^*)_2 \ ] [\text{X}^-]$$

$$[\text{RH}^- \ (\text{HX}^*)_3 \ ] [\text{X}^-]$$
wherein R, HX and HX* are as defined above.

The invention also provides a compound of the formula:

$$\text{[RH}^{\oplus}(\text{HX}^\ast)n] [\text{Y} \ominus]$$

wherein R, HX*, HY and n are as defined above.

The invention also provides a compound of the formula:

$$\text{[RH}^{\oplus}(\text{HX}^\ast)] [\text{Y} \ominus]$$

wherein R, HX* and HY are as defined above.

The invention further provides compounds of the formulae:

$$\text{[RH}^{\oplus}(\text{HX}^\ast)_{2}] [\text{Y} \ominus]$$

$$\text{[RH}^{\oplus}(\text{HX}^\ast)_{3}] [\text{Y} \ominus]$$

wherein R, HX* and HY are as defined above.

The invention also provides a process for preparing a compound of the formula:

$$\text{[RH}^{\oplus}(\text{HX}^\ast)n] [\text{X} \ominus]$$

wherein R, HX, HX* and n are as defined above

by reacting a compound of the formula R with a desired molar equivalent(s) of a compound of the formula HX.
The process may include the step of forming, as an intermediate, a compound of the formula:

\([\text{RH}] [\text{X}]\)

wherein \(R\) and \(\text{HX}\) are as defined above.

According to another aspect the invention provides a process for preparing a compound of the formula:

\([\text{RH}^{+}(\text{HX}^*)_n] [\text{Y}^\ominus]\)

wherein \(R\), \(\text{HX}^*\), \(\text{HY}\) and \(n\) are as defined above by reacting a compound of the formula \(R\) with a compound of the formula \(\text{HY}\) to form a compound of the formula:

\([\text{RH}] [\text{Y}]\)

which is reacted with a desired molar equivalent(s) of a compound of the formula \(\text{HX}\) wherein \(R\), \(\text{HX}\) and \(\text{HY}\) are as defined above.

Preferably the process is carried out in the presence of water.

Ideally the process is carried out at a temperature of from 15 to 45°C, preferably at a temperature of from 20 to 25°C.

In another aspect the invention provides a pharmaceutical composition in solid form incorporating a compound of the invention.

It has surprisingly been found that the pharmacological profile of [1:1] antibiotic-mucolytic agents can be improved. In particular the mucolytic effect can be
increased by preparing salts of macrolide antibiotics with an additional amount of mucolytic agent.

It has also surprisingly been found that novel adducts with a molar ratio higher than [1:1] (antibiotic-mucolytic agent) can be isolated via a very simple and efficient process. Such adducts can for example be integer [1:2]-,[1:3]- or [1:4] compounds bearing a one, two or three molar excess of mucolytic relative to the equivalent of antibiotic. Alternatively any type of non-integer adducts in the range between [1:1] and [1:4] may also be prepared.

Especially Erythromycin A or its pharmaceutically acceptable esters, Roxithromycin, Clarithromycin or Azithromycin are suitable to form such an adduct with mucolytically active thiols, in particular with N-acetylcysteine. The reaction is ideally performed under aqueous conditions affording the products in high yield and very good quality.

Detailed Description
The invention provides novel macrolide antibiotics bearing a mucolytically active component as shown in scheme 2:
Scheme 2

R is a radical preferably selected from Erythromycin A or its pharmaceutically acceptable esters, Clarithromycin, Roxithromycin or Azithromycin.

HX is a mucolytically active thiol, preferably selected from N-acetylcysteine, mercaptoethanesulfonic acid, tiopronin or methylcysteine.

HX* is a bound mucolytically active thiol, preferably N-acetylcysteine, mercaptoethanesulfonic acid, tiopronin or methylcysteine.

R can be converted into its acid-base addition salt (I) by reaction with a mucolytically active thiol HX.

Adduct (II) can be obtained by reacting (I) with a second equivalent of HX; alternatively R can directly be converted into (II) using two equivalents of HX.

The formation of compounds (III) and (IV) may be achieved by direct reaction of R with 3 or 4 equivalents of HX. Alternatively stepwise conversion may be performed by reacting R portion wise with HX as outlined in scheme 2.
If non-integer equivalents of HX greater than one are used, mixtures of the compounds (I), (II), (III) and (IV) may be isolated depending on the added amount of HX.

Optionally the antibiotic R can initially be reacted with an inorganic or organic acid HY into a pharmaceutically acceptable acid-base addition salt of type:

\[ \text{[RH} \text{][Y]} \]

This salt may then be further converted by reaction with HX into compounds of the following formulae and mixtures thereof:

\[ \text{[RH}^2\text{(HX)}^+] \text{[Y}^\ominus] \]
\[ \text{[RH}^3\text{(HX)}^2] \text{[Y}^\ominus] \]
\[ \text{[RH}^3\text{(HX)}^3] \text{[Y}^\ominus] \]

The reaction takes place in an analogous way to the process shown in scheme 2.

The process is preferably performed in the presence of water.

The most preferred mucolytic is N-acetylcysteine.

The invention will be more clearly understood by means of the following examples:

**General Procedure**

The macrolide antibiotic and the mucolytic are homogenised for 1-2 h preferably at room temperature. Process water is then added and homogenisation is continued for 1-2 h at a temperature of 15-45°C, preferably at 20-25°C. The
product is dried under vacuum and isolated in quantitative yield. Optionally the product may be milled. The process may, for example, be carried out using an INOX dryer as described in WO-A-9619489.

Example 1
Preparation of Erythromycin Propionate-N-acetylcysteine-[1:1]-salt

Used materials: 5.38 kg Erythromycin Propionate
1.11 kg N-acetylcysteine
1.21 process water

The reaction is carried out according to the general procedure.
Melting range: 103-128°C.
FT-IR (KBr): \( \tilde{\nu} \) [cm\(^{-1}\)] = 3450, 2974, 2940, 1737, 1653, 1464, 1377, 1169, 1084, 1056, 1009.
\([\alpha]_D^{20}\) : -57.2° (c = 10.00 in ethanol).

Powder X-ray peaks of medium to high intensity: 2\(\theta\) = 9.18, 16.70, 18.33, 19.25.

Example 2
Preparation of Erythromycin Propionate-N-acetylcysteine [1:1.8]-adduct

Used materials: 5.38 kg Erythromycin Propionate
2.00 kg N-acetylcysteine

300-600 ml process water, preferably 350-450 ml

The reaction is carried out according to the general procedure.
Melting range: 114-124°C.
FT-IR (KBr): 3466, 2974, 2941, 1738, 1464, 1378, 1169, 1083, 1053.


Powder X-ray peaks of medium and high intensity: 2\(\theta\) = 5.17, 9.10, 14.01, 16.24, 22.89, 49.73.
Example 3

Preparation of Erythromycin Propionate-N-acetylcysteine [1:3]-adduct

Used materials: 5.38 kg Erythromycin Propionate
3.33 kg N-acetylcysteine
300-600 ml process water, preferably 350-450 ml

The reaction is carried out according to the general procedure.

Melting range: 109-119.5°C.

FT-IR (KBr): 3469, 2974, 2941, 1737, 1464, 1377, 1169, 1084, 1053.

$[\alpha]_D^{10} = -38.3^\circ \text{ (c = 10.35 in ethanol).}$

Powder X-ray peaks of medium and high intensity: $2\theta = 5.25, 9.20, 16.34, 20.13, 28.64, 30.16.$

Example 4

Preparation of Erythromycin Propionate-N-acetylcysteine [1:4]-adduct

Used materials: 5.38 kg Erythromycin Propionate
4.44 kg N-acetylcysteine
300-600 ml process water, preferably 350-450 ml

The reaction is carried out according to the general procedure.

Melting range: 110-118°C.

FT-IR (KBr): 3473, 2974, 1738, 1464, 1379, 1168, 1084, 1053.

$[\alpha]_D^{10} = -31.1^\circ \text{ (c = 10.08 in ethanol).}$

Powder X-ray peaks of medium and high intensity: $2\theta = 4.91, 8.86, 15.99, 26.33, 59.07.$

Example 5

Preparation of Roxithromycin-N-acetylcysteinate-[1:1]-salt

Used materials: 1.80 kg Roxithromycin
351 g N-acetylcysteine
600-800 ml process water, preferably 700-750 ml

The reaction is carried out according to the general procedure.
Melting range: 95-100°C.
FT-IR (KBr): \( \tilde{\nu} [\text{cm}^{-1}] = 3456, 2971, 1735, 1636, 1602, 1465, 1384, 1280, 1169, 1078, 1012. \)

Example 6
Preparation of Clarithromycin-N-acetylcysteinate-[1:1]-salt

Used materials: 3.60 kg Clarithromycin
0.77 kg N-acetylcysteine
300-600 ml process water, preferably 350-450 ml

The reaction is carried out according to the general procedure.
Melting range: 173.5-183°C.
FT-IR (KBr): \( \tilde{\nu} [\text{cm}^{-1}] = 3478, 2976, 1732, 1693, 1463, 1380, 1348, 1268, 1170, 1110, 1052, 1011. \)
\([\alpha]_{D}^{30} = -72.22^\circ (c = 10.09).\)


Example 7
Preparation of Clarithromycin-N-acetylcysteinate-[1:4]-salt

Used materials: 3.60 kg Clarithromycin
3.00 kg N-acetylcysteine
300-600 ml process water, preferably 350-450 ml

The reaction is carried out according to the general procedure.
Melting range: 110-118°C.
FT-IR (KBr): \( \tilde{\nu} [\text{cm}^{-1}] = 3473, 2974, 2939, 1733, 1693, 1462, 1379, 1347, 1285, 1169, 1110, 1053, 1011. \)
\([\alpha]_{D}^{30} = -38.60^\circ (c = 9.99 \text{ in ethanol}).\)

Powder X-ray peaks of medium and high intensity: 20 = 6.34, 9.80, 13.77, 14.94, 15.93, 18.56.
Salts with other ratios of antibiotic and N-acetylcysteine of Erythromycin, Roxithromycin, Clarithromycin, Azithromycin or Dirithromycin may be prepared in an analogous way.

The same procedure may also apply to the preparation of adducts of antibiotics and mucolytically active agents other than N-acetylcysteine.

**Antibiotic Activity**

*Micrococcus luteus* from stock was streaked on a nutrient agar plate to confirm colony morphology, colour and purity. After 24 hours incubation at 37°C an isolated colony is picked and inoculated into 10 ml of nutrient broth. This is incubated overnight at 37°C and is subsequently used as the inoculum. 10 mg of each of the test compounds is weighed and dissolved in 10 ml of analar methanol in sterile 20 ml universal containers. This is then diluted with ringers buffer solution to give a concentration of 1 mg/ml.

Quantitation of activity is determined using an MIC (Mean Inhibitory Concentration) liquid tube assay. For each test substance the following concentrations are set up: 10 µg/ml, 5 µg/ml, 1 µg/ml, 0.5 µg/ml, 0.1 µg/ml, 0.05 µg/ml and 0.01 µg/ml. Each contained nutrient broth and 0.1 ml of overnight culture of *Micrococcus luteus*.

The tubes were incubated at 37°C and observed for growth after 24 hours and 48 hours. Growth is assessed by dense turbidity, optical density at 660 nm using a spectrophotometer or clarity. The MIC is the last concentration where growth inhibited.
The following table gives the MIC values for the compounds examined:

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC [µg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin-propionate</td>
<td>0.01-0.05</td>
</tr>
<tr>
<td>Erythromycin-N-acetylcysteinate [1:1]</td>
<td>0.01-0.05</td>
</tr>
<tr>
<td>Erythromycin-N-acetylcysteinate [1:1.8]</td>
<td>≤ 0.01</td>
</tr>
<tr>
<td>Erythromycin-N-acetylcysteinate [1:4]</td>
<td>0.05-0.1</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤ 0.01</td>
</tr>
<tr>
<td>Clarithromycin-N-acetylcysteinate [1:1]</td>
<td>≤ 0.01</td>
</tr>
<tr>
<td>Clarithromycin-N-acetylcysteinate [1:4]</td>
<td>0.01-0.05</td>
</tr>
</tbody>
</table>

It will be noted that in general the activity of the 1:1 compound is similar to that of the base antibiotic. Surprisingly however the activity increases to an optimum level around 1:2 and then decreases, particularly at 1:4 or greater.

The pharmaceuticals of the invention can be readily formulated into solid dosage forms such as tablets, capsules, suppositories and the like. A single dosage form without any interaction between the individual components is provided. The pharmacological profile is enhanced. There is also the added advantage of patient compliance in that a single drug may be taken to achieve an enhanced effect.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.
Claims

1. A pharmaceutical comprising:

   a mucolytic and

5

   an antibiotic, pharmaceutically acceptable salts or esters thereof,

wherein the mucolytic is present in an amount of greater than one molar equivalent of the antibiotic.

10

2. A pharmaceutical as claimed in claim 1 wherein the antibiotic is selected from:

    Erythromycin;

15

    Roxithromycin;

    Clarithromycin;

20

    Azithromycin;

    Dirithromycin; and

pharmaceutically acceptable salts or esters thereof.

25

3. A pharmaceutical as claimed in claim 1 or 2 wherein the mucolytic is a mucolytically active thiol.

4. A pharmaceutical as claimed in claim 3 wherein the mucolytically active thiol is selected from:
N-acetylcysteine;
mercaptopethanesulphonic acid;
tiopronin; and
methylcysteine.

5. A pharmaceutical as claimed in any preceding claim wherein the mucolytic is present in an amount of less than four molar equivalents of the mucolytic.

6. A pharmaceutical as claimed in claim 5 wherein the mucolytic is present in an amount of approximately two molar equivalents of the mucolytic.

7. A pharmaceutical as claimed in any preceding claim including a compound of the formula

\[ \text{RH} \cdot \text{X} \]

wherein

R is a radical selected from:

Erythromycin;

Clarithromycin;

Roxithromycin;

Azithromycin;
Dirithromycin;

pharmaceutically acceptable esters thereof; and

HX is a mucolytically active thiol.

8. A pharmaceutical as claimed in any preceding claim wherein the antibiotic is a compound of the formula

$$[RH][Y]$$

wherein

R is as defined in claim 5 and

HY is a pharmaceutically acceptable inorganic or organic acid.

9. A pharmaceutical as claimed in any preceding claim including a compound of the formula

$$[RH^\oplus(HX^\ast)_n][X\ominus]$$

wherein

R is Erithromycin, Clarithromycin, Roxithromycin or Azithromycin

$HX^\ast$ is a bound mucolytically active thiol; and

n is a number greater than zero.

10. A pharmaceutical as claimed in claim 9 wherein n is 1.

11. A pharmaceutical as claimed in claim 9 wherein n is 2.
12. A pharmaceutical as claimed in claim 9 wherein \( n \) is 3.

13. A pharmaceutical as claimed in claim 9 including a compound of the formula

\[
[RH^2(HX^*)_n] [X^-]
\]

and one or more compounds of the formulae:

\[
[RH^2(HX^*)_2] [X^-]
\]

\[
[RH^2(HX^*)_3] [X^-]
\]

wherein \( R \) and \( HX^* \) are as defined in claim 9.

14. A pharmaceutical as claimed in any preceding claim including a compound of the formula

\[
[RH^2(HX^*)_n] [Y^-]
\]

wherein

\( R \) and \( HX^* \) are as defined in claim 9;

\( HY \) is a pharmaceutically acceptable inorganic or organic acid; and

\( n \) is a number greater than zero.

15. A pharmaceutical as claimed in claim 14 wherein \( n \) is 1.

16. A pharmaceutical as claimed in claim 14 wherein \( n \) is 2.
17. A pharmaceutical as claimed in claim 14 wherein n is 3.

18. A pharmaceutical as claimed in claim 14 including a compound of the formula

\[ \text{[RH}^+\text{(HX*)]} \text{[Y\text{-}]} \]

and one or more compounds of the formulae:

\[ \text{[RH}^+\text{(HX*)}}_2 \text{]} \text{[Y\text{-}]} \]

\[ \text{[RH}^+\text{(HX*)}}_3 \text{]} \text{[Y\text{-}]} \]

wherein R, HX* and HY are as defined in claim 14.

19. A compound of the formula

\[ \text{[RH}^+\text{(HX*)}}_n \text{]} \text{[X\text{-}]} \]

wherein R, HX* and n are as defined in claim 9.

20. A compound of the formula

\[ \text{[RH}^+\text{(HX*)]} \text{[X\text{-}]} \]

wherein R and HX* are as defined in claim 9.

21. A compound of the formula

\[ \text{[RH}^+\text{(HX*)}}_2 \text{]} \text{[X\text{-}]} \]
wherein R and HX* are as defined in Claim 9.

22. A compound of the formula

\[ [RH^{\bigcirc}(HX^*)_3] [X^{\bigcirc}] \]

wherein R and HX* are as defined in Claim 9.

23. A compound of the formula

\[ [RH^{\bigcirc}(HX^*)_n] [Y^{\bigcirc}] \]

wherein R, HX*, HY and n are as defined in claim 14.

24. A compound of the formula

\[ [RH^{\bigcirc}(HX^*)] [Y^{\bigcirc}] \]

wherein R, HX* and HY are defined in claim 14.

25. A compound of the formula

\[ [RH^{\bigcirc}(HX^*)_2] [Y^{\bigcirc}] \]

wherein R, HX* and HY are as defined in claim 14.

26. A compound of the formula

\[ [RH^{\bigcirc}(HX^*)_3] [Y^{\bigcirc}] \]
wherein R, HX* and HY are as defined in claim 14.

27. A process for preparing a compound of the formula

\[ [RH^+ (HX^*)_n ] [X^-] \]

wherein R, (HX)* and n are as defined in claim 9

by reacting a compound of the formula [R] with a desired molar equivalent(s) of a compound of the formula [HX].

28. A process as claimed in claim 27 including the step of forming, as an intermediate, a compound of the formula

\[ [RH^{+2}] [X^2^-] \]

wherein R and HX are as defined in claim 9.

29. A process for preparing a compound of the formula

\[ [RH^{+2} (HX^*)_n ] [Y^2^-] \]

wherein R, HX* and n are as defined in claim 14

by reacting a compound of the formula [R] with a compound of the formula [HY] to form a compound of the formula

\[ [RH^+] [Y^-] \]
which is reacted with a desired molar equivalent(s) of a compound of the formula [HX] wherein [HY] and [HX] are as defined in claim 14.

30. A process as claimed in any of claims 27 to 29 which is carried out in the presence of water.

31. A process as claimed in any of claims 27 to 30 which is carried out at a temperature of from 15 to 45°C.

32. A process as claimed in claim 31 wherein the process is carried out at a temperature of from 20 to 25°C.

33. A compound as defined in claim 19 whenever prepared by a process as claimed in claim 31, 32, 34, 35, or 36.

34. A compound as defined in claim 19 whenever prepared by a process as claimed in any of claims 33 to 36.

35. A compound of claim 23 substantially as hereinbefore described with reference to the examples.

36. A compound of claim 19 substantially as hereinbefore described with reference to the examples.

37. A pharmaceutical composition in a solid form including a compound as claimed in any of claims 1 to 26.

38. A pharmaceutical composition substantially as hereinbefore described with reference to the examples.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/70 A61K31/195 C07H17/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07H

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>EP 0 052 909 A (REINER ALBERTO &amp; C REAL SAS) 2 June 1982 (1982-06-02) abstract; claims 6,9 page 3, paragraph D</td>
<td>1-34, 37</td>
</tr>
<tr>
<td>X</td>
<td>EP 0 052 910 A (REINER ALBERTO &amp; C REAL SAS) 2 June 1982 (1982-06-02) claims 6,10</td>
<td>1-34, 37</td>
</tr>
<tr>
<td>X</td>
<td>US 4 476 120 A (GONELLA JACQUES) 9 October 1984 (1984-10-09) column 1; claim 5</td>
<td>1-34, 37</td>
</tr>
<tr>
<td>X</td>
<td>column 2, line 48-65</td>
<td>27-32</td>
</tr>
<tr>
<td>X</td>
<td>EP 0 096 013 A (NUOVO CONSOR SANITAR NAZIONALE) 7 December 1983 (1983-12-07) abstract; claims 4-8,14; example 2</td>
<td>1-34, 37</td>
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</tbody>
</table>

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*D* document referring to an oral disclosure, use, exhibition or other means
**P** document published prior to the International filing date but later than the priority date claimed

**T** later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
**Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
**S** document member of the same patent family

Date of the actual completion of the international search:
7 March 2000

Date of mailing of the international search report:
21/03/2000

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (431-70) 340-2040, Tx. 31 651 epo rl
Fax (431-70) 340-2016

Authorized officer:
Gonzalez Ramon, N
<table>
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<th>Relevant to claim No.</th>
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<td>X</td>
<td>WO 98 05674 A (SCHICKANEDER HELMUT; RUSSINSKY LTD (IE); NIKOLOPOULOS AGGELOS (IE)) 12 February 1998 (1998-02-12) example 1 claims 1,9,13</td>
<td>1-34,37</td>
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<td>WO 96 19489 A (RUSSINSKY LTD; SCHICKANEDER HELMUT (IE); NIKOLOPOULOS AGGELOS (IE)) 27 June 1996 (1996-06-27) abstract; claim 1; example 1 page 3, line 10-20; claims 9,10</td>
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INTERNATIONAL SEARCH REPORT

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

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

1. □ Claims No.: because they relate to subject matter not required to be searched by this Authority, namely:

2. X Claims No.: 1-38
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   See FURTHER INFORMATION SHEET PCT/ISA/210

3. □ Claims No.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of Invention is lacking (Continuation of Item 2 of first sheet)

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

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

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

3. □ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims No.:

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

Remark on Protest

□ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
Continuation of Box I.2

Claims Nos.: 1-38

Present claims 1-34,37 relate to an extremely large number of possible compounds defined as "mucolytic" and "antibiotic". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples and specifically mentioned in the claims with due regard to the general idea underlying the present application. Claims 35,36,38 do not contain a technical feature defining subject matter, and consequently were found unsearchable. There appears to be an erroneous dependency in claims 33,34.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
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