Abstract: The present invention relates to the use of at least one compound of the following general formula (I): wherein R represents OH or NH₂, or of precursors or derivatives thereof, or of the pharmaceutically acceptable salts of said compound or of its precursors or derivatives, for the manufacture of a medicament intended for the prevention or the treatment of parasitic diseases, in particular of protozoan parasitic diseases, more particularly of leishmaniasis, and especially for the prevention or the treatment of parasitic diseases occurring in immunodepressed patients.
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
Protozoans belonging to the *Trypanosomatidae* family account for numerous pathologies afflicting man or animals.

Thus, among protozoans of the *Trypanosoma* genus, *T. brucei* and *T. cruzi* are for instance the etiological agents of sleep disease and Chagas disease.

Protozoans of the *Leishmania* genus, such as *L. aethiopica, L. donovani, L. infantum, L. major, L. mexicana* or *L. tropica* are responsible for leishmaniasis (also named leishmaniosis). Infections by these parasites are endemic in more than 88 countries. WHO estimates that more than 12 millions individuals are infected by these parasites and more than 350 millions would be exposed to infections daily. Three major forms of leishmaniosis are documented, among which the most dangerous form, visceral leishmaniosis, can have a lethal outcome in absence of treatment. This situation has worsened since the occurrence of HIV, because these infections are more frequently found as opportunistic infections in individuals afflicted by the acquired immunodeficiency syndrome (AIDS), in particular in South-West Europe. Parasites take advantage of the immunosuppressed status of the host to establish themselves or to reactivate.

Current leishmaniosis treatments are based on drugs difficult to handle, such as amphotericin B or drugs belonging to the antimonial family, which have serious side effects.

Niacin is the generic name for 2 compounds: nicotinamide (NAm) and nicotinic acid. Both were first used clinically in 1937, when these compounds were each shown to act as « pellagra-preventive » factor. High dose of NAm and its acid derivative nicotinic acid, are often used interchangeably to treat a number of conditions including anxiety, osteoarthritis, and psychosis. Furthermore, NAm is currently in trials as therapy to prevent cancer recurrence and insulin-dependent (Type I) diabetes (4). Beside this, activity of NAm has been evaluated in anti- *mycobacterium tuberculosis* studies performed during 1945-1961 and in anti-HIV studies performed from 1991 to the present (reviewed in 7).

It is an object of the present invention to provide new medicaments, lacking the drawbacks of the currently used medicaments, for the treatment of protozoan parasitic diseases, such as leishmaniosis.

Thus, the present invention relates to the use of at least one compound of the following general formula (I):
wherein R represents OH, NH₂,
or of precursors or derivatives thereof,

or of the pharmaceutically acceptable salts of said compound or of its precursors or derivatives,

for inhibiting the SIR2 protein expressed by parasites, in particular by protozoan parasites,

more particularly by *Leishmania*, under their respective intracellular or extracellular forms.

As intended herein “precursors or derivatives” of compounds of formula (I) represent compounds which are liable to yield compounds of formula (I) in vivo or compounds which are derived from compounds of formula (I) by means of chemical modifications.


The expression “parasites” relates to unicellular eukaryotic organisms which are able to infect mammals and to survive and/or multiply in the infected mammal.

The present invention also relates to the use of at least one compound of the following general formula (I):

wherein R represents OH or NH₂,
or of precursors or derivatives thereof,

or of the pharmaceutically acceptable salts of said compound or of its precursors or derivatives,

for the manufacture of a medicament intended for the prevention or the treatment of parasitic diseases, in particular of protozoan parasitic diseases, more particularly of leishmaniosis, and especially for the prevention or the treatment of parasitic diseases occurring in immunodepressed patients.
As intended herein “parasitic diseases” relate to diseases caused by parasites as defined above.

Advantageously, the use of compounds of formula (I) for the prevention or the treatment of parasitic diseases is sound, since numerous bioavailability studies have assessed that high plasma concentrations of these compounds, e.g. 2,3 mM, could be achieved without serious side effects.

In a preferred embodiment of the above defined use of a compound of formula (I), R represents OH, said compound corresponding to niacin (vitamin B3), of the following formula (II):

![Chemical Structure](image)

In another preferred embodiment of the above defined use of a compound of formula (I), R represents NH$_2$, said compound corresponding to nicotinamide, of the following formula (III):

![Chemical Structure](image)

According to another preferred embodiment of the above defined use, the medicament is suitable for an administration of the compound of formula (I) by oral, intravenous, topical or intralesional route.

As intended herein “intralesional” means that the medicament is suitable to be administered at the sites of parasite-caused skin lesions of patients, in particular in case of Leishmania infections.

According to a particularly preferred embodiment of the above defined use, the medicament is suitable for an administration of the compound of formula (I) at a unit dose of about 10 mg to about 10 g, in particular of about 1 g to about 6 g.

According to another particularly preferred embodiment of the above defined use, the medicament is suitable for an administration of the compound of formula (I) at a dosage of about 5 mg/m$^2$/day to about 5 g/m$^2$/day, in particular of about 500 mg/m$^2$/day to about 3 g/m$^2$/day.
In another preferred embodiment of the above defined use, the compound of formula (I) in association with at least one anti-parasitic compound, such as a compound selected from:
miltefosin, antimonials, amphotericin B, benznidazol, nifurtimox, paromomycin, pentamidin and its derivatives, arsenic derivatives, melarsopol and difluoromethylornithin.

Advantageously, the association of a compound of formula (I) with an anti-parasitic compound has additive or synergic effects which enables a diminished administration of said anti-parasitic compound and thus diminished side effects.

The present invention also relates to a pharmaceutical composition comprising as active substances:

- at least one compound of the following general formula (I):

\[
\begin{array}{c}
\text{N} \\
- \text{R} \quad \text{O}
\end{array}
\]

wherein R represents OH or NH₂,

or precursors or derivatives thereof, or of the pharmaceutically acceptable salts of said compound or of its precursors or derivatives, and

- at least one anti-parasitic compound, such as a compound selected from:
miltefosin, antimonials, amphotericin B, benznidazol, nifurtimox, paromomycin, pentamidin and its derivatives, arsenic derivatives, melarsopol and difluoromethylornithin,

- in association with a pharmaceutically acceptable carrier.

In a particular embodiment of the above defined pharmaceutical composition, R represents OH, the compound of formula (I) hence corresponding to niacin (vitamin B3).

In another particular embodiment of the above defined pharmaceutical composition, R represents NH₂, the compound of formula (I) hence corresponding to nicotinamide.

According to a preferred embodiment, the above defined pharmaceutical composition is suitable for an administration by oral intravenous, topical or intralesional route.

According to another preferred embodiment, the above defined pharmaceutical composition is suitable for the administration of the compound of formula (I) at a unit dose of about 10 mg to about 10 g, in particular of about 1 g to about 6 g.

According to yet another preferred embodiment, the above defined pharmaceutical composition is suitable for the administration of the compound of formula (I) at a dosage of
about 5 mg/m²/day to about 5 g/m²/day, in particular of about 500 mg/m²/day to about 3 g/m²/day.

The present invention also relates to products containing:

- at least one compound of the following general formula (I):

\[
\begin{array}{c}
\text{N} \\
\text{R} \\
\end{array}
\]

(I)

wherein R represents OH or NH₂,

or precursors or derivatives thereof,

or the pharmaceutically acceptable salts of said compound or of its precursors or derivatives, in association with

- at least one anti-parasitic compound, such as a compound selected from:
miltêfôsin, antimonials, amphotericin B, benznidazol, nifurtimox, paromomycin, pentamidin
and its derivatives, arsenic derivatives, melarsopol and difluoromethylornithin,
as a combined preparation for simultaneous, separate or sequential use in the prevention or
the treatment of parasitic diseases, in particular of protozoan parasitic diseases, more
particularly of leishmaniosis, and especially for the prevention or the treatment of parasitic
diseases occurring in immuno-depressed patients.

In a preferred embodiment of the above defined products, R represents OH, the
compound of formula (I) hence corresponding to niacin (vitamin B₃).

In another preferred embodiment of the above defined product, R represents NH₂, the
compound of formula (I) hence corresponding to nicotinamide.

The present invention also relates to a method for the prevention or the treatment of
parasitic diseases, in particular of protozoan parasitic diseases, more particularly of
leishmaniosis, and especially for the prevention or the treatment of parasitic diseases
occurring in immuno-depressed patients, characterized in that at therapeutically effective
amount of at least one compound of the following general formula (I):

\[
\begin{array}{c}
\text{N} \\
\text{R} \\
\end{array}
\]

(I)

wherein R represents OH, NH₂,
or of precursors or derivatives thereof,
or of the pharmaceutically acceptable salts of said compound or of its precursors or derivatives,

is administered to a patient in need thereof.

In a preferred embodiment of the above defined method, R represents OH, the compound of formula (I) hence corresponding to niacin (vitamin B3).

In another preferred embodiment of the above defined method, R represents NH₂, the compound of formula (I) hence corresponding to nicotinamide.

According to a particular embodiment of the above defined method, the compound of formula (I) is administered by oral intravenous, topical or intralesional route.

According to another particular embodiment of the above defined method, the compound of formula (I) is administrated at a unit dose of about 10 mg to about 10 g, in particular of about 1 g to about 6 g.

According to yet another particular embodiment of the above defined method, the compound of formula (I) is administered at a dosage of about 5 mg/m²/day to about 5 g/m²/day, in particular of about 500 mg/m²/day to about 3 g/m²/day.

In another preferred embodiment of the above defined method, the compound of formula (I) is administered in association with at least one anti-parasitic compound, such as a compound selected from:
miltefosin, antimonials, amphotericin B, benznidazol, nifurtimox, paromomycin, pentamidin and its derivatives, arsenic derivatives, melarsoprol and difluoromethylornithin.

DESCRIPTION OF THE FIGURES

Figure 1A, Figure 1B, Figure 1C, and Figure 1D

Figure 1A represents the mean number of viable leishmania at the promastigote stage (vertical axis, x10⁶ / ml) as a function of time (horizontal axis, days), in presence of no nicotinamide (Nam) (control, white circles), 10 mM Nam (grey circles), or 20 mM Nam (black circles).

Figure 1B represents the mean number of viable axenically grown amastigotes leishmania (vertical axis, x10⁶ / ml) as a function of time (horizontal axis, days), in presence of no nicotinamide (Nam) (control, white squares), 10 mM Nam (grey squares), or 20 mM Nam (black squares).

Figure 1C represents the mean percentage of YOPRO-1-positive axenically grown amastigotes (i.e. apoptotic cells) (vertical axis) as a function of time (horizontal axis, days) in
presence of 25 mM Nam (squares), 50 mM Nam (diamonds), or 100 mM Nam (circles). Results are expressed as a mean of a triplicate experiment.

Figure 1D represents the parasitic index (vertical axis) as a function of NAm concentration (horizontal axis, mM). Results are representative of one over two experiments carried out in sextuplicate (one star (*) corresponds to P<0.05, two stars (**) correspond to P<0.005, and three stars (***) correspond to P<0.001).

**Figure 2A and Figure 2B**

Figure 2A represents the NAD-dependent deacetylase activity of the SIRT1 enzyme expressed as the fluorescence at 355 nm to fluorescence at 460 nm ratio (F355/F460) (vertical axis, counts) for (from left to right) a control assay without NAD (first histogram), a control assay with NAM (second histogram), an assay with 5 mM Nam (third histogram), an assay with 20 mM Nam (fourth histogram), an assay with 5 mM NAc (fifth histogram), an assay with 20 mM NAc (sixth histogram) and a control assay (seventh histogram).

Figure 2B represents the NAD-dependent deacetylase activity detected in leishmania expressed as the relative fluorescence at 355 nm to fluorescence at 460 nm ratio (F355/F460) (vertical axis, counts) for leishmania carrying an empty pTEX plasmid (first histogram), leishmania carrying a plasmid expressing LmSIR2 (pTEX-LmSIR2) (second histogram), leishmania carrying a plasmid expressing LmSIR2 (pTEX-LmSIR2) in presence of 5 mM NAM and leishmania carrying a plasmid expressing LmSIR2 (pTEX-LmSIR2) in presence of 50 µM pentamidine. Results are given as a mean of two duplicate experiments.

**Figure 3A and Figure 3B**

Figure 3A represents the percentage of growth inhibition (vertical axis) as a function of NAM concentration (horizontal axis, mM) for wild type (WT) leishmania (black histogram), leishmania carrying a pTEX-LmSIR2 plasmid (vertically hatched histogram) or leishmania carrying a control pTEX plasmid (horizontally hatched histogram).

Figure 3B represents the percentage of YOPRO-1 positive cells (vertical axis) as a function of NAM concentration (horizontal axis, mM) for wild type (WT) leishmania (black histogram), or leishmania carrying a pTEX-LmSIR2 plasmid (vertically hatched histogram).

Results are expressed as mean value of a quadruplicate experiments.
EXAMPLES

Example 1

The growth of *Leishmania* amastigotes and promastigotes was followed in axenic culture conditions in the presence or absence of NAm.

A cloned line of *L. infantum* (MHOM/MA/67/ITMAP-263) was used in all experiments. Each subculture was initiated at $5 \times 10^5$ parasites/ml of medium. Axenically grown amastigote forms of *L. infantum* were maintained at 37°C with 5% CO$_2$ by weekly subpassages in a cell-free medium called MAA/20 (medium for axenically grown amastigotes) in 25-ml flasks, as previously described (10). Promastigote forms were maintained at 26°C by weekly subpassage in SDM 79 medium supplemented with 10% foetal calf serum (FCS) and 100 units/ml penicillin and 100 µg/ml streptomycin. Nicotinamide (SIGMA, St Louis) was added at the appropriate concentration and the mean number of viable parasites determined using FACs analysis, as previously described (11).

As shown in **Figures 1A and 1B**, NAm strongly inhibited the proliferation of both promastigotes and amastigotes with promastigote forms showing less sensitivity to NAm than amastigotes. At 20 mM NAm, the capacity of axenic amastigotes to proliferate was virtually completely abrogated, whereas a delay in the growth of promastigotes occurred. The growth inhibitory activity of nicotinamide was not restricted to *L. infantum* since *L. amazonensis* amastigotes were also found to be sensitive to the activity of NAm. Furthermore, it was found that the acid derivative of NAm, the nicotinic acid (NicotAc or NAc), exerted a growth inhibitory activity towards *Leishmania* parasites, although at higher concentrations.

Example 2

The nature of NAm-induced amastigotes growth arrest was then investigated

Cells were seeded at $5 \times 10^5$ parasites/ml and NAm was added at various concentrations ranging from 25 to 100 mM. After 24, 48 and 72 hours of incubation aliquots ($10^6$ parasites) were collected, washed and incubated for 10 min with 10 µM of YOPRO-1, an apoptotic cell marker (Molecular probes). The mean percentage of YOPRO-1 positive cells was determined as previously described (9). At concentrations higher than 25 mM, NAm exerted a strong dose-dependent leishmanicidal activity against axenic amastigote, as demonstrated by the occurrence of YOPRO-1 positive cells. Maximal effect was observed after 3 days of culture in the presence of 100 mM of NAm (**Figure 1C**).
Having observed that NAm induced axenic amastigotes death, it was of interest to examine its effect on intracellular amastigotes proliferation.

In a first series of experiments, THP-1 monocytes were incubated during 3 days with various concentrations of NAm and the growth and viability of cells were recorded. Up to 10 mM of NAm, no effect on cell growth and viability was observed. In contrast, 20 mM NAm inhibited the proliferation of THP-1 monocyte by about 45% in agreement with the values recorded for other cell types: SupT1 and PBLs cells (6).

Thus, THP-1 differentiated macrophages were infected with stationary phase amastigotes at a host cell-parasite ratio of 5:1. After 4 hours, non adherent parasites were removed and nicotinamide was added to the medium at the appropriate concentration. After 3 days of incubation time, cells were fixed with methanol and stained with giemsa. Parasitic index PI (mean percentage of infected macrophages X number of amastigotes per macrophage) was determined. As shown in Figure 1D, NAm significantly inhibited the in vitro proliferation of intracellular amastigote. Maximal activity was observed with 10 mM of NAm. At this concentration a reduction of almost 70% of PI was observed. Interestingly, at low dosage 2.5 mM NAm is also able to significantly inhibit intracellular amastigote proliferation when compared to control non treated cultures (p<0.05).

Example 3

It has been recently demonstrated that NAm is a substrate of sir2-like enzymes in vitro (5). Therefore, complementary experiments were conducted in order to examine whether NAm could interfere with Leishmania deacetylase activity in vitro. To test this possibility, a commercially available “cyclex SIR2 assay kit” and SIRT1 as a standard enzyme (MBL, Japan) were used.

As shown in Figure 2A, the deacetylase activity of SIRT1 is strictly dependent on the presence of NAD, addition of 5 mM or 20 mM NAm in the assay almost completely abrogated the enzymatic activity of SIRT1. In contrast, 5 mM of NicotAc had no significant effect, in agreement with the data reported by other investigators (2), whereas 20 mM of NicotAc showed a significant effect.

Having established a standard inhibitory assay, the effect of NAm was then examined on the NAD-dependent deacetylase activity contained in Leishmania extracts from mutant parasites carrying extra copies of LmSIR2 gene (pTEX-LmSIR2) or empty plasmid DNA (pTEX) (11).
Briefly, 2 $10^5$ parasites were collected and washed two times with PBS 0.01M pH 7.2 and incubated in a lysis solution (100 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1% NP40, 5 $\mu$M Trichostatin A, pH 8.8), cells were then centrifuged for 20 min at 10 000 rpm at 4°C. Deacetylase activity in the presence or absence of 200 $\mu$M NAD was measured. Results are expressed as relative F355/F460 counts = F355/F460 counts in the presence of NAD - F355/F460 counts in the absence of NAD. This allowed to discriminate between fluorescence due to the action of LmSIR2 to fluorescence due to the presence of compounds which could interfere with the test. As shown in Figure 2B, parasites overexpressing LmSIR2 had more NAD-dependent deacetylase activity than parasites carrying the empty pTEX vector. 5 mM of NAm significantly inhibited the NAD dependent deacetylase activity detected in parasites overexpressing LmSIR2 (Figure 2B).

Example 4

In yeast and C. elegans, SIR2 is a limiting component of longevity (reviewed in 3) and NAm is able to accelerate yeast ageing by inhibiting SIR2 in vivo (2). In the protozoan parasite L. infantum, amastigotes carrying extracopies of LmSIR2 (LiSIR2) gene, when maintained under normal axenic culture conditions, showed striking increase in the survival due to an inherent resistance to apoptosis-like death, leading to a longer stationary phase of growth (11).

To further examine the possible correlation between the level of SIR2 expression and the sensitivity/resistance to NAm-induced Leishmania amastigotes death, NAm was added to cultures of mutant L. infantum amastigotes which overexpress LmSIR2 or carrying the empty pTEX plasmid as controls.

As shown in Figures 3A and 3B, adding extra copies of LmSIR2 to amastigotes did not confer significant resistance to NAm-induced death. Thus, even if the NAD-dependent deacetylase activity of LmSIR2 is readily inhibited by NAm and that LmSIR2 play a role in the survival of Leishmania amastigotes it should represent only one of the target of NAm mediated cell growth arrest.

The microbicidal mechanism of action of NAm is not currently known. Its activity may come to be understood as that of an indirect antimicrobial that has primarily a prohost effect. Among the reasons to suggest effect is the body of literature that reports an immunomodulatory role for nicotinamide in a wide variety of experimental systems (8, 7). Moreover, antioxidant and cryoprotective effect of NAm is well documented (12).
Thus, the present invention represents the first report showing the anti-parasitic activity of NAm. Furthermore, although NAm could inhibit the NAD-dependent deacetylase activity of SIR2-like enzymes, its main target in *Leishmania* seems not to be LmSIR2. In fact *Leishmania* possesses two other SIR2 related proteins whose function and localization are currently unknown. Implication of this protein family in the survival of *Leishmania* parasite has to be investigated. It can be hypothesized that one or all of them are essential for the parasite survival, and that their inhibition leads to the parasite death. Alternatively, other essential physiological functions would be the targets for NAm. The concentration of NAm and Nicotinic acid found to inhibit the intracellular growth of *Leishmania infantum* (IC50 inferior to 2.5 mM) are far higher than those found in whole blood (about 45 µM) but is closer to the plasmatic concentration of nicotinamide achievable (0.7 to 2.3 mM) in patient treated with accelerated radiotherapy for head and Neck cancer (1).

In conclusion, nicotinamide is an inexpensive and orally available agent without significant side effects. Since nicotinamide and its derivatives are potentially beneficial components, leishmaniasis will benefit from therapeutic use of such components, optionally in combination with anti-parasitic drugs.

References


CLAIMS

1. The use of at least one compound of the following general formula (I):

\[
\text{R} \quad \text{(I)}
\]

wherein \( \text{R} \) represents OH or NH\(_2\),

or of precursors or derivatives thereof,

or of the pharmaceutically acceptable salts of said compound or of its precursors or derivatives,

for the manufacture of a medicament intended for the prevention or the treatment of parasitic diseases, in particular of protozoan parasitic diseases, more particularly of leishmaniosis, and especially for the prevention or the treatment of parasitic diseases occurring in immunodepressed patients.

2. The use according to claim 1, of a compound of general formula (I), wherein \( \text{R} \) represents OH, said compound corresponding to niacin (vitamin B3), of the following formula (II):

\[
\text{R}\text{OH} \quad \text{(II)}
\]

3. The use according to claim 1, of a compound of general formula (I), wherein \( \text{R} \) represents \( \text{NH}_2 \), said compound corresponding to nicotinamide, of the following formula (III):

\[
\text{R}\text{NH}_2 \quad \text{(III)}
\]

4. The use according to any of claims 1 to 3, wherein the medicament is suitable for an administration by oral, intravenous, topical or intralesional route.
5. The use according to any of claims 1 to 4, wherein the medicament is suitable for an administration of the compound of formula (I) at a unit dose of about 10 mg to about 10 g, in particular of about 1 g to about 6 g.

6. The use according to any of claims 1 to 5, wherein the medicament is suitable for an administration of the compound of formula (I) at a dosage of about 5 mg/m²/day to about 5 g/m²/day, in particular of about 500 mg/m²/day to about 3 g/m²/day.

7. The use according to any of claims 1 to 6, wherein the compound of formula (I) is in association with at least one anti-parasitic compound, such as a compound selected from: miltefosin, antimonials, amphotericin B, benznidazol, nifurtimox, paromomycin, pentamidin and its derivatives, arsenic derivatives, melarsoprol and difluoromethylornithin.

8. A pharmaceutical composition comprising as active substances:

- at least one compound of the following general formula (I):

\[
\begin{align*}
\text{N} & \quad \text{R} \\
& \quad \text{O}
\end{align*}
\]

wherein R represents OH or NH₂, or precursors or derivatives thereof, or of the pharmaceutically acceptable salts of said compound or of its precursors or derivatives, and
- at least one anti-parasitic compound, such as a compound selected from: miltefosin, antimonials, amphotericin B, benznidazol, nifurtimox, paromomycin, pentamidin and its derivatives, arsenic derivatives, melarsoprol and difluoromethylornithin,
- in association with a pharmaceutically acceptable carrier.

9. A pharmaceutical composition according to claim 8, wherein R represents OH, the compound of formula (I) hence corresponding to niacin (vitamin B₃).

10. A pharmaceutical composition according to claim 8, wherein R represents NH₂, the compound of formula (I) hence corresponding to nicotinamide.
11. A pharmaceutical composition according to any of claims 8 to 10, suitable for an administration by oral, intravenous, topical or intralesional route.

12. A pharmaceutical composition according to any of claims 8 to 11, suitable for the administration of the compound of formula (I) at a unit dose of about 10 mg to about 10 g, in particular of about 1 g to about 6 g.

13. A pharmaceutical composition according to any of claims 8 to 12, suitable for the administration of the compound of formula (I) at a dosage of about 5 mg/m²/day to about 5 g/m²/day, in particular of about 500 mg/m²/day to about 3 g/m²/day.

14. Products containing
- at least one compound of the following general formula (I):

```
  \[ \text{R} \]
  \[ \text{O} \]
```

wherein R represents OH, NH₂, or precursors or derivatives thereof,

- or of the pharmaceutically acceptable salts of said compound or of its precursors or derivatives, in association with
- at least one anti-parasitic compound, such as a compound selected from: miltefosin, antimonials, amphotericin B, benznidazol, nifurtimox, paromomycin, pentamidin and its derivatives, arsenic derivatives, melarsoprol and difluoromethylornithin,

as a combined preparation for simultaneous, separate or sequential use in the prevention or the treatment of parasitic diseases, in particular of protozoan parasitic diseases, more particularly of leishmaniosis, and especially for the prevention or the treatment of parasitic diseases occurring in immunodepressed patients.

15. Products according to claim 14, wherein R represents OH, the compound of formula (I) hence corresponding to niacin (vitamin B3).

16. Products according to claim 14, wherein R represents NH₂, the compound of formula (I) hence corresponding to nicotinamide.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/455 A61P33/02

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 A61P

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

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

EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
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<td>1,2,4-6, 8-16</td>
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Further documents are listed in the continuation of box C.

* Special categories of cited documents :

*A* document defining the general state of the art which is not considered to be of particular relevance

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*L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

*O* document referring to an oral disclosure, use, exhibition or other means

*P* document published prior to the international filing date but later than the priority date claimed

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*\"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

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*\"O\"* document member of the same patent family

Date of the actual completion of the international search

30 September 2005

Date of mailing of the international search report

13/10/2005

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Authorized officer

Loher, F
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