Convention Application for a Patent

We, ROUSSEL-UCLA, a French Body Corporate,

of 35, Boulevard des Invalides, 75007 Paris, France.

hereby apply for the grant of a Patent

"NEW DERIVATIVES OF 4-OH QUINOLINE CARBOXYLIC ACID
SUBSTITUTED IN POSITION 2 BY A POSSIBLY ETHYLIZED OR ETHYLIZED DIHYDROXYL GROUP, THE PROCESS AND INTERMEDIATES FOR PREPARATION, THEIR APPLICATION AS MEDICAMENTS AND THE COMPOSITIONS CONTAINING THEM"

which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered 85-11389 for a patent or similar protection made in France on 25th July, 1985.

Our address for service is: CALLINAN AND ASSOCIATES Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Dated this 24th day of July, 1986.

ROUSSEL-UCLA
By its Patent Attorneys:
CALLINAN AND ASSOCIATES

To The Commissioner of Patents.
AUSTRALIA
Patents Act 1952-1973

Declaration in Support of
(a) A Convention Application
(b) An Application
for a Patent or Patent of Addition

In support of the Application/Convention Application made by
(c) ROUSSEL-UCLAF (hereinafter termed "the said Company")

for a patent/patent of addition for an invention entitled:
"NEW DERIVATIVES OF 4-OH QUINOLINE CARBOXYLIC ACID SUBSTITUTED IN
POSITION 2 BY A POSSIBLY ESTERIFIED OR ESTERIFIED DIHYDROXY GROUP,
THE PROCESS AND INTERMEDIATES FOR PREPARATION, THEIR APPLICATION
AS MEDICAMENTS AND THE COMPOSITIONS CONTAINING THEM"

I/we (to) Hubert Fritel,
of (t) 35, Boulevard des Invalides,
75007 Paris, France

do solemnly and sincerely declare as follows:-

1. (a) I am/we are the applicant(s) for the patent/patent of addition

or

(b) I am/we are authorised by the said Company

the applicant for the patent/patent of addition to make this declaration on its behalf.

2. (a) The basic application(s) as defined by Section 141 of the Act was/were made

in France on the 25th day of July 1985

by the said Company.

3. (a) I am/we are the actual inventor(s) of the invention

or

(b) I am/we are the actual inventor(s) of the invention referred to in the basic application.

FRANÇOIS CLEMENCE, of 2, rue Turgot, 75009 PARIS, France;
ODILE LE MARTRET, of 42, Avenue de Versailles, 75016 PARIS, France;
and FRANCOISE DELVILLE, of 48-50, avenue de la Dame Blanche,
94120 FONTEVRAULT-SOUS-BOIS, France

The said Company would, if a patent were to be granted

upon an application made by the said actual inventors,

be entitled to have the patent assigned to it.

Declared at Paris, France this 30th day of June 1986.

SIGN X

PAR PREPARATION: Hubert Fritel

THE BASIC APPLICATION REFERRED TO IN PARAGRAPH 2 OF THIS DECLARATION WAS THE FIRST APPLICATION MADE IN A CONVENTION COUNTRY IN RESPECT OF THE INVENTION THE SUBJECT OF THE APPLICATION.
Claim

1) Compounds with the formula (I):

\[
\begin{array}{c}
\text{OH} \\
\text{CONH-R}_1 \\
\text{CH-CH-R}_2 \\
\text{OR}_2 \quad \text{OR}_3 \\
\end{array}
\]

in which X in position 5, 6, 7 or 8 represents a hydrogen atom, a halogen atom, a linear or branched alkyl radical containing from 1 to 5 carbon atoms, a linear or branched alkoxy radical containing from 1 to 4 carbon atoms, a trifluoromethyl radical, a trifluoromethylthio radical or a trifluoromethoxy radical, R_1 represents a radical chosen from the following radicals: thiazolyl, 4,5-dihydrothiazolyl, pyridinyl, oxazolyl, isoxazolyl, imidazolyl, pyrimidyl and tetrazolyl, possibly substituted by an alkyl radical containing from 1 to 4 carbon atoms.
atoms or \( R_1 \) represents a phenyl radical possibly substituted by one or more radicals chosen from the group formed by the hydroxy radical, the alkyl radicals containing from 1 to 4 carbon atoms, the alkoxy radicals containing from 1 to 4 carbon atoms, the trifluoromethyl radical, the nitro radical and the halogen atoms, \( R_2 \) and \( R_3 \), identical or different, each represent a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms, an aryl radical, or a \(-\text{C}-R_5\) radical, \( R_5 \) representing an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, or \( R_2 \) and \( R_3 \) together form an acetonide residue, \( R_4 \) represents a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, as well as the salts of addition of the products with the formula (I) with acids and bases.

9) Preparation process for compounds with the formula (I) characterized in that a compound with the formula (II):

\[
\begin{align*}
\text{II} & \\
\text{R}_4 & \\
\text{R}_3 & \\
\text{X} & \\
\text{X'} & \\
\end{align*}
\]

in which \( X \) and \( R_4 \) have the significance already given, \( R'_3 \) is an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, \( X' \) is a halogen atom, is made to react
- either with a compound with the formula (III\(_A\)):

\[
\begin{align*}
\text{III}_A & \\
\text{CH}_2-\text{CONHR}_1 & \\
\end{align*}
\]

in which \( R_1 \) has the previous significance, so as to obtain a compound with the formula (IV):

\[
\begin{align*}
\text{IV} & \\
\text{R}_4 & \\
\text{R}_3 & \\
\text{X} & \\
\text{X'} & \\
\end{align*}
\]
To The Commissioner of Patents.

- or in the presence of a base with a compound with the formula (III_B):

\[
RO-\overset{\text{O}}{\text{C-CH}_2-\text{C-NH-R}_1}
\]

(III_B)

in which \( R_1 \) has the previous significance and \( R \) is an alkyl radial containing from 1 to 8 carbon atoms, so as to obtain a compound with the formula (A):

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \\
\text{CH} \\
\text{CO} \\
\text{NH} \\
\text{R}_1 \\
\hline
\text{X} \\
\text{X'} \\
\hline
\text{R}_3 \\
\end{array}
\]

(A)

which is decarbalkoxyxylized so as to obtain a compound with the formula (IV) previously defined, which compound with the formula (IV) thus obtained is cyclized in the presence of an alkaline agent so as to obtain a compound with the formula (V):

\[
\begin{array}{c}
\text{OH} \\
\text{CONH-R}_1 \\
\hline
\text{X} \\
\text{X'} \\
\hline
\text{R}_3 \\
\end{array}
\]

(V)

which is converted to a compound with the formula (VI):

\[
\begin{array}{c}
\text{OH} \\
\text{N-R}_1 \\
\hline
\text{CH-OR}_3' \\
\text{R}_4 \\
\end{array}
\]

(VI)
which compound with the formula (VI) is treated:
- either by an acid hydrolysis so as to obtain a compound with the
formula (I) in which $X$, $R_1$ and $R_4$ have the previous significance, $R_2$ is
a hydrogen atom and $R_3$ a radical containing from 1 to 4 carbon
atoms or an aryl radical, which is converted, if desired, into a
compound with the formula (I) in which $X$, $R_1$, $R_2$ and $R_4$ have the
significance given above and $R_3$ represents a hydrogen atom, then, if
desired, one or both hydroxyl functions are etherified or esterified,
so as to obtain a compound with the formula (I) in which $R_2$ and/or $R_3$,
identical or different, each represents an alkyl radical containing from
1 to 4 carbon atoms, an aryl radical or a $\text{C}-R_5$ group, as previously
defined, or, if desired, a compound with the formula (I) in which $R_2$
and $R_3$ represent a hydrogen atom is treated by acetone in the presence
of an acid agent, so as to obtain the corresponding acetonide,
- or by an acid with the formula $R_5\text{-COOH}$, $R_5$ having the previous
significance, so as to obtain a product with the formula (I) in which
$X$, $R_1$ and $R_4$ have the previous significances, $R_2$ represents a $\text{C}-R_5$
radical and $R_3$ an alkyl radical containing from 1 to 4 carbon atoms or
an aryl radical, which compounds with the formula (I) thus obtained are
converted, if desired, into salts by the action of an acid or a base.
10) Preparation process for compounds with the formula (I) as
previously defined, characterized in that a compound with the formula
$(\text{II}_A)$:

\[
\begin{align*}
\text{II}_A
\end{align*}
\]
$R_4$ having the previous significance, is submitted to the action of a compound with the formula (III$_A$):

$$\text{CH}_3-\text{CONH-}R_1 \quad (\text{III}_A)$$

in which $R_1$ retains its previous significance, so as to obtain a compound with the formula (IVA):

\[
\begin{align*}
\text{COCH}_2-\text{CONH-}R_1 \\
\text{NH-} \text{CO-} \text{CH=CH-}R_4 \\
\end{align*}

(IVA)
\]

which is cyclized in the presence of an alkaline agent so as to obtain a compound with the formula (VA):

\[
\begin{align*}
\text{OH} \\
\text{CONH-}R_1 \\
\text{CH=CH-}R_4 \\
\end{align*}

(VA)
\]

which is converted into a compound with the formula (I) in which $X$, $R_1$ and $R_4$ have the significance given previously and $R_2$ and $R_3$ represent a hydrogen atom, of which compound with the formula (I), one or both hydroxyl functions are possibly etherified or esterified, so as to obtain a compound with the formula (I) in which $R_2$ and/or $R_3$ represent either an alkyl radical containing from 1 to 4 carbon atoms, an aryl radical, or a $-\text{C-R}_5$ radical, $R_5$ having the significance already given, or compounds with the formula (I) in which $R_2$ and $R_3$ represent a hydrogen atom, which, if desired, is treated by acetone in the

The dioxan is eliminated under reduced pressure, the residue is taken up in a mixture of water and 2N hydrochloric acid, and the...
presence of an acid agent, so as to obtain the corresponding acetonide, then if necessary, the compounds with the formula (I) are converted into salts by the action of an acid or a base.

14) As new industrial compounds, compounds with the formulae (II), (IV), (A), (V) and (VI) as defined in claim 9.
15) As new industrial compounds, compounds with the formulae (IIA), (IVA), (VA) as defined in claim 10.
Australia

PATENTS ACT 1952

COMPLETE SPECIFICATION
(ORIGINAL)

FOR OFFICE USE

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NEW DERIVATIVES OF 4-OH QUINOLINE CARBOXYLIC ACID SUBSTITUTED IN POSITION 2 BY A POSSIBLY ETHERIFIED OR ESTERIFIED DIHYDROXYL GROUP, THE PROCESS AND INTERMEDIATES FOR PREPARATION, THEIR APPLICATION AS MEDICAMENTS AND THE COMPOSITIONS CONTAINING THEM

The following statement is a full description of this invention, including the best method of performing it known to me:

* Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.
The present invention is concerned with new derivatives of 4-OH quinoline carboxylic acid substituted in position 2 by a group containing two hydroxyl functions, possibly etherified or esterified, their preparation processes, the new intermediates obtained, their use as medicaments and the compositions containing them.

The subject of the invention is compounds with the formula (I):

\[
\text{OH} \quad \text{CONH-R}_1 \\
\text{X} \quad \text{CH} - \text{CH} - \text{R}_4 \\
\text{OR}_2 \quad \text{OR}_3
\]

in which X in position 5, 6, 7 or 8 represents a hydrogen atom, a halogen atom, a linear or branched alkyl radical containing from 1 to 5 carbon atoms, a linear or branched alkoxy radical containing from 1 to 4 carbon atoms, a trifluoromethyl radical, a trifluoromethylthio radical or a trifluoromethoxy radical, R₁ represents a radical chosen from the radicals: thiazolyl, 4,5-dihydrothiazolyl, pyridinyl, oxazolyl, isoxazolyl, imidazolyl, pyrimidyl and tetrazolyl, possibly substituted by an alkyl radical containing from 1 to 4 carbon atoms or R₁ represents a phenyl radical, possibly substituted by one or more
radicals chosen from the group formed by the hydroxy radical, alkyl radicals containing from 1 to 4 carbon atoms, alkoxy radicals containing from 1 to 4 carbon atoms, the trifluoromethyl radical, the nitro radical, and halogen atoms, R₂ and R₃, identical or different, each represents a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms, an aryl radical, or a -C-R₅ radical, R₅ representing an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, or R₂ and R₃ together form an acetonide residue, R₄ represents a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, or R₁ represents a substituted phenyl radical, it is preferred to be a phenyl radical substituted by at least one radical chosen from the group formed by the hydroxy radical, the methyl and ethyl radicals, the methoxy- and ethoxy radicals, the trifluoromethyl radical, the nitro radical and the chlorine atom.

When X represents a halogen atom, it is preferred to be a chlorine atom.

When X represents an alkyl radical, it is preferred to be one of the following radicals: methyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl or isobutyl.

When X represents an alkoxy radical, it is preferred to be the methoxy, ethoxy or n-propoxy radical.

When R₄ represents a heterocyclic radical substituted by an alkyl radical, it is preferred to be a heterocyclic radical substituted by a methyl or ethyl radical.

When R₁ represents a substituted phenyl radical, it is preferred to be a phenyl radical substituted by at least one radical chosen from the group formed by the hydroxy radical, the methyl and ethyl radicals, the methoxy- and ethoxy radicals, the trifluoromethyl radical, the nitro radical and the chlorine atom.

When R₂ or R₃ or R₄ represents an alkyl radical, it is preferred to be the methyl, ethyl, propyl, isopropyl, butyl or isobutyl radical.

When they represent an aryl radical, this is preferably a phenyl radical.

When R₂ or R₃ represents a -C-R₅ radical, R₅ is preferably a methyl, ethyl, n-propyl or phenyl radical.

Among the salts of addition with acids, there can be cited those formed with mineral acids such as hydrochloric, hydrobromic, sulphuric
or phosphoric acid as well as those formed with sulphonic acids such as alkyl or arylsulphonic acids, for example, methanesulphonic or paratoluencesulphonic acid.

Among the salts of addition with bases, there can be cited those formed with alkali metals such as sodium and potassium and amines, for example, trimethylamine or dimethylamine.

The subject of the invention is, in particular, compounds for which X is in position 8, as well as their salts of addition with acids and bases and those for which X represents a trifluoromethyl radical, as well as their salts of addition with acids and bases.

The subject of the invention is also, in particular, compounds for which X is in position 7 and represents a chlorine atom, as well as their salts of addition with acids and bases.

The subject of the invention is, more particularly, compounds for which $R_1$ represents the thiazolyl radical, as well as their salts of addition with acids and bases, and those for which $R_2$ and $R_3$ represent a hydrogen atom and $R_4$ represents a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, as well as their salts of addition with acids and bases.

There are held in regard more particularly the products described in the examples and more particularly:

- 2-(1,2-dihydroxyethyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its salts of addition with acids and bases,

- 2-(1,2-dihydroxy-propyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its salts of addition with acids and bases,

- 2-[1,2-bis{1-oxopropoxy}ethyl]-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its salts of addition with acids and bases.

The subject of the invention is also a preparation process for compounds with the formula (I) characterized in that a compound with the formula (II):
in which \(X\) and \(R_4\) have the significance already given, \(R'_3\) is an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, \(X'\) is a halogen atom, is made to react.

- either with a compound with the formula (III\(_A\)):

\[
\text{CH}_3-\text{CONH}-R_1 \quad \text{(III\(_A\))}
\]

in which \(R_1\) has the previous significance, so as to obtain a compound with the formula (IV):

\[
\text{COCH}_2-\text{CONH}-R_1
\]

\[
\text{X} \quad \text{NH} - \text{C} - \text{CH} - \text{CH} - \text{OR'}_3 \quad \text{O} \quad X' \quad R_4
\]

- or in the presence of a base with a compound with the formula (III\(_B\))

\[
\text{RO-C-CH}_2-\text{C-NH}-R_1 \quad \text{(III\(_B\))}
\]

in which \(R_1\) has the previous significance and \(R\) is an alkyl containing from 1 to 8 carbon atoms, so as to obtain a compound with the formula (A):

\[
\text{CO}_2\text{R}
\]

\[
\text{X} \quad \text{NH} - \text{CO} - \text{CH} - \text{CO-NH}-R_1
\]

\[
\text{X} \quad \text{NH} - \text{CO} - \text{CH} - \text{CH} - \text{OR'}_3 \quad \text{X'} \quad R_4
\]
which is decarbalkoxylated so as to obtain a compound with the formula (IV) previously defined, which composition with the formula (IV) thus obtained is cyclized in the presence of an alkaline agent so as to obtain a compound with the formula (V):

\[ \text{OH} \quad \text{CONH-}R_1 \]

\[ \text{CH-CH-OR'} \]

\[ X \quad X' \]

\[ R_3 \]

\[ R_4 \]

which is converted into a compound with the formula (VI):

\[ \text{OH} \quad \text{N-R}_1 \]

\[ \text{CH-OR'} \]

\[ R_4 \]

which compound with the formula (VI) is treated:

- either by an acid hydrolysis agent so as to obtain a compound with the formula (I) in which \( X, R_1 \) and \( R_4 \) have the previous significance, \( R_2 \) is a hydrogen atom and \( R_3 \) is an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, which is converted, if desired, into a compound with the formula (I) in which \( X, R_1, R_2 \) and \( R_4 \) have the significance given above and \( R_3 \) represents a hydrogen atom, then, if desired, one or both of the hydroxyl functions are etherified or esterified, so as to obtain a compound with the formula (I) in which \( R_2 \) and/or \( R_3 \), identical or different, each represents an alkyl radical containing from 1 to 4 carbon atoms, an aryl radical or a \(-\text{C-}R_5\) group, as previously defined, or, if desired, a compound with the formula (I) in which \( R_2 \) and \( R_3 \) represent a hydrogen atom is treated by an acetone in the presence of an acid agent, so as to obtain the corresponding acetonide,

- or by an acid with the formula \( R_5\text{-COOH} \), \( R_5 \) having the previous
significance, so as to obtain a product with the formula (I) in which X, R₁ and R₄ have the previous significance, R₂ represents a C₂H₅ radical and R₃ represents an alkyl radical containing from 1 to 4 carbon atoms, or an aryl radical;

then the compounds with the formula (I) thus obtained are converted, if desired, into salts by the action of an acid or of a base.

In the preferred conditions for putting the invention into operation, the process described above is carried out in the following way:

- X' is a chlorine atom in the compound with the formula (II).
- the reaction between the compound with the formula (II) and the compound with the formula (IIIA) takes place in the presence of an organo-lithium compound or a lithium amide, for example, in the presence of a butyl-lithium or a lithium diisopropylamide; this reaction takes place at a low temperature, of the order of -70°C.

When the compound with the formula (II) reacts with the compound with the formula (III), the base used is, for example, sodium hydroxide and the reaction takes place at ambient temperature.

The operating conditions concerning this stage of the process and those of the decarbalkoxylation of the compound with the formula (A) are similar to those described in European Patent No 0141713.

The cyclization of the compound with the formula (IV) is carried out in the presence of an alkaline agent, such as a hydride or an alkaline carbonate or an amine, for example, in the presence of the following: sodium hydride, sodium or potassium carbonate, piperidine, 4-aminopyridine, dimethyl aminopyridine, triethylamine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,4-diazabicyclo[2,2,2]octane or 1,5-diazabicyclo[5,4,0]undec-5-ene.

This cyclization is carried out in the presence of a solvent, which is preferably tetrahydrofuran, but other solvents like dimethylformamide, benzene, or toluene can also be used.

Acid hydrolysis of the compound with the formula (VI) is carried out preferably by hydrochloric acid, but other acids can be used, such as sulphuric acid.

The transition of a compound with the formula (I), in which R₃ is
an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, to a compound with the formula (I), in which $R_3$ represents a hydrogen atom, can for example be carried out in the presence of trimethylsilane iodide or boron tribromide.

The operation can be carried out in a solvent such as acetonitrile or methylene chloride.

The reactions of etherification or esterification of the products with the formula (I) having one or two hydroxyl functions is carried out by the usual methods.

The acid agent which is made to react during the formation of the acetamide is for example paratoluensulphonic acid.

The invention is also concerned with another preparation process for compounds with the formula (I) as previously defined, characterized in that a compound with the formula (IIA):

(IIA)

in which $R_3$ has the previous significance, is submitted to the action of a compound with the formula (IIIA)

(IIIA)

in which $R_4$ keeps its previous significance, so as to obtain a compound with the formula (IVA):

(IVA)

which is cyclized in the presence of an alkaline agent so as to obtain a compound with the formula (VA):

(VA)
which is converted into a compound with the formula (I) in which X, R₁
and R₄ have the significance previously given and R₂ and R₃ represent a
hydrogen atom, of which compound with the formula (I), one or both
hydroxyl functions are possibly etherified or esterified, so as to
obtain a compound with the formula (I) in which R₂ and/or R₃ represent
either an alkyl radical containing from 1 to 4 carbon atoms, an aryl
radical, or a -C-R₅ radical, as previously defined, or compounds with
the formula (I) in which R₂ and R₃ represent a hydrogen atom, which, if
desired, are treated by acetone in the presence of an acid agent, so
as to obtain the corresponding acetonide, then, if desired, the
compounds with the formula (I) are converted into salts by the action
of an acid or of a base.

The transition of the compound with the formula (IIₐ) to the
compound with the formula (IVA), then the cyclization of this into a
compound with the formula (VA) takes place under the same preferential
conditions as those described previously for the first process of the
invention.

The conversion of the product with the formula (VA) into a
dihydroxylized product with the formula (I) takes place preferably by
the action of potassium permanganate, in the presence of triethyl
benzyl ammonium chloride.

The etherification or esterification of one or both hydroxyl
functions of the product with the formula (I) takes place by the usual
methods.

The acid agent which is made to react during the formation of
acetonide is for example, as previously, paratoluene sulphonic acid.

The compounds with the formula (I), as defined above, as well as
their salts of addition with acids and bases present useful pharmacological properties. These are compounds endowed with analgesic and anti-inflammatory properties, which are very active in cases of chronic inflammation.

These properties justify their therapeutic use, and the subject of the invention is also products with the formula (I), as well as their pharmacetically acceptable salts of addition with acids and bases, as medicaments.

The subject of the invention is more particularly, as medicaments:

- 2-(1,2-dihydroxy-ethyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its pharmaceutically acceptable salts of addition with acids and bases, and
- 2-(1-2-dihydroxy-propyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its pharmaceutically acceptable salts of addition with acids and bases.
- 2-[1,2-bis(1-oxopropoxy)-ethyl]-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its salts of addition with acids and bases.

The medicaments which are the subject of the present invention can be recommended in the treatment of degenerative inflammatory illnesses such as osteoarthrosis, the various collagenoses (tendinitis, etc.), rheumatic illnesses (rheumatoid polyarthritis, ankylosing spondylarthitis), as well as in the treatment of other illnesses of auto-immune nature such as disseminated lupus erythematosus, glomerulonephritis, multiple sclerosis.

The medicaments which are the subject of the invention can also be used in the treatment of muscular, nervous or articular algias, toothache, migrains, shingles, and also as a complementary treatment in infectious and feverish states.

The invention extends to pharmaceutical compositions containing as active principle the medicaments defined above.

These pharmaceutical compositions can be administered by oral or rectal route, by parenteral route or by local route through topical application to the skin and the mucosa.

These compositions can be solid or liquid and come in the pharmaceutical forms currently used in human medicine as, for example, plain
or sugar-coated tablets, capsules, granules, suppositories, injectable preparations, ointments, creams, gels and preparations in aerosols; they are prepared according to the usual methods. The active principle can be incorporated with the excipients usually employed in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, the various moistening, dispersing or emulsifying agents and preservatives.

The posology varies in particular as a function of the administration route, the affection treated and the subject concerned. For example, with an adult, it can vary between 20 mg and 2 g of active principle per day, by oral route.

The products with the formula (II) and (II\textsubscript{A}) can be prepared by the process described in the European Patent No 40573.

The products with the formulae (II), (II\textsubscript{A}), (IV), (IVA), (V), (VA), (A) and (VI) are new chemical products; the subject of the invention is therefore these products as new industrial products.

The following examples illustrate the invention without however limiting it.
Example 1: 4-hydroxy-2-[(1-hydroxy-2-methoxy-ethyl)-N-(2-thiazolyl)-
-8-(trifluoromethyl)-3-quinoline carboxamide.

Stage A: 2-[(2-chloro-3-methoxy-1-oxopropyl)amino]3-oxo-N-
-(2-thiazolyl)-3-trifluoromethyl benzene propanamide.

At 0°C, 350 cm³ of n-butyl lithium in solution in hexane is
introduced into a suspension of 34 g of 2-acetylamino thiazole in
1100 cm³ of tetrahydrofuran. After cooling this to -70/75°C, there
is added to it a solution of 36.78 g of 2-(1-chloro-2-methoxyethyl)-
-8-trifluoromethyl-4-H-3,1-benzoxazine-4-one (product prepared as at
stage A of example 12 of the European patent 40 573, starting with
2-chloro-3-methoxy propanoic acid (Chem.Ber. 92 1 081-7 (1959), and
2-amino-3-trifluoromethyl benzoic acid in 250 cm³ of tetrahydrofuran).

The solution obtained is poured into an aqueous solution of
hydrochloric acid and extracted with ether. The extracts are washed
with N hydrochloric acid, then with water, dried and concentrated
under reduced pressure.

The residue is triturated in ether, separated, washed with ether,
dried under reduced pressure, and 33.35 g of the expected product is
obtained, melting at 190°C.

Analysis: C₁₇H₁₅N₃O₄F₃SCl : 449.845
Calculated: C% 45.39 H% 3.36 N% 9.34 F% 12.67 Cl% 7.88 S% 7.13
Found: 45.6 3.4 9.0 12.4 7.8 7.1

Stage B: 2-(1-chloro-2-methoxyethyl)-4-hydroxy-N-(2-thiazolyl)-
-8-trifluoromethyl-3-quinoline carboxamide.

33.35 g of the product from stage A and 10 g of dimethylamino-
pyridine are heated to reflux for 30 minutes in 300 cm³ of tetra-
hydrofuran.

After cooling to ambient temperature, this is poured into a
mixture of water and 2N hydrochloric acid and extracted with ethyl
acetate. The extracts are washed, dried, and concentrated under
reduced pressure. The residue is triturated in ether, then separated
washed, dried under reduced pressure at 60°C, and 28.2 g of the
expected product is obtained, melting at 186°C.

Stage C: 1,3-dihydro-3-(methoxymethyl)-1-[(2-thiazolyl)-imino]-
-5-trifluoromethylfuro[3,4,b]quinolin-9-ol.

23.9 g of the product from stage B and 7.7 g of potassium
tertbutylate are taken to reflux for 30 minutes in 550 cm³ of dioxan.
The dioxan is eliminated under reduced pressure, the residue is taken up in a mixture of water and 2N hydrochloric acid, and the insoluble matter is extracted with a mixture of ethyl acetate and tetrahydrofuran (80/20). The organic phase is washed with water, and the aqueous phases are put together.

The aqueous phase is neutralized by the addition of a saturated aqueous solution of sodium bicarbonate, and is then extracted with ethyl acetate. The extracts are washed with water, dried and concentrated under reduced pressure. 22 g of the expected product is obtained.

Stage D: 4-hydroxy-2-(1-hydroxy-2-methoxyethyl)-N-(2-thiazolyl)-8-(trifluoromethyl)-3-quinoline carboxamide.

A solution containing 22 g of the product from stage C, 70 cm$^3$ of water and 130 cm$^3$ of concentrated hydrochloric acid is agitated for 16 hours at ambient temperature.

The precipitate formed is separated and washed with water, then taken up in 200 cm$^3$ of water and extracted with a mixture of ethyl acetate and tetrahydrofuran (50/50). The organic phase is washed with water, dried and concentrated under reduced pressure, so obtaining 15 g of product which is purified by chromatography on silica under pressure (eluent: ethyl acetate). 12.5 g of product is obtained which is triturated in ether, separated, washed with ether and dried under reduced pressure at 100$^\circ$C.

11.83 g of the expected product is obtained, which melts at 216-218$^\circ$C.

Analysis: $C_{17}H_{14}O_4N_3F_3S_4$ : 413.384
Calculated: C% 49.39  H% 3.41  N% 10.16  F% 13.76  S% 7.76
Found: 49.5 3.4 10.2 13.9 7.7

Example 2: 2-(1,2-dihydroxyethyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide.

Under an inert atmosphere, 6.7 cm$^3$ of trimethylsilane iodide is introduced slowly into a mixture containing 6.5 g of the product from example 1 and 120 cm$^3$ of acetonitrile; after agitating for 16 hours at ambient temperature, the mixture is poured on to 400 cm$^3$ of water to which is added 50 cm$^3$ of sodium bisulphate.

The suspension obtained is agitated for 45 minutes at ambient temperature, 100 cm$^3$ of ethyl ether is added, with agitation for a
further 30 minutes. After separating, washing with water and drying under reduced pressure at 75°C for 16 hours, 5.9 g of product is obtained which is dissolved in 75 cm³ of dimethylformamide, then filtered. Ether is added to the filtrate, which is then cooled, and the crystals obtained are separated, washed with ether and dried under reduced pressure at 120°C. 4.86 g of the expected product is obtained, which melts at 255°C.

Analysis: C₁₆H₁₁N₃F₃O₄ S: 399.356
  C%  H%  N%  F%  S%
Calculated: 48.12 3.03 10.52 14.27 8.03
Found: 48.0 3.0 10.4 14.1 8.0

Example 3: 2-(1,2-dihydroxypropyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide.

Stage A: 3-oxo-2-[(1-oxo-2-butenyl)-amino]-N-(2-thiazolyl)-8-trifluoromethyl benzene propanamide.
The operation is done as at stage A of example 1, starting with 19.44 g of 2-acetylamino thiazole and 17.3 g of 2-(1-propenyl)-8-trifluoromethyl-4-H-3,1-benzoazin-4-one; the product is prepared as at stage A of example 12 of the European patent 40,573, starting with 2-amino-trifluoromethyl benzoic acid and crotonyl chloride.

19.03 g of the expected product is obtained, melting at 206-208°C.

Stage B: 4-hydroxy-2-(1-propenyl)-N-(2-thiazolyl)-8-(trifluoromethyl)-3-quinoline carboxamide.
17.5 g of the product from stage A in solution in 175 cm³ of dimethyl acetamide is added to a mixture containing 2.11 g of sodium hydride dispersed at 50% in oil and 100 cm³ of dimethyl acetamide. The whole is heated to 120°C and kept for 30 minutes at that temperature. The solution is cooled, then poured on to a mixture of water and 2N hydrochloric acid. The precipitate obtained is es-ored, washed with water and dried under reduced pressure at 80°C, so obtaining 16.7 g of the expected product, which melts at 265°C.

Stage C: 2-(1,2-dihydroxypropyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide.
A mixture containing 12.2 g of product from stage B in 300 cm³ of methylene chloride, 9.16 g of methylbenzyl ammonium chloride and 6.32 g of potassium permanganate is agitated for 1 hour
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150 cm$^3$ of water, and then 150 cm$^3$ of a solution of sodium bisulphite are added; the insoluble matter obtained is separated, washed with water, and partially dissolved in tetrahydrofuran.

The organic solution is dried and concentrated under reduced pressure, and 5.8 g of crude product is obtained, which is dissolved in warm dimethylformamide. The solution obtained is filtered and concentrated to about 40 cm$^3$, then 60 cm$^3$ of ethyl ether is added to it. After cooling, the crystals obtained are separated, washed with ether, dried under reduced pressure at 100$^\circ$ C, and the product obtained is dissolved in tetrahydrofuran.

The solution is filtered, concentrated under reduced pressure, and the residue is triturated in ethyl acetate, then separated, washed, dried under reduced pressure at 100$^\circ$ C, and 3.04 g of the expected product is obtained, which melts at 275$^\circ$ C.

Analysis:

C$_{17}$H$_{14}$N$_3$O$_4$F$_4$: 413,384
Calculated: C% 49.39, H% 3.41, N% 10.16, F% 13.79, S% 7.76
Found: 49.3, 3.3, 10.1, 14.1, 7.8

Example 4: 2-[1,2-bis(1-oxopropoxy)ethyl]-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinolone carboxamide

At 20$^\circ$ C, 2.15 g of the product obtained at example 2, 70 cm$^3$ of methylene chloride and 0.96 cm$^3$ of propionic acid are mixed together. After 5 minutes, 2.9 g of dicyclohexylcarbodiimide, and then 2.4 g of dimethylaminopyridine are added, and the whole is kept under agitation for 1 hour 30 minutes, then filtered. The filtrate is washed with a saturated aqueous solution of sodium carbonate, with an aqueous solution of hydrochloric acid and then with water. The residue, after drying and evaporating to dryness, is re-crystallized from acetonitrile. 1.34 g of the expected product is obtained, m.p. 206$^\circ$ C.

Analysis:

C$_{22}$H$_{20}$F$_3$N$_3$O$_6$: 511.479
Calculated: C% 51.66, H% 3.94, N% 8.22, S% 6.27, F% 11.14
Found: 51.7, 3.9, 8.1, 6.2, 11.1

Example 5: 2-[2-methoxy-1-(1-oxopropoxy)ethyl]-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinolone carboxamide.

The operation is done in a similar way to that described at example 4, using at the start 2 g of the product obtained at example.
1. 0.4 cm$^3$ of propionic acid, 1.2 g of dicyclohexylcarbodiimide and 0.3 g of dimethylaminopyridine. After recrystallization from ethyl acetate, 1 g of the expected product is obtained, m.p. = 190$^\circ$ C.

Analysis: $C_{20}H_{18}F_3N_3O_5S : 469.442$
Calculated: C% 51.17 H% 3.87 F% 12.14 N% 8.95 S% 6.83

Example 6: 2-[1,2-(dibenzoyloxy)]ethyl]-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide.

The operation is done in a similar manner to that described in example 4, using at the start 0.5 g of the product obtained in example 2, 0.37 g of benzoic acid, 0.67 g of dicyclohexylcarbodiimide and 0.075 g of dimethylaminopyridine. 0.8 g of crude product is obtained, which is dissolved in 15 cm$^3$ of tetrahydrofuran, and to this is added 0.3 cm$^3$ of a 5.7 N solution of hydrochloric acid in ethanol. The crystals formed are separated and dissolved in a mixture of ethyl acetate and water, then extracted with ethyl acetate, dried and concentrated to dryness. The residue is dissolved in tetrahydrofuran, ethyl ether is added, followed by cooling to 0$^\circ$ C for 2 hours. The crystals are separated and dried, and 0.33 g of the expected product is obtained. m.p. = 240$^\circ$ C.

Analysis: $C_{30}H_{20}F_3N_3O_6S : 607.658$
Calculated: C% 49.69 H% 3.34 N% 8.69 F% 11.79 S% 6.8

Example 7: 2-[1,2-(diazexyl)ethyl]-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide.

The operation is done similarly to that described in example 4, using at the start 2 g of the product obtained in example 2, 0.7 cm$^3$ of acetic acid, 2.7 g of dicyclohexylcarbodiimide and 0.3 g of dimethylaminopyridine. 0.9 g of crude product is obtained, containing a little dicyclohexylurea which is eliminated by washing with tetrahydrofuran, by recrystallizing from dimethylformamide, and then by formation of the hydrochloride in tetrahydrofuran to which a solution in ethanol of hydrochloric acid is added. After recrystallizing from acetic acid, 0.38 g of the expected product is obtained. m.p. = 270$^\circ$ C.

Analysis: $C_{20}H_{18}F_3N_3O_5S : 483.432$
Calculated: C% 49.69 H% 3.34 N% 8.69 F% 11.79 S% 6.53

Example 8: 2-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide.
3 g of the product obtained at example 2 is put into suspension in 80 cm³ of acetone, and taken to reflux; 0.3 g of paratoluene sulphonamide is added, and the whole is kept at reflux for 5 hours. After cooling to 20°C, the solids formed are separated and dried under reduced pressure, then dissolved in 100 cm³ of tetrahydrofuran by warming this to 40°C. After filtering, concentrating to half volume, cooling to 20°C, and adding ethyl ether, the crystals are separated, washed with ethyl ether and dried.

1.2 g of the expected product is obtained, m.p. = 250°C.

Analysis: C₁₉H₁₆F₃N₅O₄S : 439.417
Calculated: C% 51.94  H% 3.67  N% 9.56  F% 12.97  S% 7.30
Found: C% 51.8  H% 3.5  N% 9.4  F% 12.8  S% 7.1

Example 9: 4-hydroxy-2-(1-hydroxy-2-methoxyethyl)-N-(2-thiazolyl)-7-chloro-3-quinoline carboxamide.

The operation is done in a similar manner to that described at stage A of example 1, using at the start 2-(1-chloro-2-methoxyethyl)-7-chloro-3-quinoline carboxamide. The expected product is obtained, melting at 180°C, with a yield of 76%.

Stage B: 2-(1-chloro-2-methoxyethyl)-4-hydroxy-N-(2-thiazolyl)-7-chloro-3-quinoline carboxamide.

The operation is done in a similar manner to that described at stage C of example 1. The product is used for the following stage without being isolated.

Stage C: 1,3-dihydro-3-(methoxymethyl)-1-[(2-thiazolyl)imino]-6-chloro-3-quinoline-9-ol.

The operation is done similarly to that described at stage C of example 1, without having intermediates isolated the quinoline of stage B above, and operating at reflux of the tetrahydrofuran for 24 hours. The expected product is obtained with a yield of 65%.

Stage D: 4-hydroxy-2-(1-hydroxy-2-methoxyethyl)-N-(2-thiazolyl)-7-chloro-3-quinoline carboxamide.
The operation is done in a similar manner to that described at stage D of example 1, maintaining under agitation in 6N hydrochloric acid for 36 hours. The expected product is obtained, m.p. > 270° C.

Example 10: 2-(1,2-dihydroxyethyl)-4-hydroxy-N-(2-thiazolyl)-7-chloro-3-quinoline carboxamide.

Example of pharmaceutical composition:
Example 11:
Tablets have been prepared answering to the following formula:
Product of example 2 ........................................... 50 mg
Excipient q.s. for a tablet finished at ..................... 350 mg
(detail of excipient: lactose, talc, amidon, magnesium stearate).
Pharmacological Study.

Anti-inflammatory activity: chronic arthritis with adjuvant (preventive treatment)

The injection of an adjuvant of Freund type in a hind paw of a rat causes the rapid appearance of a primary inflammatory lesion in this paw, then, after a latency period of 13 to 15 days, the activating of a secondary arthritis affecting in particular the other hind paw. The test is carried out on male rats, aged from 42 to 50 days, which receive an intraplantar injection of 0.1 ml of "Freund" type adjuvant (suspension in vaseline oil of 6 mg per ml of killed mycobacterium butyricum).

The animals receive the product under study by oral route from day 0 (day when the adjuvant is injected) up to the day before they are killed, which is done on day 17. Control a thritic animals and normal control animals receive only the vehicle. The criteria of evaluation of the activity of the substances studied are the increases in volume of the injected hind paws (primary and secondary inflammation) and those not injected (secondary inflammation) in comparison with the mean volume of the corresponding paws of the controls.

The DA50 is determined, that is to say, the dose which reduces by 50% the increases in volume of the hind paws of the treated animals in comparison with the control animals.

The DA50 found are about 2 mg/Kg, 0.7 mg/Kg, 3 mg/Kg, 1 mg/Kg, and 5 mg/Kg respectively for the products of examples 1, 2, 3, 4 and 5.
- or by an acid with the formula $R_5$-COOH, $R_5$ having the previous.
The claims defining the invention are as follows:

1) Compounds with the formula (I):

![Chemical Structure](image)

in which X in position 5, 6, 7 or 8 represents a hydrogen atom, a halogen atom, a linear or branched alkyl radical containing from 1 to 5 carbon atoms, a linear or branched alkoxy radical containing from 1 to 4 carbon atoms, a trifluoromethyl radical, a trifluoromethylthio radical or a trifluoromethoxy radical, R₁ represents a radical chosen from the following radicals: thiazolyl, pyridinyl, oxazolyl, isoxazolyl, imidazolyl, pyrimidyl and tetrazolyl, possibly substituted by an alkyl radical containing from 1 to 4 carbon atoms or R₁ represents a phenyl radical possibly substituted by one or more radicals chosen from the group formed by the hydroxy radical, the alkyl radicals containing from 1 to 4 carbon atoms, the alkoxy radicals containing from 1 to 4 carbon atoms, the trifluoromethyl radical, the nitro radical and the halogen atoms, R₂ and R₃ identical or different, each represent a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms, an aryl radical, or a \(-\text{C}_\text{R}_\text{g}\) radical, R₅ representing an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, or R₂ and R₃ together form an acetonide residue, R₄ represents a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, as well as the salts of addition of the products with the formula (I) with acids and bases.

2) Compounds with the formula (I), as defined in claim 1, for which X is in position 8, as well as their salts of addition with acids and bases.

3) Compounds with the formula (I), as defined in claim 1 or 2, for which X represents a trifluoromethyl radical, as well as their salts of addition with acids and bases.
addition with acids and bases.

4) Compounds with the formula (I), as defined in claim 1, for which X is in position 7, as well as their salts of addition with acids and bases.

5) Compounds with the formula (I), as defined in claim 1 or 4, for which X represents a chlorine atom, as well as their salts of addition with acids and bases.

6) Compounds with the formula (I), as defined in any one of the claims 1 to 5, for which R represents the thiazolyl radical, as well as their salts of addition with acids and bases.

7) Compounds with the formula (I) as defined in any one of the claims 1 to 6, for which R and R represent hydrogen atom and R represents a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, as well as their salts of addition with acids and bases.

8) Any one of the compounds with the formula (I) of which the names follow:

- 2-(1,2-dihydroxy-ethyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its salts of addition with acids and bases.

- 2-(1,2-dihydroxy-propyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its salts of addition with acids and bases.

- 2-(1,2-bis(1-oxopropoxy)-ethyl)-4-hydroxy-N-(2-thiazolyl)-8-trifluoromethyl-3-quinoline carboxamide as well as its salts of addition with acids and bases.

9) Preparation process for compounds with the formula (I) characterized in that a compound with the formula (II):

\[
\begin{array}{c}
\text{CH-CH-OR}_3 \\
\text{X-R}_4 \\
\end{array}
\]

(II)
in which X and R₄ have the significance already given, R₃ is an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, X' is a halogen atom, is made to react

- either with a compound with the formula (IIIₐ) :

\[
CH₃-CONHR₁ \tag{IIIₐ}
\]

in which R₁ has the previous significance, so as to obtain a compound with the formula (IV) :

\[
\begin{array}{c}
\text{COCH₂-CONH-R₁} \\
\text{X} \\
\text{NH-C-CH-CH₂-OR₃} \\
\text{X'} \quad \text{R₄}
\end{array}
\tag{IV}
\]

- or in the presence of a base with a compound with the formula (IIIₐ) :

\[
RO-C-CH₂-C-NH-R₁ \tag{IIIₐ}
\]

in which R₁ has the previous significance and R is an alkyl radical containing from 1 to 8 carbon atoms, so as to obtain a compound with the formula (A) :

\[
\begin{array}{c}
\text{CO₂-R} \\
\text{O} \\
\text{C-CH-CO-NH-R₁} \\
\text{X} \\
\text{NH-C-CH-CH₂-OR₃} \\
\text{X'} \quad \text{R₄}
\end{array}
\tag{A}
\]

which is decarbalkoxylized so as to obtain a compound with the formula (IV) previously defined, which compound with the formula (IV) thus obtained is cyclized in the presence of an alkaline agent so as to obtain a compound with the formula (V) :

\[
\begin{array}{c}
\text{OH} \\
\text{CONH-R₄} \\
\text{CH-CH-OR₃} \\
\text{X'} \quad \text{R₄}
\end{array}
\tag{V}
\]
which is converted to a compound with the formula (VI):

![Diagram of compound (VI)](image)

which compound with the formula (VI) is treated:

10 - either by an acid hydrolysis so as to obtain a compound with the formula (I) in which X, R₁ and R₄ have the previous significance, R₂ is a hydrogen atom and R₃ an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, which is converted, if desired, into a compound with the formula (I) in which X, R₁, R₂ and R₄ have the significance given above and R₃ represents a hydrogen atom, then, if desired, one or both hydroxyl functions are etherified or esterified, so as to obtain a compound with the formula (I) in which R₂ and/or R₃, identical or different, each represents an alkyl radical containing from 1 to 4 carbon atoms, an aryl radical or a \(-\overset{\ominus}{R}_5\) group, as previously defined, or, if desired, a compound with the formula (I) in which R₂ and R₃ represent a hydrogen atom is treated by acetone in the presence of an acid agent, so as to obtain the corresponding acetonide, or by an acid with the formula \(R_5-\text{COOH}\), \(R_5\) having the previous significance, so as to obtain a product with the formula (I) in which X, R₁ and R₄ have the previous significances, R₂ represents a \(-\overset{\ominus}{R}_5\) radical and R₃ an alkyl radical containing from 1 to 4 carbon atoms or an aryl radical, which compounds with the formula (I) thus obtained are converted, if desired, into salts by the action of an acid or a base.

10 Preparation process for compounds with the formula (I) as previously defined, characterized in that a compound with the formula (IIₐ)
\[ R_4 \text{ having the previous significance, is submitted to the action of a} \]
\[ \text{compound with the formula (III}_A) : \]
\[ \text{CH}_3-\text{CONH-}R_1 \]  
\[ (\text{III}_A) \]
\[ \text{in which } R_1 \text{ retains its previous significance, so as to obtain a} \]
\[ \text{compound with the formula (IVA)} : \]

\[ \text{COCH}_2-\text{CONH-}R_1 \]
\[ \text{NH-CO-CH=CH-}R_4 \]
\[ (\text{IVA}) \]

\[ \text{which is cyclized in the presence of an alkaline agent so as to obtain} \]
\[ \text{a compound with the formula (VA)} : \]

\[ \text{OH} \]
\[ \text{CONH-}R_1 \]
\[ \text{CH=CH-}R_4 \]
\[ (\text{VA}) \]

\[ \text{which is converted into a compound with the formula (I) in which } X, R_1 \]
\[ \text{and } R_4 \text{ have the significance given previously and } R_2 \text{ and } R_3 \text{ represent a} \]
\[ \text{hydrogen atom, of which compound with the formula (I), one or both} \]
\[ \text{hydroxyl functions are possibly etherified or esterified, so as to} \]
\[ \text{obtain a compound with the formula (I) in which } R_2 \text{ and/or } R_3 \text{ represent} \]
\[ \text{either an alkyl radical containing from 1 to 4 carbon atoms, an aryl} \]
\[ \text{radical, or a } -C-R_5 \text{ radical, } R_5 \text{ having the significance already given,} \]
\[ \text{or compounds with the formula (I) in which } R_2 \text{ and } R_3 \text{ represent a} \]
\[ \text{hydrogen atom, which, if desired, is treated by acetone in the} \]
presence of an acid agent, so as to obtain the corresponding acetonide, then if necessary, the compounds with the formula (I) are converted into salts by the action of an acid or a base.

11) As medicaments, compounds with the formula (I) as defined in any one of the claims 1 to 7 and their salts of addition with pharmaceutically acceptable acids and bases.

12) As medicaments, any one of the compounds with the formula (I), as defined in claim 8.

13) Pharmaceutical compositions containing as active principle one of the medicaments as defined in claim 11 or 12.

14) As new industrial compounds, compounds with the formulae (II), (IV), (A), (V) and (VI) as defined in claim 9.

15) As new industrial compounds, compounds with the formulae (IIA), (IVA), (VA) as defined in claim 10.

16) A method of treatment of degenerative inflammatory maladies, collagenoses, rheumatic illnesses, other illnesses of auto-immune nature or algias wherein is administered as active principle one or more compounds of formula (I) as defined in any one of claims 1 to 8.

17) A compound of formula (I) as defined in any one of claims 1 to 8 substantially as hereinbefore described with reference to any one of Examples 1 to 9.

18) A preparation process as claimed in either claim 9 or claim 10 substantially as hereinbefore described with reference to any one of Examples 1 to 9.

19) A medicament as claimed in either claim 11 or claim 12 substantially as hereinbefore described.

20) A pharmaceutical composition as claimed in claim 13 substantially as hereinbefore described with reference to Example 11.

21) A method of treatment as claimed in claim 16 substantially as hereinbefore described.

DATED this 24th day of July, 1986.

ROUSSEL-UCLAF

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