

Description

This invention relates to novel 2-imidazoline derivatives and a process for the preparation thereof.

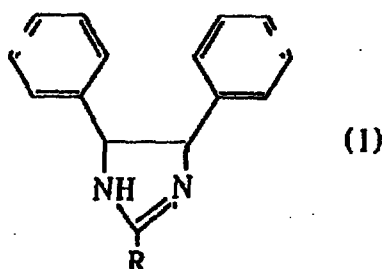
2,4,5-Triphenyl-, 2,4,5-tris(4-chlorophenyl)- and 2,4,5-tris(4-methylphenyl)-derivatives of imidazoline are known [Merck Index 9, 379 Croatica Chemica Acta, 45, 519 (1973) and Canadian Journal of Chemistry 50, 669 (1972)]. Among them, the 2,4,5-triphenyl derivative is known to show cardiac inhibitory effect, but there have been known pharmacological effect of the other two derivatives.

US-A- 4424 229, EP-A- 5219 and EP-A- 77024 refer to 2,4,5-Triphenylimidazole derivatives showing inter alia an antiinflammatory activity; CH-A-442979 discloses similar imidazole derivatives useful in photo imaging.

As a result of various investigations, it has been found that, while the above known imidazoline compounds have the same substituents at 2-, 4- and 5-positions on the imidazoline ring, a group of 2-imidazoline derivatives having different substituents between 2-position and 4- and 5-positions on the imidazoline ring are useful as an immunomodulator.

Thus, the objects of the invention are to provide novel 2-imidazoline derivatives and a pharmaceutical composition containing the same. Another object of the invention is to provide a process for preparing said compounds.

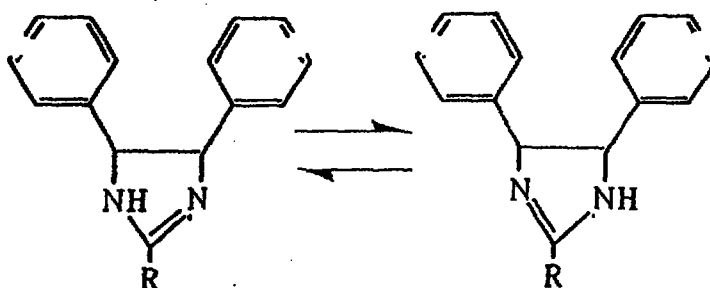
This invention relates to 2-imidazoline derivatives of the formula:



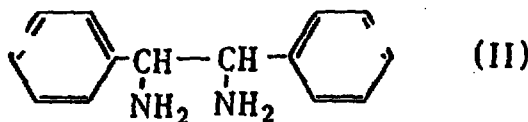
wherein R is a halogenophenyl group or a pharmaceutically acceptable salt thereof.

The compounds (I) of the invention or salts thereof have a variety of excellent characteristics as an immunomodulator. For example, they show potent macrophage migration enhancement activity in a macrophage migration assay which is used in measurement of cell-mediated immune activity. The 2-imidazoline derivatives (I) of the invention also show such a potent immunomodulatory effect that a suppressed immune activity is raised and an augmented one is lowered to restore to a normal level. Further, the 2-imidazoline derivatives (I) or pharmaceutically acceptable salts thereof have low toxicity and show high safety.

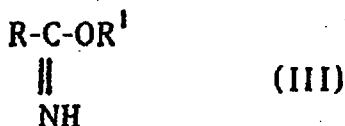
The 2-imidazoline derivatives (I) of the invention may exist in the form of stereoisomers due to two asymmetric carbon atoms and two tautomeric isomers shown in the formula:



wherein R, is the same as defined above, and this invention includes these isomers and a mixture thereof. Among cis- and trans- isomers of the 2-imidazoline derivative (I) of the invention, cis- isomers are more preferred for pharmaceutical use. According to the invention, the 2-imidazoline derivatives (I) can be prepared by condensing a compound of the formula (II)



or a salt thereof and a compound of the formula (III)



wherein R is the same as defined above and R¹ is a lower alkyl group, or a salt thereof.

The condensation reaction proceeds in the presence or absence of a base in a solvent. The base includes alkali metal alkoxides, alkali metal hydroxides, alkali metal carbonates, alkali metal hydrogen carbonates, or tri(lower alkyl)amines. Examples of the salt of the starting compound (II) and (III) are conventional inorganic or organic acid addition salts. A lower alkanol, dioxane, tetrahydrofuran, dimethylformamide or dimethylsulfoxide can be used as a solvent. The reaction is preferably carried out at a temperature of 0 to 100 °C.

In this invention, a cis 2-imidazoline derivative (I) can be obtained when an erythro compound is used as the starting material (II). On the other hand, a trans 2-imidazoline derivative (I) can be obtained from a threo type starting material (II), and an optically active compound (I) can be obtained from an optically active starting material (II), respectively.

As mentioned hereinbefore, the compounds (I) of the invention or salts thereof show a potent immunomodulatory effect. Especially, compounds (I) activate the migration of macrophage (i.e., the macrophage staying in a chronic inflammatory part) to allow it to leave the inflammatory part, and at the same time, they allow the suppressive T-cell level to be restored. Therefore, the compounds (I) are e.g. useful for the treatment and/or prophylaxis of rheumatoid arthritis, multiple sclerosis, systemic lupus, erythematodes, or rheumatic fever.

The 2-imidazoline derivatives (I) of the invention can be used for pharmaceutical use either in the form of a free base or a salt. Pharmaceutically acceptable salts of the compound (I) include, for example, inorganic acid addition salts such as hydrochloride, hydrobromide, phosphate and sulfate, and organic acid addition salts such as oxalate, acetate, lactate, citrate, tartarate, fumarate, maleate, aspartate, methanesulfonate and benzoate.

The 2-imidazoline derivative (I) or a salt thereof may be administered either orally or parenterally to a warm-blooded animal, including human beings, and may also be used in the form of a pharmaceutical preparation containing the same compound in admixture with pharmaceutical excipients suitable for oral or parenteral administration. The pharmaceutical preparations may be in solid form such as tablets, granules, capsules and powders, or in liquid form such as solutions, suspensions or emulsions. Moreover, when administered parenterally, it may be used in the form of injections.

The dose of the 2-imidazoline derivative (I) or a salt thereof may vary depending on the route of administration, age, weight and condition of the patient and a kind of disease, and is preferably 0.01 to 50 mg/kg a day, especially 0.1 to 10 mg/kg a day.

Experiment 1

Effect on alveolar macrophage migration

Japanese white female rabbits, weighing between 3 and 4kg, were sacrificed under anesthesia. Alveolar macrophages were obtained by pulmonary lavage with saline. In a "test group", the macrophages were migrated in the RPMI - 1640 medium containing 5% rabbit serum and 10⁻⁷ or 10⁻⁹ M of a test compound. Said migration test was carried out at 37 °C for 24 hours according to the method described in Journal of Leukocyte Biology 42: 197-203 (1987). The resulting migration was projected at about 15 times magnification and traced. Then, the migration area was measured with a planimeter.

The migration of macrophages in a "positive control group" was measured by the use of the RPMI-1640 medium containing 5% rabbit serum and 5mM of L-fucose, instead of the medium containing the test compound.

On the other hand, in a "control group", the experiment was carried out by the use of a medium containing 5 % rabbit serum only. The migration index was calculated by the following formula:

$$\text{Migration index} = \frac{\left(\begin{array}{c} \text{migration area of} \\ \text{test group} \end{array} \right) - \left(\begin{array}{c} \text{migration area of} \\ \text{control group} \end{array} \right)}{\left(\begin{array}{c} \text{migration area of} \\ \text{positive control group} \end{array} \right) - \left(\begin{array}{c} \text{migration area of} \\ \text{control group} \end{array} \right)}$$

The results are shown as Table 1.

Table 1.

Effect on alveolar macrophage migration

Test Compounds	Migration index	
	10 ⁻⁹ (M)	10 ⁻⁷ (M)
(the compound of the present invention) Cis-2-(4-chlorophenyl)-4,5-diphenyl-2-imidazoline hydrochloride	113.9	142.5
(Known compound) Cis-2,4,5-tris(4-chlorophenyl)-2-imidazoline hydrochloride (Note 1)	0	40.2
(Known compound) Cis-2,4,5-triphenyl-2-imidazoline hydrochloride (Note 2)	0	34.2

Note 1: Canadian Journal of Chemistry 50, 669 (1972)

Note 2: Merck Index 9, 379

Experiment 2.Effect on normalization of the number of plaque-forming cells of immunoenhancing animal.

Colchicine (1mg/kg) was administered abdominally to female BALB/C mice (10 weeks old, one group: 5 mice) and, immediately thereafter, protein antigen [the bentonite particles absorbing 2,4,5-trinitrobenzene (TNP)-Keyhole Limpet Hemocyanin (KLH)] was administered abdominally to the mice (0.1mg protein / mouse). 5 days after administration of the antigen, the mice were sacrificed under anesthesia, and the spleen cells were harvested. When the number of plaque-forming spleen cells was calculated according to the method described in Drugs under Experimental and Clinical Research, 8(1), 5-10 (1982), this group of mice showed 129 % increase in said spleen cell number as compared with a group of mice to which colchicine was not administered. On the other hand, when cis-2-(4-chlorophenyl)-4,5-diphenyl-2-imidazoline hydrochloride of the invention (Dose: 2 mg/kg) was administered orally to the mice two days before, one day before, at the day, one day after, two days after, three days after and four days after administration of the antigen, said medicated group of mice showed only 18 % increase in the number of plaque-forming spleen cells as compared with a group of mice to which colchicine was not administered.

Experiment 3.Effect on normalization of the number of plaque-forming cells of immunosuppressing animal.

A solution containing sheep red blood cells (antigen) as a floating matter was administered abdominally to female BALB/C mice (10 weeks old, one group: 8 mice) [The number of red blood cells was about 5×10^7]. The mice were soaked in water to give restraint stress for every four hours immediately after, one day after, two days after, three days after and four days after administration of the antigen. 5 days after administration of the antigen, the mice were sacrificed under anesthesia, and the spleen cells were harvested. This group of mice showed 47 % decrease in the number of plaque-forming spleen cells as compared with a group of mice which were not soaked in water. On the other hand, when cis-2-(4-chlorophenyl)-4,5-diphenyl-2-imidazoline-hydrochloride of the invention (Dose: 2 mg/kg) was administered orally to the mice two days before, one day before, at the day, one day after, two days after, three days after and four days after administration of the antigen, said medicated group of mice showed only 6 % decrease in the number of plaque-forming cells as compared with a group of mice which were not soaked in water.

Example 1.

14.8ml of triethylamine are added to a mixture of 16.1g of erythro-1,2-diamino-1,2-diphenylethane-diacetate, 13.7g of 4-chlorobenzimidazoethyl ether hydrochloride and 260 ml of ethanol, and the mixture is refluxed for four hours. After the reaction, the solvent is distilled off. 77ml of a 1N aqueous sodium hydroxide solution are added to the residue, and the solution is extracted with chloroform. The extract is washed with water, dried and evaporated to remove the solvent. The residue is recrystallized from methanol to give 12.0g of cis-2-(4-chlorophenyl)-4,5-diphenyl-2-imidazoline.

Yield : 75 %

M.P. : 152 to 153 °C

Nujol

IR ν (cm⁻¹) : 3200, 1619, 1595
Max

Hydrochloride	: M.P. >280°C
Maleate	: M.P. 199 to 200°C (decomp.)
Fumalate	: M.P. 233 to 235°C (decomp.)
D,L-Lactate	: M.P. 143 to 144°C (decomp.)
L-Tartrate	: M.P. 92 to 95°C (decomp.)
Methanesulfonate	: M.P. > 280°C

Example 2.

2.8ml of triethylamine are added to a mixture of 2.9g of erythro-1,2-diamino-1,2-diphenylethane · dihydrochloride, 1.8g of 4-pyridyliminoethyl ether and 60ml of ethanol, and the mixture is refluxed for two hours. After the reaction, the solvent is distilled off. 20ml of a 10% aqueous sodium hydroxide solution are added to the residue, and the solution is extracted with chloroform. The extract is washed with water, dried and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform : methanol = 7 : 1). The product obtained above is dissolved in ethanol, and the solution is made acidic with a 10 % hydrogen chloride-dioxane solution. The resulting crystals are collected by filtration to give 1.9g of cis-2-(4-pyridyl)-4,5-diphenyl-2-imidazoline-dihydrochloride.

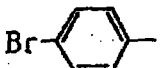
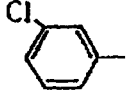
M.P. : >280 °c

Nujol
IR v (cm⁻¹) : 1600, 1580
Max

Examples 3 to 5

The corresponding erythro starting compounds (II) are treated in the same manner as described in Example 2 to give the cis-2-imidazoline derivatives as shown in Table 2.

Table 2

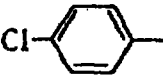
Ex.No.	Imidazoline derivative (I) (hydrochloride)	
	R	Physical properties
3		M.P. >280 °c IR* : 1620, 1608
4		M.P. >280 °c IR* : 1615, 1598
5		M.P. 251 to 253 °c IR* : 1620, 1600, 1580

Nujol
IR* means IR v (cm⁻¹) (the same in the following
Max Table)

Example 6

The corresponding threo starting compound (II) is treated in the same manner as described in Example 2 to give the trans 2-imidazoline derivative as shown in Table 3.

Table 3

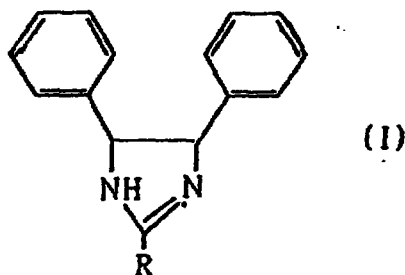
Ex.No.	Imidazoline derivative (I) (hydrochloride)	
	R	Physical properties
6		M.P. 281 to 284°C IR* : 2650, 1615, 1595

Other 2-imidazoline derivatives in addition to those set forth in Table 3 may be used.

Claims

Claims for the following Contracting States : DE,GB,FR,IT,NL,SE,LI,CH,BE,AT,LU

1. A 2-imidazoline derivative of the formula (I)



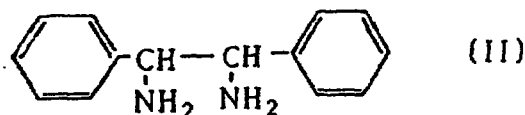
wherein R is a halogenophenyl group or a pharmaceutically acceptable salt thereof.

2. 2-(4-chlorophenyl)-4,5-diphenyl-2-imidazoline or a pharmaceutically acceptable salt thereof.

3. The compound claimed in Claim 1 or Claim 2 wherein the 2-imidazoline derivative has cis configuration.

4. A pharmaceutical composition which comprises as an active ingredient an effective amount of the compound as set forth in any one of Claims 1 to 3 in admixture with a pharmaceutically acceptable carrier or diluent.

5. A process for the preparation of a 2-imidazoline derivative as defined in Claim 1 which comprises condensing a compound of the formula (II)



a salt thereof and a compound of the formula (III)

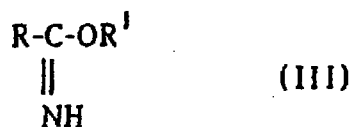
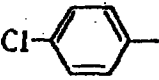


Table 3

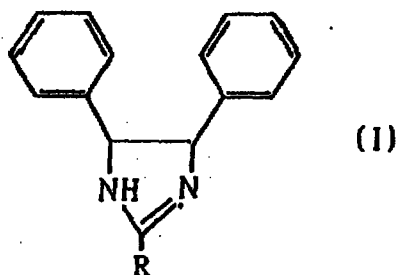
Ex.No.	Imidazoline derivative (I) (hydrochloride)	
	R	Physical properties
6		M.P. 281 to 284°C IR* : 2650, 1615, 1595

Other 2-imidazoline derivatives in addition to those set forth in Table 3 may be used.

Claims

Claims for the following Contracting States : DE,GB,FR,IT,NL,SE,LI,CH,BE,AT,LU

1. A 2-imidazoline derivative of the formula (I)



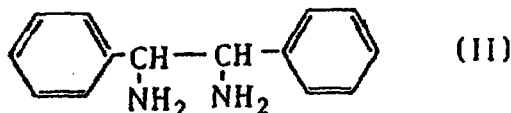
wherein R is a halogenophenyl group or a pharmaceutically acceptable salt thereof.

2. 2-(4-chlorophenyl)-4,5-diphenyl-2-imidazoline or a pharmaceutically acceptable salt thereof.

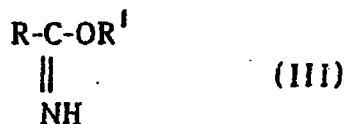
3. The compound claimed in Claim 1 or Claim 2 wherein the 2-imidazoline derivative has cis configuration.

4. A pharmaceutical composition which comprises as an active ingredient an effective amount of the compound as set forth in any one of Claims 1 to 3 in admixture with a pharmaceutically acceptable carrier or diluent.

5. A process for the preparation of a 2-imidazoline derivative as defined in Claim 1 which comprises condensing a compound of the formula (II)



a salt thereof and a compound of the formula (III)

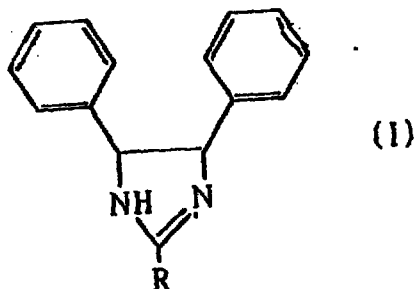


wherein R is as defined in Claim 1 and R¹ is a lower alkyl group, or a salt thereof, and if required, further converting the product into a pharmaceutically acceptable salt thereof.

6. Compounds as claimed in any one of Claims 1 to 3 for use as immunomodulator.

Claims for the following Contracting States : GR, ES

1. A method of making a pharmaceutical composition which comprises admixing an effective amount of at least one 2-imidazoline derivative of the formula (I)

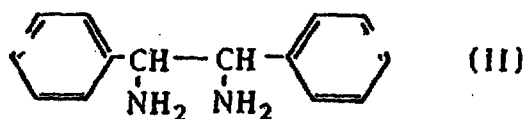


wherein R is a halogenophenyl group, or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier or diluent.

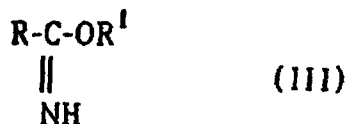
2. A method as claimed in Claim 1 wherein the 2-imidazoline derivative is 2-(4-chlorophenyl)-4,5-diphenyl-2-imidazoline or a pharmaceutically acceptable salt thereof.

3. A method as claimed in Claim 1 or Claim 2 wherein the 2-imidazoline derivative has cis configuration.

4. A process for the preparation of a 2-imidazoline derivative as defined in Claim 1 which comprises condensing a compound of the formula (II)



or a salt thereof and a compound of the formula (III)



wherein R is as defined in Claim 1 and R¹ is a lower alkyl group, or a salt thereof, and if required, further converting the product into a pharmaceutically acceptable salt thereof.

5. A process as claimed in Claim 4 wherein the reactants are chosen so as to produce 2-(4-chlorophenyl)-4,5-diphenyl-2-imidazoline or a pharmaceutically acceptable salt thereof.

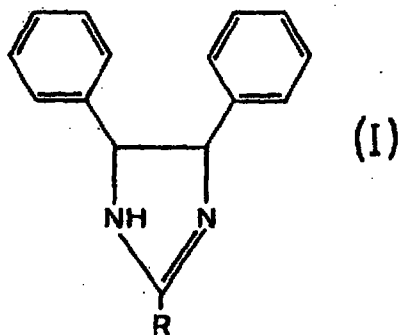
6. A process as claimed in Claim 5 wherein the resulting 2-imidazoline derivative is purified and mixed with a pharmaceutically acceptable carrier or diluent to form a pharmaceutical composition.

7. Compounds as defined in Claim 1 for use as immunomodulator.

Patentansprüche für folgende Vertragsstaaten : DE, GB, FR, IT, NL, SE, LI, CH, BE, AT, LU

1. 2-Imidazolinderivat der Formel (I),





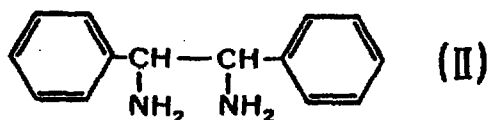
worin R eine Halogenophenylgruppe ist, oder ein pharmazeutisch akzeptables Salz davon.

2. 2-(4-Chlorphenyl)-4,5-diphenyl-2-imidazolin oder ein pharmazeutisch akzeptables Salz davon.

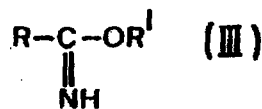
3. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das 2-Imidazolinderivat cis-Konfiguration aufweist.

4. Pharmazeutische Zusammensetzung, umfassend als einen aktiven Bestandteil eine wirksame Menge der Verbindung nach einem der Ansprüche 1 bis 3, in Zumischung mit einem pharmazeutisch akzeptablen Träger oder Verdünnungsmittel.

5. Verfahren zur Herstellung eines 2-Imidazolinderivates nach Anspruch 1, umfassend die Kondensation einer Verbindung der Formel (II)



oder eines Salzes davon und einer Verbindung der Formel (III)

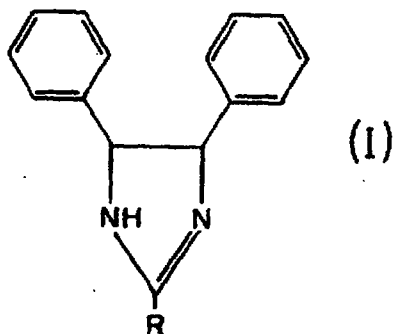


worin R wie in Anspruch 1 definiert ist und worin R¹ eine Niedrigalkylgruppe ist, oder eines Salzes davon, und, falls erforderlich, weiteres Umwandeln des Produktes in ein pharmazeutisch akzeptables Salz davon.

6. Verbindungen nach einem der Ansprüche 1 bis 3 für die Verwendung als Immunomodulator.

Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend die Vermischung einer effektiven Menge von zumindest einem 2-Imidazolinderivat der Formel (I),



worin R eine Halogenophenylgruppe ist, oder ein pharmazeutisch akzeptables Salz davon mit einem phar-

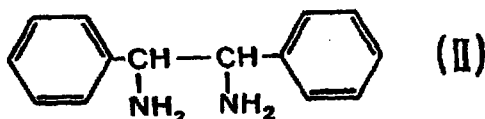


mazeutisch akzeptablen Träger oder Verdünnungsmittel.

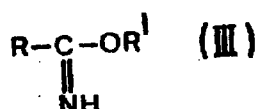
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß 2-Imidazolinderivat 2-(4-Chlorophenyl)-4,5-diphenyl-2-imidazolin oder ein pharmazeutisch akzeptables Salz davon ist.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das 2-Imidazolinderivat cis-Konfiguration aufweist.

4. Verfahren zur Herstellung eines 2-Imidazolinderivates nach Anspruch 1, umfassend die Kondensation einer Verbindung der Formel (II)



oder eines Salzes davon und einer Verbindung der Formel (III)



worin R wie in Anspruch 1 definiert ist und worin R¹ eine Niedrigalkylgruppe ist, oder eines Salzes davon, und, falls erforderlich, weiteres Umwandeln des Produktes in ein pharmazeutisch akzeptables Salz davon.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die Reaktanten so ausgewählt werden, daß 2-(4-Chlorophenyl)-4,5-diphenyl-2-imidazolin oder ein pharmazeutisch akzeptables Salz davon gebildet wird.

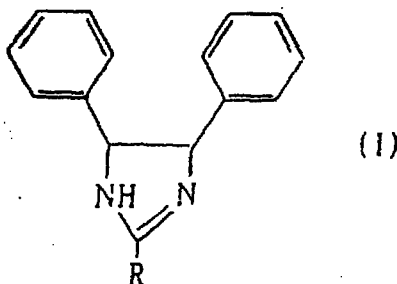
6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das resultierende 2-Imidazolinderivat gereinigt und mit einem pharmazeutisch akzeptablen Träger und Verdünnungsmittel zur Bildung einer pharmazeutischen Zusammensetzung vermischt wird.

7. Verbindungen nach Anspruch 1 für die Verwendung als Immunomodulator.

Revendications

Revendications pour les Etats contractants suivants : DE, GB, FR, IT, NL, SE, LI, CH, BE, AT, LU

1. Dérivé de la 2-imidazoline de la formule (I)



dans laquelle R représente un radical halogénophényle, ou un sel pharmaceutiquement acceptable d'un tel composé.

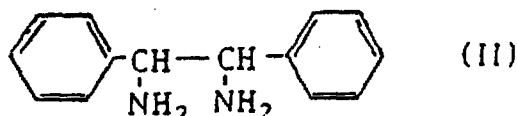
2. 2-(4-Chlorophényl)-4,5-diphényl-2-imidazoline, ou un sel pharmaceutiquement acceptable de celle-ci.

3. Composé suivant la revendication 1 ou la revendication 2, caractérisé en ce que le dérivé de la 2-imidazoline se présente sous la configuration cis.

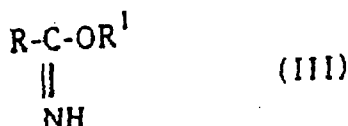
4. Composition pharmaceutique, caractérisée en ce qu'elle comprend, à titre d'ingrédient actif, une quantité efficace du composé suivant l'une quelconque des revendications 1 à 3, en mélange à un diluant, véhicule ou excipient pharmaceutiquement acceptable.



5. Procédé de préparation d'un dérivé de la 2-imidazoline tel que défini dans la revendication 1, caractérisé en ce que l'on condense un composé de la formule (II)



ou un sel de celui-ci et un composé de la formule (III)

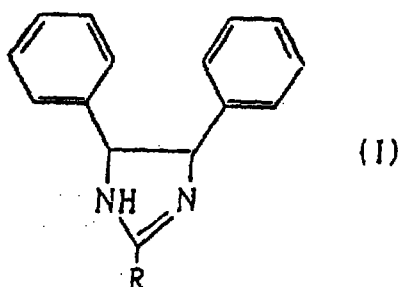


dans laquelle R possède la signification qui lui a été attribuée dans la revendication 1 et R¹ représente un radical alkyle inférieur, ou un sel de celui-ci et, si cela se révèle nécessaire, on poursuit la conversion du produit en un sel pharmaceutiquement acceptable de celui-ci.

6. Composés suivant l'une quelconque des revendications 1 à 3, à utiliser à titre d'immunomodulateurs.

Revendications pour les Etats contractants suivants : GR, ES

1. Procédé de préparation d'une composition pharmaceutique, caractérisé en ce que l'on mélange une quantité efficace d'au moins un dérivé de la 2-imidazoline de la formule (I)

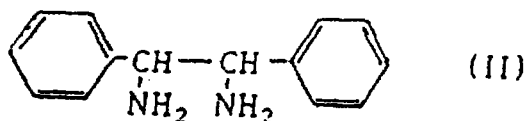


dans laquelle R représente un radical halogénophényle, ou un sel pharmaceutiquement acceptable de ce composé et un diluant, véhicule ou excipient pharmaceutiquement acceptable.

2. Procédé suivant la revendication 1, caractérisé en ce que le dérivé de la 2-imidazoline est la 2-(4-chlorophényl)-4,5-diphényl-2-imidazoline, ou un sel pharmaceutiquement acceptable de ce composé.

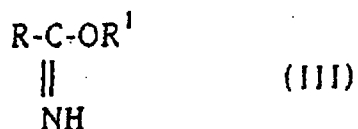
3. Procédé suivant la revendication 1 ou la revendication 2, caractérisé en ce que le dérivé de la 2-imidazoline se présente sous la configuration cis.

4. Procédé de préparation d'un dérivé de la 2-imidazoline tel que défini dans la revendication 1, caractérisé en ce que l'on condense un composé de la formule (II)



ou un sel de celui-ci et un composé de la formule (III)





dans laquelle R possède la signification qui lui a été attribuée dans la revendication 1 et R¹ représente un radical alkyle inférieur, ou un sel de celui-ci et, si cela se révèle nécessaire, on poursuit la conversion du produit en un sel pharmaceutiquement acceptable de celui-ci.

5. Procédé suivant la revendication 4, caractérisé en ce que l'on choisit les réactifs de manière à produire la 2-(4-chlorophényl)-4,5-diphényl-2-imidazoline, ou un sel pharmaceutiquement acceptable de ce composé.

6. Procédé suivant la revendication 5, caractérisé en ce que l'on purifie le dérivé de la 2-imidazoline obtenu et on le mélange à un diluant, véhicule ou excipient pharmaceutiquement acceptable de manière à former une composition pharmaceutique.

7. Composés suivant la revendication 1, à utiliser à titre d'immunomodulateurs.

