EUROPEAN PATENT SPECIFICATION

Date of publication of patent specification: 11.09.91
Application number: 88100825.4
Date of filing: 21.01.88

Derivative of thiazolidine-4-carboxylic acid, its preparation and pharmaceutical compositions containing it.

Priority: 26.01.87 IT 1916587
Date of publication of application: 03.08.88 Bulletin 88/31
Publication of the grant of the patent: 11.09.91 Bulletin 91/37
Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

References cited:
DE-A- 2 514 381
DE-A- 2 630 757
DE-A- 3 024 256


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The present invention concerns 3-L-pyroglutamyl-L-thiazolidine-4-carboxylic acid, having formula I

\[
\text{H} \quad \text{CO} \quad \text{N} \quad \text{S}
\]

(\text{I})

its pharmaceutically acceptable salts, a process for its preparation and pharmaceutical compositions endowed with anti-toxic, anti-oxidant, immunostimulating, anti-inflammatory and anti-aging properties.

Examples of salts according to the invention are those with non-toxic and pharmaceutically acceptable bases such as lysine, arginine, alkali or earth-alkali hydroxides, trimethamine, triethylamine, triethanolamine, piperidine, etc. Some salts may be endowed with peculiar advantages such as higher solubility, better pharmacokinetic or organoleptic properties, higher stability, etc.: all these aspects are in any way subsidiary to the main physiological action of the acid I. The compound I is in fact endowed with advantageous pharmacological properties such as the ability of protecting rat’s liver from paracetamol intoxication, the ability of decreasing in mice the effects of exposure to ionizing radiation and the ability of positively influencing the immune system.

In the following pharmacological tests hereinafter reported, the compound I, also referred to as PGTCA, has been compared with pyrogallitic acid (PGA) and with thiazolidine-4-carboxylic acid (TCA).

**Effects on paracetamol intoxication in the rat**

Male Wistar rats, mean weight of 150±10 g were used, which, after suitable housing, were subjected to the test:

a) Test after single i.p. administration

The animals were divided in 7 groups, comprising 20 animals each, according to the following scheme:

- I group: control
- II group: PGTCA 4.1 \( \mu \)moles/kg i.p.
- III group: PGTCA 41 \( \mu \)moles/kg i.p.
- IV group: PGTCA 205 \( \mu \)moles/kg i.p.
- V group: PGA 4.1 \( \mu \)moles/kg + TCA 4.1 \( \mu \)moles/kg
- VI group: PGA 41 \( \mu \)moles/kg + TCA 41 \( \mu \)moles/kg
- VII group: PGA 205 \( \mu \)moles/kg + TCA 205 \( \mu \)moles/kg.

The animals of each group, fasting since 12 hours, were treated with paracetamol at the dose of 5000 mg/kg by the oral route. The different pharmacological treatments were carried out contemporaneously with the paracetamol administration. After 48 hours from treatment, the death-rate was assessed in the various experimental groups. The liver was taken from the surviving animals, sacrificed by decapitation, and from the dead animals and a histopathologic examination was carried out.

The degree of liver impairment has been evaluated as:

- degree 0: normal histologic examination
- degree I: centrolobular necrosis extended to less than 25% of the lobule
- degree II: extended centrolobular necrosis, with lesions bridging adjacent centrolobular areas
- degree III: massive necrosis.

In order to evaluate the lesion degree, 6 different sections were taken from each organ.

b) Test after repeated i.p. administration

The same treatment schedule as in a) was used.

The animals of groups II-VII were treated daily for 8 days. At the 8th day, contemporaneously to the various considered pharmacological treatments, the animals of the 7 groups (fasting since 12 hours) were administered with paracetamol (5000 mg/kg per os). The animals were observed for the subsequent 48
hours; the animals of groups II-VII were continuously treated as above reported.

After 48 hours from the paracetamol administration, the surviving animals were examined and the liver was subjected to the histopathologic examination.

The results, reported in the following table I, show that the acute treatment with PG TCA, both at the highest dose (205 µmoles/kg i.p.) and at the intermediate dose (41 µmoles/kg i.p.) induces a significant decrease of liver impairment by an high dose of paracetamol.

The combination PGA + TCA induces a significant decrease of the liver impairment only at the highest dose (205 µmoles/kg i.p. of PGA and TCA).

PG TCA, finally, reduces the death-rate by paracetamol both at the highest and at the intermediate dose, whereas the effect of the combination of PGA + TCA is shown only at the highest dose.

Even in the test after repeated administration the superiority of the PG TCA treatment with respect to the treatment with the combination of PGA + TCA (table II) is evident.

**Effects on the consequences of the exposure to the ionizing radiation.**

Swiss male mice weighing 30±5 g, divided in 7 groups of 20 animals each, were used according to the above reported schedule.

The pharmacological treatments were carried out for 15 days before the irradiation and prosecuted up to the end of the experiment. The control animals received the vehicle alone.

At the 15th day, all the animals were irradiated (Philips Metalix® apparatus, 180 KV, 15 mA, with Cu filter 0.5 mm + Al mm) with the administration of 700 r of x rays.

All the animals were checked daily, for 15 days after irradiation. The radio-protection degree was calculated as survival % at 10 and 15 days. The results, reported in table III, show that PG TCA has a remarkable radio-protective activity both at the highest and at the intermediate dose.

The activity of the combination PGA + TCA appears only at the highest dose.

**ACTIVITY ON SOME IMMUNOLOGICAL PARAMETERS IN THE MALE RAT.**

In order to evaluate a possible immunostimulating or immunomodulating activity, models of physiological or paraphysiological immunodeficiency must be used. One of the most used model for this purpose in the aging. Aging, in fact, is associated with a decrease of the T helper lymphocytes function and with a depression of the T-lymphocytes immunodependent responses: delayed-type hypersensitivity, proliferative response to mitogens, differentiation of cytolytic T-cells. The mechanisms involved in this phenomenon may comprise a decreased production of thymic hormones correlated with thymic involution, induction of suppressor T-cells and impaired synthesis or utilization of interleukin.

The B cells are usually less impaired. For this reason, the effect of the in vivo PG TCA treatment of young and old animals was studied, using 2 tests indicative of the status of cellular lymphocyte reactivity.

For this purpose, male adult rats (5-6 months old) were used as animal model with normal immunocompetent system, and old rats (17-18 months) as a paraphysiological immunodeficiency model.

The PG TCA treatment has been carried out i.p. at the dose of 1, 10 to 50 mg/kg twice a day for 4 weeks. The used immunological tests were the delayed type hypersensitivity induced by dinitrochlorobenzene (DNCO) and the T-lymphocyte response to concanavaline A (ConA).

**Sensitization with DNBC**

After 4 weeks of PG TCA pre-treatment (or vehicle), 0.02 ml of DNBC (solubilized in acetone at the concentration of 200 mg/ml) was applied to each animal (5 rats per group) on the cutis of the back, on an area of about 1 cm². The subsequent inflammatory reaction was evaluated by measuring the diameter of the reddish area by means of a thickness gauge from day 1 to day 7.

During this period the animals were constantly treated.

**Test of blastization with ConA**

After 4 weeks of PG TCA treatment at the doses of 1,10 and 50 mg/kg, the animals were sacrificed and the spleen was removed in sterile conditions. The isolation of lymphocytes was obtained by an isolumph gradient. The lymphocytes were incubated in micro-wells, at the concentration of 1 x 10⁶ cells/ml, in the presence of ConA (2.5 µg/ml), for 48 hours. The mitogen activity was evaluated by incorporation of ³H-thymidine for 16 hours.
From the results obtained, it is evident that the old animals show a reduction of the response to DNCB, evaluated as inflammation area. The PGTCA treatment caused a significant increase of the response only at the dose of 50 mg/kg in young animals, whereas in the old ones a maximum enhancing increase was noted already at the dose of 10 mg/kg. The immunostimulating activity of PGTCA was confirmed by the test of blastization by ConA (table IV). Also in this case the response proved to be more enhanced in the old animals presenting a certain degree of cellular immunity deficiency.

In the mouse, a cytotoxic-kind of hypersensitivity reaction, evaluated in the test of T cells forming rosettes with sheep red blood cells, was used (S.D. Wilson Immunology, 1971, 21, 233).

The treatment was carried out by intraperitoneal route at the dose of 50 mg/kg twice a day, according to the methods shown in tables V A/B.

CD-I male mice weighing about 25 g are treated with PGTCA for 8 days. After 4 days from the start of the treatment the animals were immunized with $5 \times 10^8$ sheep red blood cells in 0.2 ml of PBS i.p. The rosette test was carried out 8 days after the immunization. The mice were killed and the spleen was removed and placed in ice cold Hank solution, triturated, homogenized and gauze filtered.

$6 \times 10^7$/ml of spleen cells + 100 µl of red blood cell suspension $3 \times 10^8$/µl were mixed in 0.8 ml of Hank and stirred for 1 min.

The samples were incubated for 24 h at 4°C without stirring and then, after stirring, the number of rosette forming cells/ml was determined by the Bürker apparatus. In the rosette test, the PGTCA treatment causes a significant increase of the rosette number in comparison with the control in sensitized animals, whereas no significant change was noticed in not sensitized animals. These results allow to affirm that PGTCA is active on T lymphocyte cell population and do not increase the lymphocyte B number, showing therefore a specific immunostimulation.
### TABLE I

<table>
<thead>
<tr>
<th>Dose (microm/kg ip)</th>
<th>Control</th>
<th>PG TCA</th>
<th>PGA + TCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.1 41 205</td>
<td>(4.1+4.1)(41+41)</td>
<td>(205+205)</td>
</tr>
<tr>
<td>n.</td>
<td>20 20 20 20</td>
<td>20 20 20 20</td>
<td>90 85 75 60</td>
</tr>
<tr>
<td>Death rate %</td>
<td>90 85 75 60</td>
<td>90 85 75 65</td>
<td>90 85 75</td>
</tr>
<tr>
<td>Liver impairment</td>
<td>% distribution of liver impairment degree</td>
<td>0 0 0 5 0 0 0 0 0 0 5 15 0 10 0 10 15 0 10 15</td>
<td>0 0 0 5 15 0 0 10 0 10 15 0 10 15</td>
</tr>
<tr>
<td>degrees</td>
<td>0 0 0 5 0 0 0 0 0 0 5 15 0 10 0 10 15 0 10 15</td>
<td>0 0 0 5 15 0 0 10 0 10 15 0 10 15</td>
<td>0 0 0 5 15 0 0 10 0 10 15 0 10 15</td>
</tr>
</tbody>
</table>

### TABLE II

<table>
<thead>
<tr>
<th>Dose (microm/kg ip)</th>
<th>Control</th>
<th>PG TCA</th>
<th>PGA + TCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.1 41 205</td>
<td>(4.1+4.1)(41+41)</td>
<td>(205+205)</td>
</tr>
<tr>
<td>n.</td>
<td>20 20 20 20</td>
<td>20 20 20 20</td>
<td>90 85 70 50</td>
</tr>
<tr>
<td>Death rate %</td>
<td>90 85 70 50</td>
<td>90 85 75 65</td>
<td>90 85 75 65</td>
</tr>
<tr>
<td>Liver impairment</td>
<td>% distribution of liver impairment degree</td>
<td>0 0 0 5 0 0 0 0 0 0 5 15 0 10 0 10 15 0 10 15</td>
<td>0 0 0 5 15 0 0 10 0 10 15 0 10 15</td>
</tr>
<tr>
<td>degrees</td>
<td>0 0 0 5 0 0 0 0 0 0 5 15 0 10 0 10 15 0 10 15</td>
<td>0 0 0 5 15 0 0 10 0 10 15 0 10 15</td>
<td>0 0 0 5 15 0 0 10 0 10 15 0 10 15</td>
</tr>
</tbody>
</table>
### TABLE III

<table>
<thead>
<tr>
<th>Dose (microm/kg ip)</th>
<th>Control</th>
<th>PGTCA</th>
<th>PGA + TCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n.</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Death-rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 gg</td>
</tr>
<tr>
<td>15 gg</td>
</tr>
</tbody>
</table>

### TABLE IV

<table>
<thead>
<tr>
<th>PGTCA treatment</th>
<th>(^3)H-thymidine cpm/well</th>
<th>increase %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult rats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5-6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32500 ± 1130</td>
<td>==</td>
<td>==</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>31806 ± 970</td>
<td>- 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>34165 ± 540</td>
<td>+ 5.1</td>
<td>NS</td>
</tr>
<tr>
<td>50 mg/kg</td>
<td>35785 ± 240</td>
<td>+ 10.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Old rats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-18 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23163 ± 841</td>
<td>==</td>
<td>==</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>23553 ± 923</td>
<td>+ 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>26012 ± 316</td>
<td>+ 12.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>50 mg/kg</td>
<td>27540 ± 439</td>
<td>+ 18.9</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
TABLE V
T-cells forming rosette with sheep red blood cells

<table>
<thead>
<tr>
<th>Treatment: for 8 days</th>
<th>Mice sensitized with red blood cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>No. mice</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
</tr>
<tr>
<td>(NaCl 0.9% i.p.)</td>
<td>A)</td>
</tr>
<tr>
<td>PGTCA</td>
<td>10</td>
</tr>
<tr>
<td>100 mg/kg b.i.d.</td>
<td>i.p.</td>
</tr>
<tr>
<td>Treatment: for 8 days</td>
<td>Mice not sensitized with red blood cells</td>
</tr>
<tr>
<td>Groups</td>
<td>No. mice</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>5</td>
</tr>
<tr>
<td>(NaCl 0.9% i.p.)</td>
<td>B)</td>
</tr>
<tr>
<td>PGTCA</td>
<td>100 mg/kg b.i.d.</td>
</tr>
<tr>
<td>i.p.</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05

Compound I is also active, at the dose of 10 mg/kg and even more at 50 mg/kg, in improving the neurocerebral performances in the old rat. A similarly favourable influence was noticed on the sexual behaviour of the male rat, with reduction of latencies and increase of the frequencies of sexual acts.

For the considered therapeutic use, the compound I is suitably formulated into pharmaceutical compositions using usual methods and excipients, such as those described in "Remington's Pharmaceutical
Examples of said pharmaceutical compositions comprise tablets, capsules, sugar-coated tablets, granulates or solutions for oral or parenteral use.

Typically, a unit dose will contain from 10 to 500 mg of active principle. The daily dose will depend on the patient's condition and on the seriousness of the pathology: it will be usually ranging from 0.1 to 4 g daily, in 2 or 3 administrations by the oral route, whereas by parenteral administration 50 to 2000 mg per day will generally suffice.

The present invention concerns also a process for the preparation of the compound of formula I, characterized by reacting an activated ester of pyroglutamic acid with L-thiazolidine-4-carboxylic acid in the presence of an organic base such as triethylamine, diethylisopropylamine or higher trialkylamine in solvents such as DMF, aliphatic dialkylamides or DMSO.

As an activated ester, the ester with pentachlorophenol, 2,4,5-trichlorophenol, N-hydroxysuccinimide or L-thiazolidine-4-carboxylic acid in an alkaline solution with L-pyroglutamoyl chloride, may be used.

The structure of the product has been confirmed by elemental analysis (C, H, N, S) and from the NMR and IR spectra.

The following non-limitative examples illustrate the invention.

**EXAMPLE 1**

60 g (0.158 mol.) of pentachlorophenyl-L-pyroglutamate, prepared as described in J. Med. Chem. 13, 844 (1970), 20.85 g (0.158 mol.) of 4-thiazolidine carboxylic acid and 16 g (0.158 mol.) of triethylamine in 450 ml of dimethylformamide were stirred for 24 h at room temperature.

After filtration and solvent evaporation at reduced pressure and at a temperature lower than 15°C, the residue was treated with water, the pentachlorophenol extracted with ethyl ether, the aqueous phase was acidified with hydrochloric acid and the precipitate formed was filtered at 10°C, which was crystallized from water obtaining a white crystalline product melting at 192-194°C (70% yield).

**Analysis for C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>S:**

<table>
<thead>
<tr>
<th></th>
<th>C%</th>
<th>H%</th>
<th>N%</th>
<th>S%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calc.</td>
<td>44.25</td>
<td>4.95</td>
<td>11.46</td>
<td>13.12</td>
</tr>
<tr>
<td>Found</td>
<td>44.35</td>
<td>4.89</td>
<td>11.50</td>
<td>13.16</td>
</tr>
</tbody>
</table>

<sup>1</sup> H-NMR (DMSO/TMS int.)

δ

2.15 (m, 4H) -CH<sub>2</sub>-CH<sub>2</sub>-

3.25-3.35 (m, 2H) -S-CH<sub>2</sub>-CH-
IR (K Br)

\( \tilde{\nu} \) (cm\(^{-1}\))

3300 (NH)

1710 (CD-NH)

1680-1620 (COOH; N-C = 0)

\( \tilde{\alpha}_D^{25} \) \(-150^\circ\) (C2 in HCl 5N)

**EXAMPLE 2**

2N NaOH and a solution of 14.8 g (0.1 mol.) of L-pyroglutamoylchloride (US 4 278 681) in 25 ml of acetone were added to a stirred solution of 13.3 g (0.1 mol.) of L-thiazolidine-4-carboxylic acid in 25 ml of acetone, keeping the temperature at 0 °C and the pH from 7.5 to 8.5.

When the addition was over, the mixture was concentrated to half volume under reduced pressure, acidified with conc. HCl, the formed crystals were filtered after standing at 0 °C and re-crystallized from water, obtaining 12 g (49%) of product having the same characteristics of Example 1.

**Claims**

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

1. 3-L-pyroglutamyl-L-thiazolidine-4-carboxylic acid 5 of formula I

\[ \text{COOH} \]

\[ \text{CO} \]

\[ \text{N} \]

\[ \text{S} \]

(I)

and its pharmaceutically acceptable salts.

2. A process for the preparation of compound I characterized by reacting an activated ester of L-pyroglutamic acid or its acid chloride with L-thiazolidine-4-carboxylic acid.

3. A process according to claim 2 characterized in that the reaction is carried out in inert solvents selected in the group of dimethylsulfoxide, dimethylformamide and aliphatic dialkylamides in the presence of bases, or in water at 0 °C in the presence of NaOH.

4. A process according to claims 2 or 3 characterized in that the activated ester of pyroglutamic acid is
the ester with pentachlorophenol, 2,4,5-trichlorophenol, N-hydroxy-succinimide.

5. Pharmaceutical compositions containing as the active principle the compound of claim 1 or a salt thereof, in admixture with a pharmaceutically acceptable vehicle.

6. Compositions according to claim 5 in form of tablets, capsules, sugar coated tablets, granules or solutions for parenteral or oral administration.

7. Compound of claim 1 for use as a medicament.

8. Use of compound of claim 1 or of a salt thereof for the preparation of a medicament having immunomodulating, antitoxic antinflammatory, antioxidant and anti-aging activities.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of compound

\[
\text{COOH}
\]
\[
\text{H} \quad \text{CO} \quad \text{N} \quad \text{S}
\]

25 characterized by reacting an activated ester of L-pyroglutamic acid or its acid chloride with L-thiazolidine-4-carboxylic acid.

2. A process according to claim 1 characterized in that the reaction is carried out in inert solvents selected in the group of dimethylsulfoxide, dimethylformamide and aliphatic dialkylamides in the presence of bases, or in water at 0°C in the presence of NaOH.

3. A process according to claim 1 characterized in that the activated ester of pyroglutamic acid is the ester with pentachlorophenol, 2,4,5-trichlorophenol, N-hydroxysuccinimide.

Revendications

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

1. Acide 3-L-pyroglutamyl-L-thiazolidine-4-carboxylique de formule

\[
\text{COOH}
\]
\[
\text{H} \quad \text{CO} \quad \text{N} \quad \text{S}
\]

et ses sels pharmaceutiquement acceptables.

2. Un procédé pour la préparation du composé 1, caractérisé en ce qu'on fait réagir un ester activé d'acide L-pyroglutamique ou son chlorure d'acide avec l'acide L-thiazolidine-4-carboxylique.

3. Un procédé selon la revendication 1, caractérisé en ce que la réaction est conduite dans des solvants inertes choisis dans le groupe constitué par le diméthylsulfoxide, le diméthylformamide et les dialkylamides aliphatiques en présence de bases, ou dans l'eau à 0°C en présence de NaOH.
4. Un procédé selon les revendications 2 ou 3, caractérisé en ce que l'ester activé d'acide pyroglutamique est l'ester formé avec le pentachlorophénol, le 2,4,5-trichlorophénol, le N-hydroxy-succinimide.

5. Compositions pharmaceutiques contenant comme principe actif, le composé de la revendication 1 ou un sel de celui-ci, en mélange avec un véhicule pharmaceutiquement acceptable.

6. Compositions selon la revendication 5 sous la forme de comprimés, capsules, comprimés dragéifiés, granules ou solutions pour l'administration parentérale ou orale.

7. Composé de la revendication 1 destiné à être utilisé en tant que médicament.

8. Utilisation du composé de la revendication 1 ou d'un sel de celui-ci pour la préparation d'un médicament doué d'activités antitoxique, anti-inflammatoire, antioxydante et anti-vieillissement.

Revedications pour les Etats contractants suivants : GR, ES

1. Un procédé pour la préparation de l'acide 3-L-pyroglutamyl-L-thiazolidine-4-carboxylique de formule I

![Chemical Structure](image)

2. Un procédé selon la revendication 1, caractérisé en ce que la réaction est conduite dans des solvants inertes choisis dans le groupe constitué par le diméthylsulfoxide, le diméthylformamide et les dialkylamides aliphatiques en présence de bases, ou dans l'eau à 0 °C en présence de NaOH.

3. Un procédé selon les revendications 1 ou 2, caractérisé en ce que l'ester activé d'acide pyroglutamique est l'ester formé avec le pentachlorophénol, le 2,4,5-trichlorophénol, le N-hydroxy-succinimide.

Patentansprüche

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

1. 3-L-Pyroglutamyl-L-thiazolidin-4-carbonsäure der Formel I

![Chemical Structure](image)

and deren pharmazeutisch annehmbaren Salze.

2. Verfahren zur Herstellung von Verbindung 1, gekennzeichnet durch Umsetzen eines aktivierten Esters der L-Pyroglutaminsäure oder deren Säurechlorid mit L-Thiazolidin-4-carbonsäure.

EP 0 276 752 B1


5. Pharmazeutische Zusammensetzungen enthaltend als aktiven Bestandteil die Verbindung nach Anspruch 1 oder ein Salz davon im Gemisch mit einem pharmazeutisch annehmbaren Träger.


7. Verbindung nach Anspruch 1 zur Verwendung als ein Medikament.

8. Verwendung der Verbindung nach Anspruch 1 oder eines Salzes davon zur Herstellung eines Medikamentes mit Immunmodulierenden, antitoxischen, entzündungshemmenden, oxidationshemmenden und anti-alternden Aktivitäten.

Patentansprüche für folgende Vertragsstaaten: GR, ES

1. Verfahren zur Herstellung von 3-L-Pyroglutamyl-L-thiazolidin-4-carbonsäure der Formel 1

![Chemical Structure](image)

gekennzeichnet durch Umsetzen eines aktivierten Esters der L-Pyroglutaminsäure oder deren Säurechlorid mit L-Thiazolidin-4-carbonsäure.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Reaktion in inertem Lösungsmitteln, ausgewählt aus der Gruppe von Dimethylsulfoxid, Dimethylformamid und aliphatischen Dialkylamiden, in Gegenwart von Basen oder in Wasser bei 0 °C in Gegenwart von NaOH durchgeführt wird.