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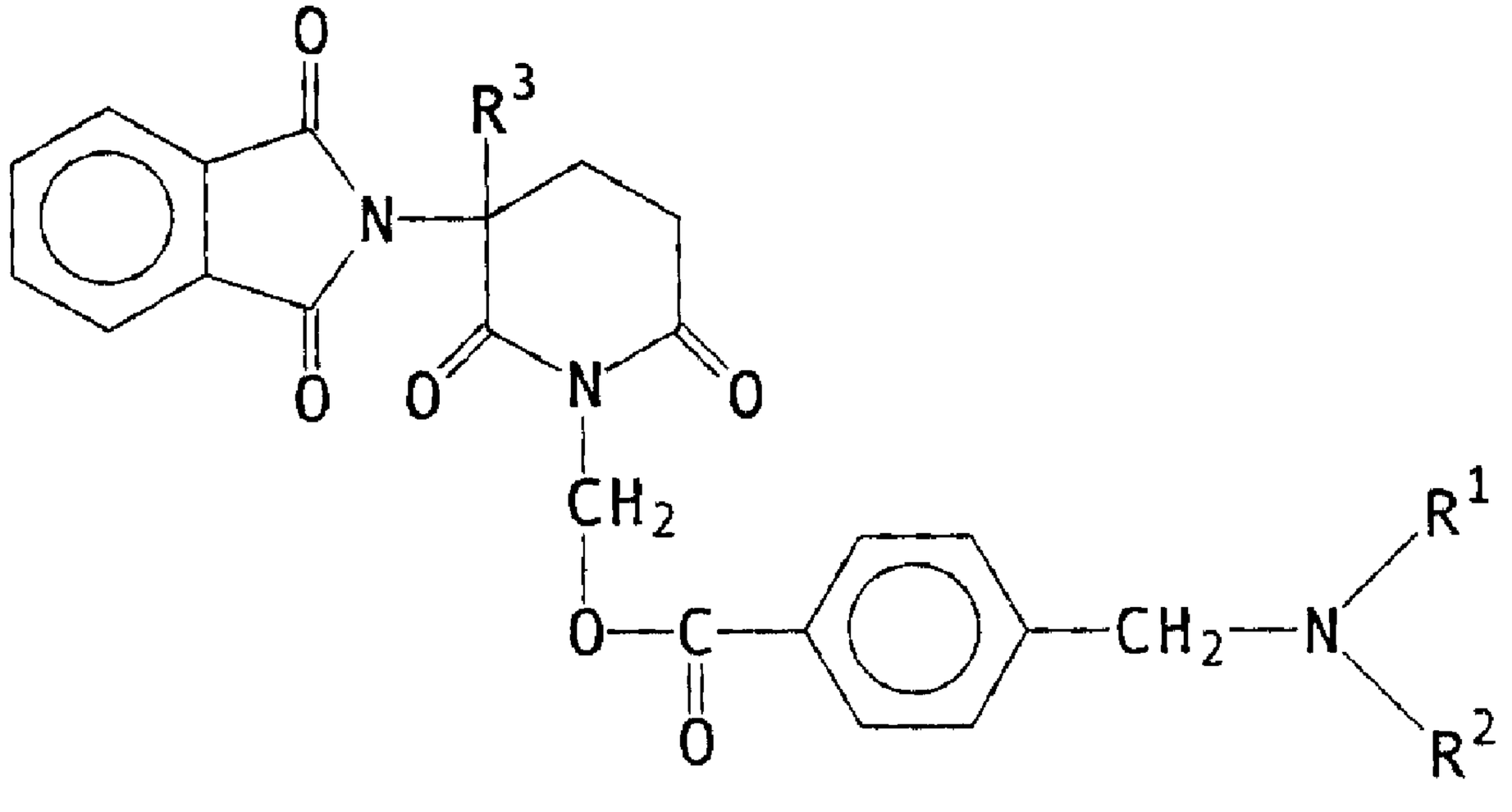
(54) Titre : DERIVES DE LA THALIDOMIDE, METHODE POUR LEUR FABRICATION ET LEUR UTILISATION DANS DES MEDICAMENTS

(54) Title: THALIDOMIDE DERIVATIVES, METHOD OF MANUFACTURE AND USE THEREOF IN MEDICAMENTS



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(57) Abrégé/Abstract:
New thalidomide derivatives, pharmaceutical compositions containing those compounds and a process for preparing those compounds and compositions are disclosed.

Abstract

New thalidomide derivatives, pharmaceutical compositions containing those compounds and a process for preparing those compounds and compositions are disclosed.

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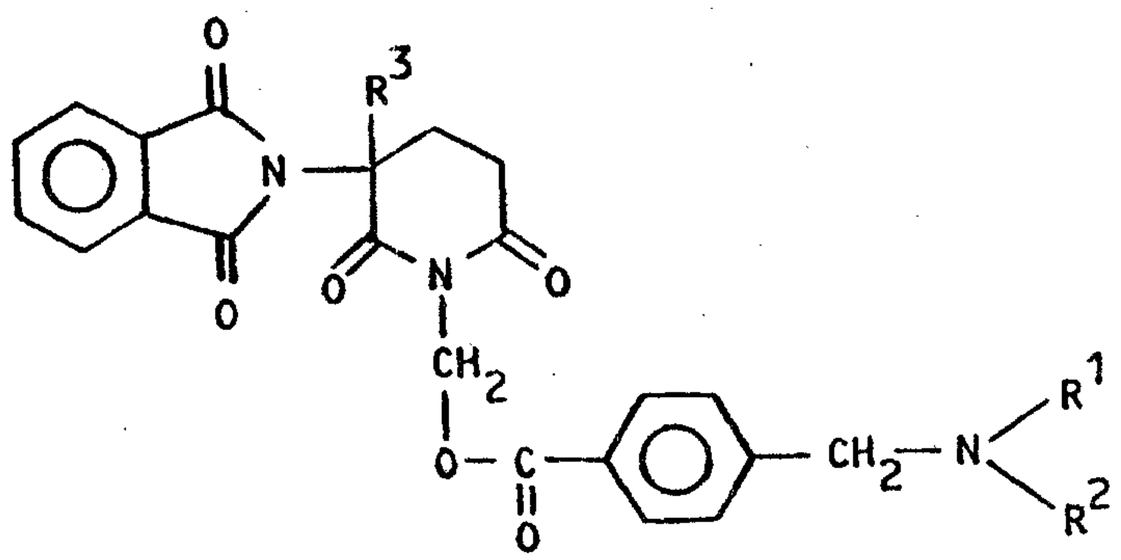
New thalidomide derivatives, process of preparing them and use of these derivatives in medicaments (G 2105)

The invention relates to new thalidomide derivatives of formula I



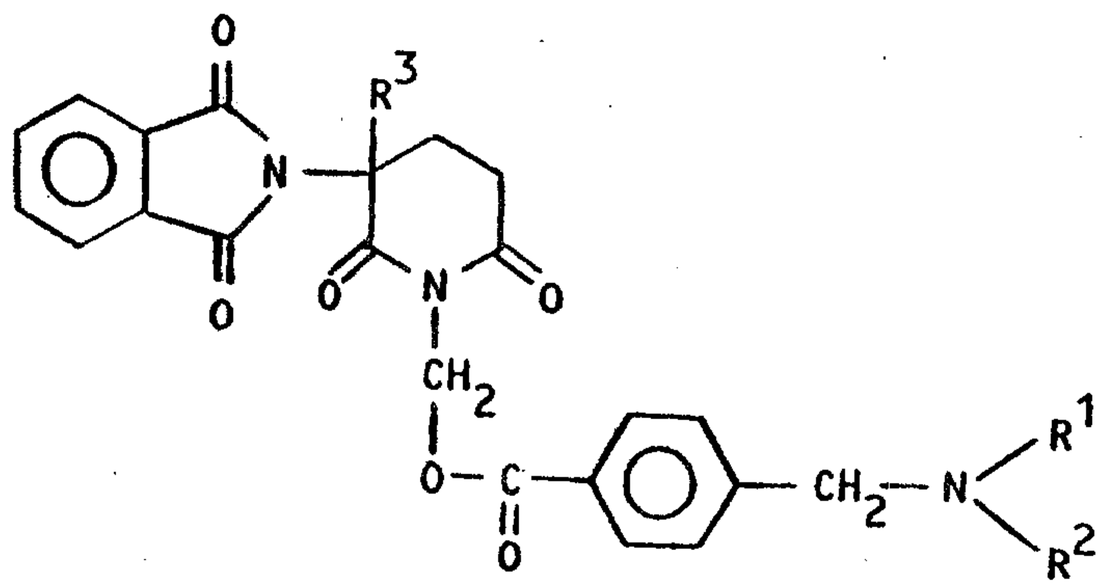
medicaments containing at least one of these compounds and a process for preparing these compounds and medicaments.

It is known that thalidomide (3-phthalimido-piperidine-2,6-dione) has immunosuppressive and immunomodulating properties. The poor water solubility of this compound, however, is disadvantageous in respect to its therapeutic use. The result is that up to now thalidomide can only be orally administered which causes disturbances of resorption and considerable variations in plasma levels in case of disorders which are associated with mucosa defects in the gastrointestinal tract, e.g. the graft-versus-host disease.

The invention provides water-soluble derivatives of thalidomide which are suitable for parenteral administration. Further the immunosuppressive and immunomodulating properties of these derivatives

are equal or better compared to the corresponding properties of thalidomide.

Accordingly, the present invention relates to thalidomide derivatives of formula I



in which the residues R^1 and R^2 independently represent a C_{1-6}-alkyl group or R^1 and R^2 together represent $-CH_2CH_2-X-CH_2CH_2-$, R^3 represents H or CH_3 and X represents O or NH, and/or the salts thereof in racemic or optically active form.

Derivatives of thalidomide in which the residue R^3 is H are preferred. Derivatives of thalidomide wherein the residues R^1 and R^2 together represent $-CH_2CH_2OCH_2CH_2-$ or $-CH_2CH_2NHCH_2CH_2-$, especially $-CH_2CH_2OCH_2CH_2-$ are particularly preferred.

Due to their solubility in water and their stability in aqueous solutions or dispersions the compounds of the invention are especially suitable for parenteral administration.

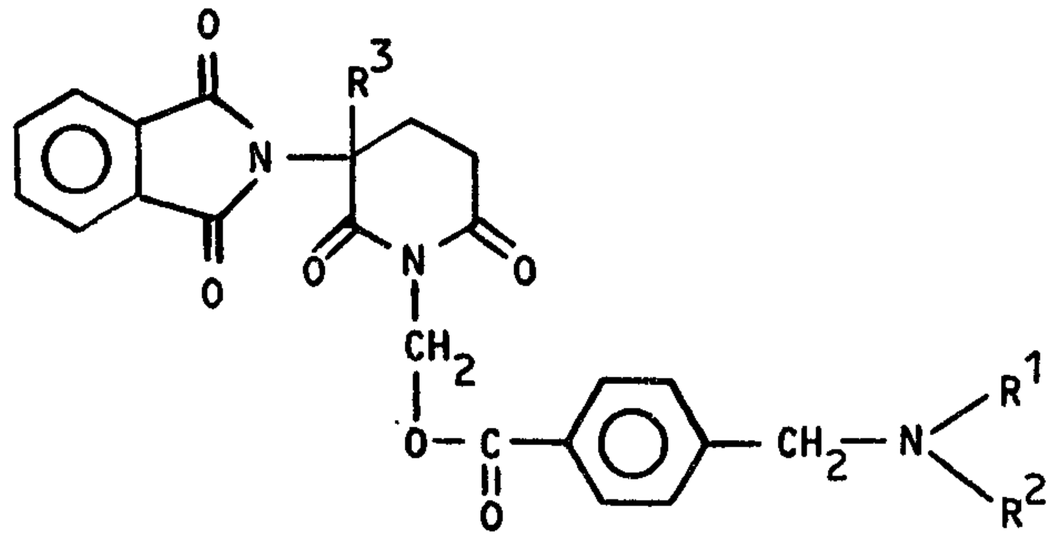
Accordingly the invention also relates to medicaments containing as active ingredient at least one thalidomide

derivative and/or at least one salt thereof in racemic or optically active form.

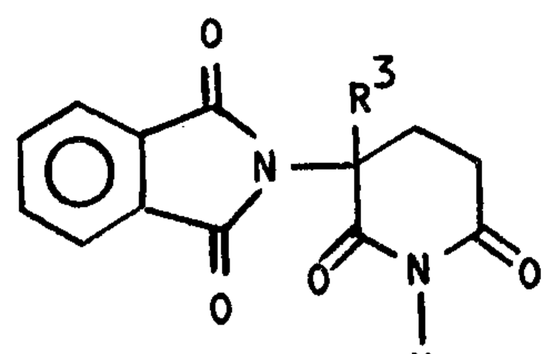
Compositions for parenteral administration may be solutions, suspensions, dry formulations suitable for easy reconstitution, ointments, pastes, gels, depots of an active ingredient in diluted form or plasters. All of the foregoing general types of pharmaceutical compositions to which the invention is applicable as well as the preparation of these compositions are known. The incorporation of the thalidomide derivatives according to the invention into these pharmaceutical compositions in the form and dosage desired poses no problems for an ordinarily skilled pharmacist. In the production of pharmaceutical compositions according to the invention the usual care must naturally be taken in the selection of carriers and inorganic or organic adjuvants such as diluents, solvents, stabilizers, dispersing agents, wetting agents, binders, coloring agents and flavorings. In particular care should be taken to achieve sterility and if the compositions are in liquid form, isotonicity.

The medicaments according to the invention are suitable in the treatment of immunological disorders such as leprosy, Becet's syndrome, lupus erythematosus, prurigo nodularis, mundaphtene in AIDS-patients, colitis ulcerosa and especially in the treatment of the graft-versus-host disease. The medicaments may be intravenously, intradermally, intramusculary, intranasally and locally administered. The local application is especially suitable in the treatment of infections of the skin, mucosae and eyes.

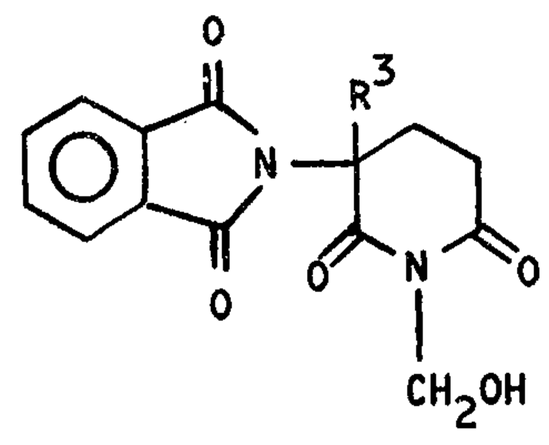
Further, the invention provides a process for preparing thalidomide derivatives of formula I



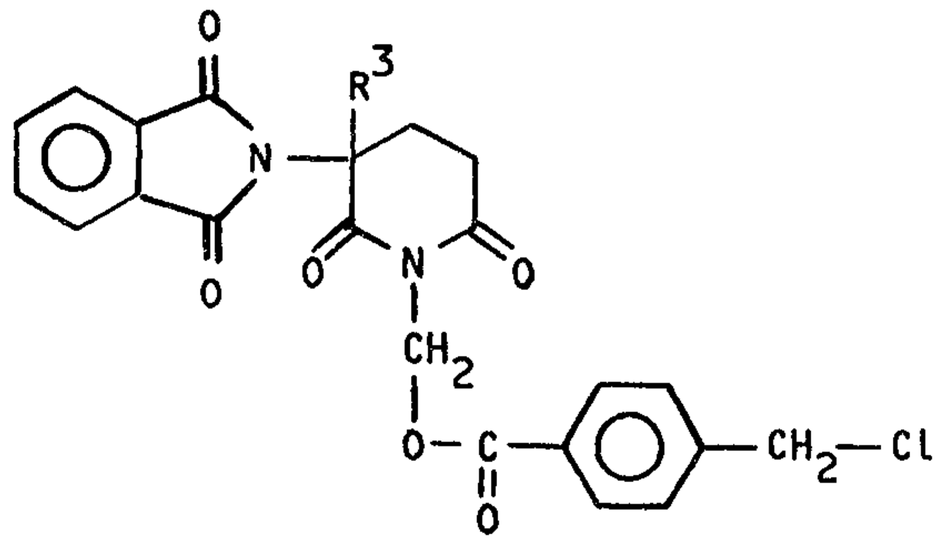
in which the residues R^1 and R^2 independently represent a C_{1-6}-alkyl group or R^1 and R^2 together represent $-CH_2CH_2-X-CH_2CH_2-$, R^3 represents H or CH_3 and X represents O or NH, and/or the salts thereof in racemic or optically active form, said process comprising the steps of reacting a compound of formula II



in racemic or optically active form with formaldehyde to form a N-hydroxymethyl compound of formula III



reacting the resulting N-hydroxymethyl compound with 4-chloromethylbenzoic acid in the presence of dicyclohexylcarbodiimide to form an ester of formula IV



transforming the resulting ester into a thalidomide derivative of formula I by reaction with a di(C_{1-6}-alkyl)amine, morpholine or piperazine, and optionally converting the resulting thalidomide derivative with an acid into a corresponding salt.

To prepare thalidomide derivatives according to the invention the preferably used starting compound thalidomide is hydroxymethylated with formaldehyde at the glutarimide nitrogen atom. After reaction with 4-chloromethylbenzoic acid in the presence of dicyclohexylcarbodiimide in a solvent or solvent mixture, followed by reaction preferably with morpholine or piperazine, especially with morpholine in the presence of an alkali halide, e.g. sodium iodide, in an anhydrous solvent or solvent mixture a thalidomide derivative according to the invention is obtained which may be converted with an acid, e.g. hydrochloric acid, optionally in presence of a C_{1-3}-alkyl alcohol into a corresponding salt.

The invention also provides a kit, comprising:

(a) a container containing therein a pharmaceutical composition according to the invention; and

(b) a written matter associated therewith, the written matter describing indications of the pharmaceutical composition for use in treating an immunological disorder or graft-versus-host disease.

Example

Preparation of N-(4-morpholinomethyl-benzoyloxymethyl)thalidomide, hydrochloride salt

2.58 g of thalidomide in 30 ml of an aqueous solution containing 35 % by weight of formaldehyde were heated under reflux. After formation of a clear solution the mixture was allowed to cool to 20° C. After 24 hours the mixture was filtered and the resulting residue washed with an aqueous solution containing 3 % by weight of formaldehyde. The N-hydroxymethyl-thalidomide obtained (yield: 70 %) melted at 165° C.

1.1 g of N-hydroxymethyl-thalidomide, 0.68 g of 4-chloromethylbenzoic acid, 1.03 g of dicyclohexylcarbodiimide and 0.06 g of 4-pyrrolidinopyridin in 25 ml of dichloromethane were stirred at 20° C for 24 hours. After removal of cyclohexylurea by filtration and dichloromethane by destillation the resulting residue was recrystallized from ethanol to yield N-(4-chloromethyl-benzoyloxymethyl)thalidomide (yield: 60 %) melting at 215 to 220° C.

880 mg of N-(4-chloromethyl-benzoyloxymethyl)thalidomide, 350 mg of morpholine and 20 mg of sodium iodide in anhydrous acetone were stirred at 20° C for 24 hours. After removal of acetone by destillation the resulting oily residue was purified by column chromatography ("Kieselgel 60" from E. Merck of Darmstadt, Germany) with ethyl acetate. The resulting oil was dissolved in ethanolic hydrochloric acid and precipitated by addition of diethyl ether. After recrystallization from ethanol N-(4-morpholinomethyl-benzoyloxymethyl)thalidomide, hydrochloride salt was obtained (yield: 40 %) melting at 236° C.

^{1}H-NMR (200 MHz, DMSO-d_6):

2.08, 2.62 (m, m, 2H, C$\underline{H}_2$-CH);

2.84, 2.91 (m, m, 2H, CH_2CO);

3.10, 3.70 (m, m, 8H, -CH_2-CH_2);

4.41 (s, 2H, -CH_2-N);

5.35, 5.43 (dd, 1H, C$\underline{H}$-CH_2);

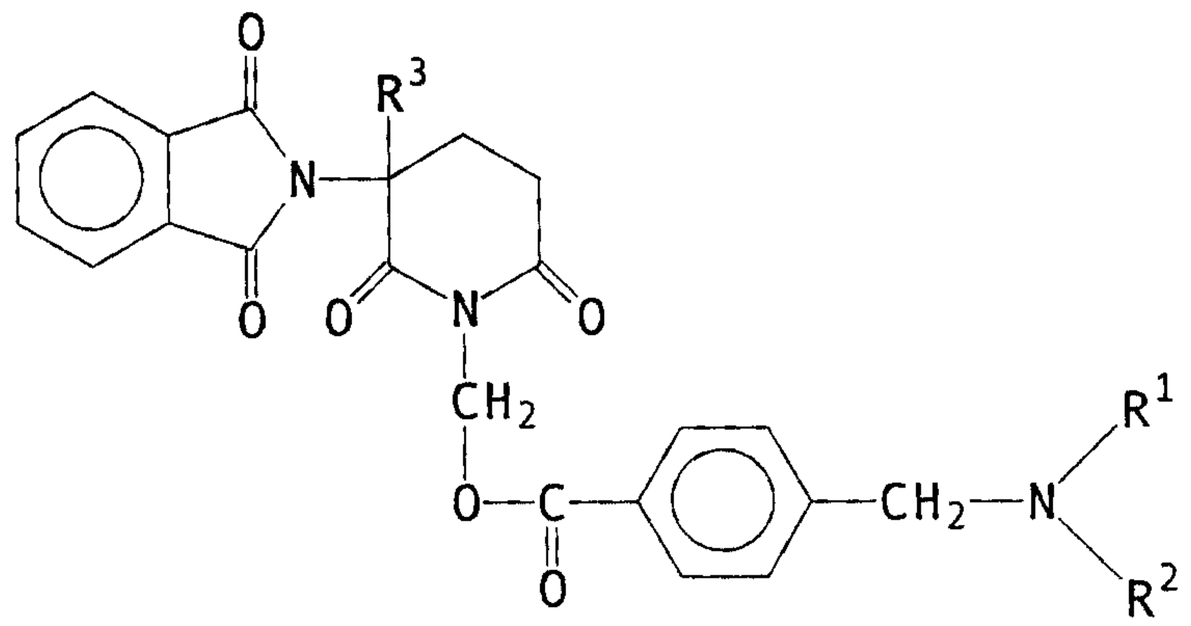
5.92 (d, 2H, N-CH_2-O);

7.72, 7.92 (m, m, 8H, aromat.);

11.20 (s, 1H, H^+)

CLAIMS:

1. A thalidomide derivative of general formula I:



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wherein: R^1 and R^2 independently represent a C_{1-6}-alkyl group, or R^1 and R^2 together represent $-CH_2CH_2-X-CH_2CH_2-$; R^3 represents H or CH_3; and X represents O or NH; or a salt thereof; in racemic or optically active form.

2. A thalidomide derivative according to claim 1, wherein R^3 is H.

3. A thalidomide derivative according to claim 1 or 2, wherein R^1 and R^2 together represent $-CH_2CH_2-X-CH_2CH_2-$.

4. A thalidomide derivative according to claim 3, wherein R^1 and R^2 together represent $-CH_2CH_2-O-CH_2CH_2-$.

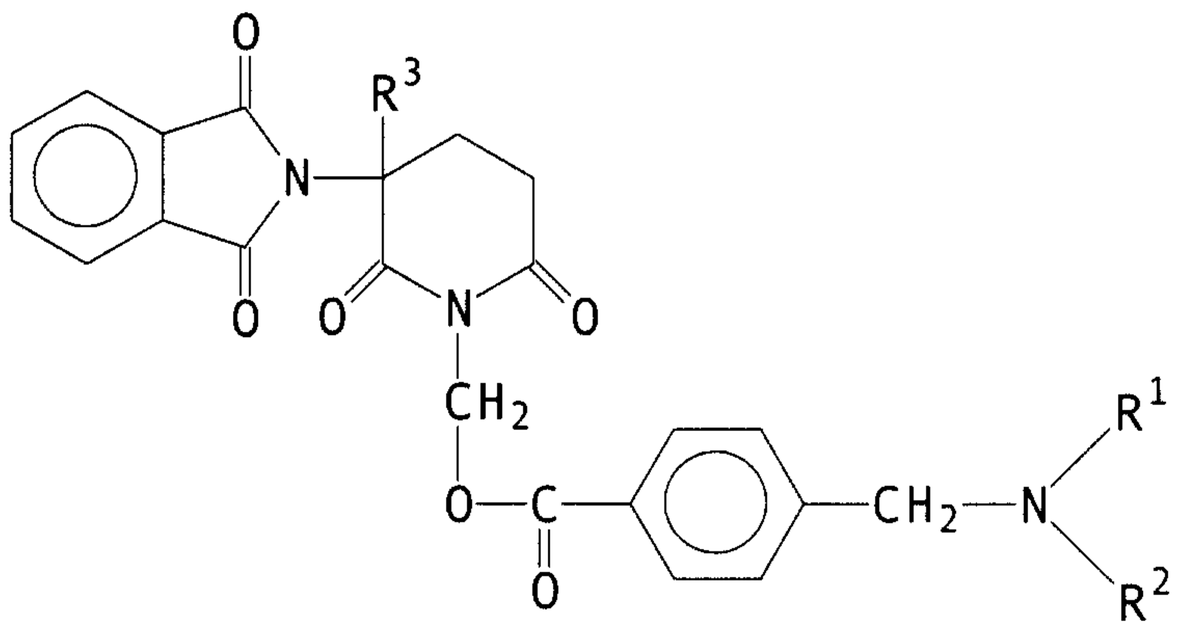
5. A pharmaceutical composition, comprising: as active ingredient, at least one thalidomide derivative or a pharmaceutically acceptable salt thereof in racemic or optically active form according to any one of claims 1 to 4; and a pharmaceutically acceptable diluent or carrier.

6. A pharmaceutical composition according to claim 5, in a dosage format adapted for parenteral administration.

7. A process for preparing a pharmaceutical composition comprising admixing at least one thalidomide

derivative or a pharmaceutically acceptable salt thereof in racemic or optically active form according to any one of claims 1 to 4, and a pharmaceutically acceptable diluent or carrier, optionally with one or more auxiliary agents and preparing a dosage form from the resulting admixture.

8. A process for preparing a thalidomide derivative of general formula I:



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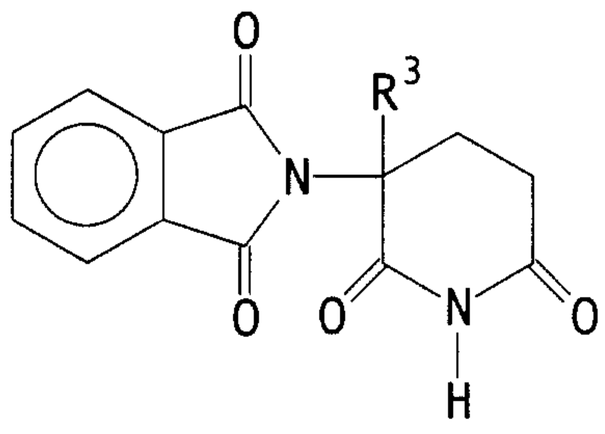
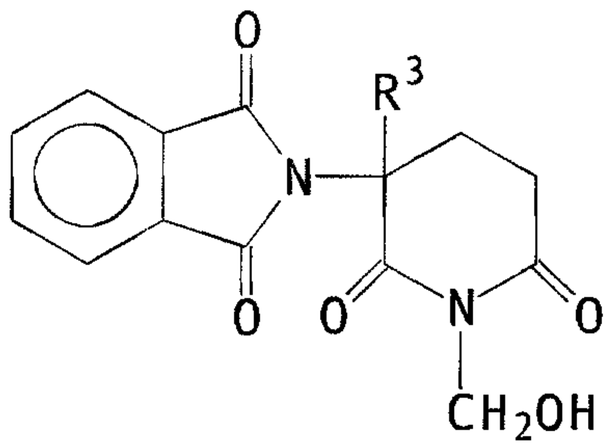
wherein R^1, R^2 and R^3 are as defined in any one of claims 1 to 4, or a salt thereof in racemic or optically active form, said process comprising: reacting a compound of general formula II:



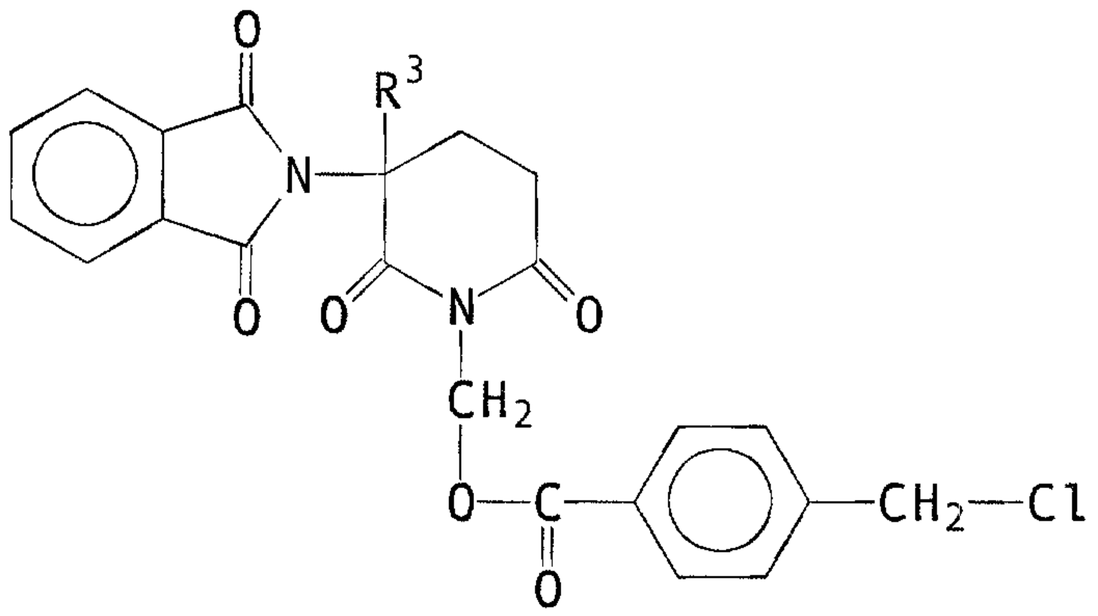
II

wherein R^3 is as defined above in racemic or optically active form with formaldehyde to form a N-hydroxymethyl compound of general formula III:



III

wherein R^3 is as defined above and reacting the resulting N-hydroxymethyl compound with 4-chloromethylbenzoic acid in the presence of dicyclohexylcarbodiimide to form an ester of general formula IV:



IV

wherein R^3 is as defined above and transforming the resulting ester into a thalidomide derivative of general formula I by reaction with a di(C_{1-6}-alkyl)amine, morpholine or piperazine and, if desired, converting the resulting thalidomide derivative with an acid into a corresponding salt.

9. A process according to claim 8, wherein said ester of general formula IV is reacted with morpholine or piperazine.

10. A process according to claim 9, wherein said ester of general formula IV is reacted with morpholine.

11. Use of a thalidomide derivative or a pharmaceutically acceptable salt thereof in racemic or

optically active form according to any one of claims 1 to 4, for treating an immunological disorder.

12. Use of a thalidomide derivative or a pharmaceutically acceptable salt thereof in racemic or optically active form according to any one of claims 1 to 4, for treating graft-versus-host disease.

13. Use of a pharmaceutical composition according to claim 5 or 6, for treating an immunological disorder.

14. Use of a pharmaceutical composition according to claim 5 or 6, for treating graft-versus-host disease.

15. A kit, comprising:

(a) a container containing therein a pharmaceutical composition according to claim 5 or 6; and

(b) a written matter associated therewith, the written matter describing indications of the pharmaceutical composition for use in treating an immunological disorder.

16. A kit, comprising:

(a) a container containing therein a pharmaceutical composition according to claim 5 or 6; and

(b) a written matter associated therewith, the written matter describing indications of the pharmaceutical composition for use in treating graft-versus-host disease.

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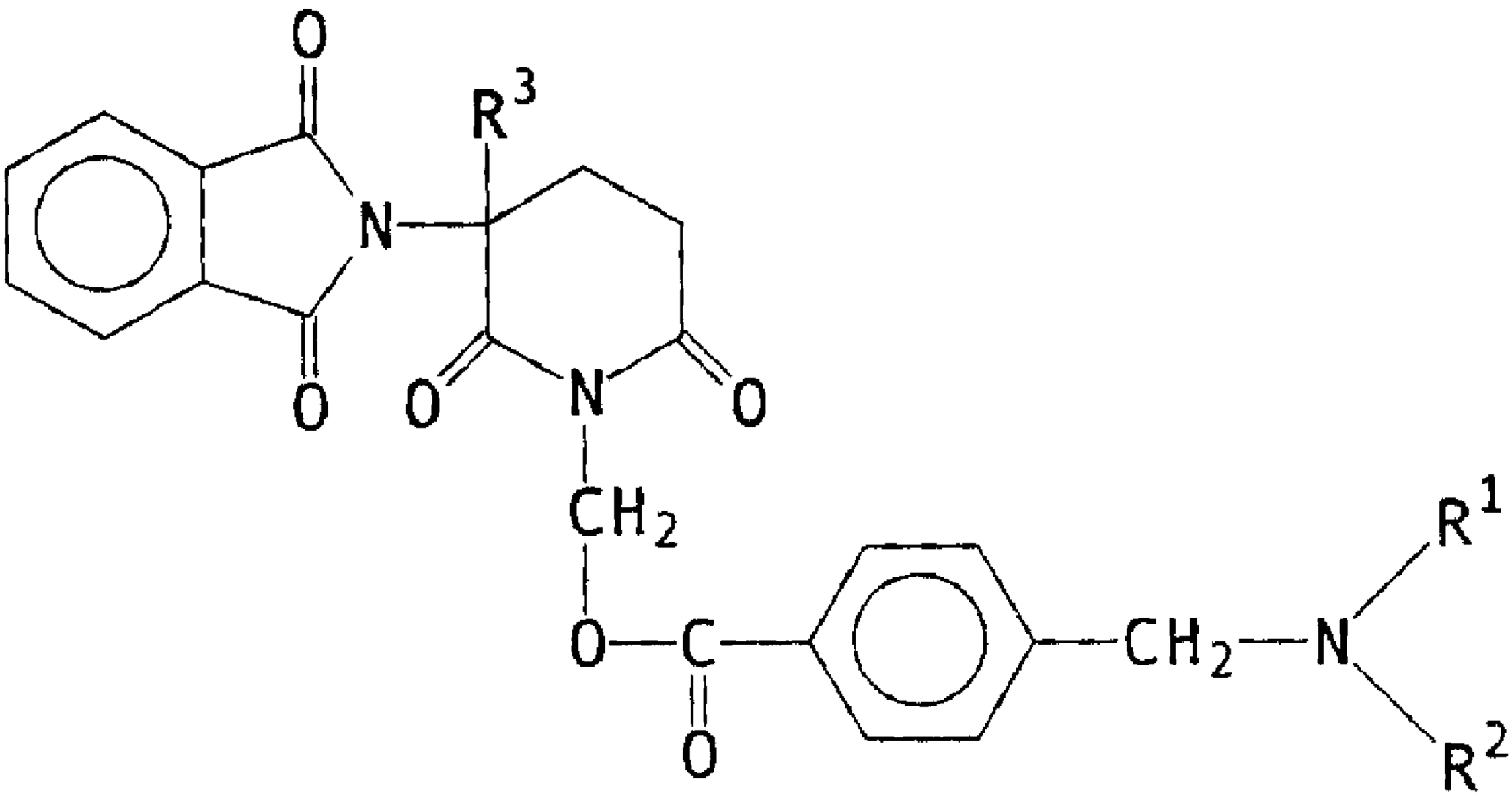
PATENT AGENTS



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