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(71) Applicant (for all designated States except US): **CIPLA LIMITED** [IN/IN]; 289 Bellasis Road, Mumbai Central, Mumbai 400 008, Maharashtra (IN).

(71) Applicant (for MW only): **CURTIS, Philip, Anthony** [GB/GB]; A.A. Thornton & Co., 235 High Holborn, London WC1V 7LE (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **RAO, Dharmaraj, Ramachandra** [IN/IN]; 4/403 Garden Enclave, Pokhran Road 2, Thane (West) 400 601, Maharashtra (IN). **KANKAN, Rajendra, Narayanrao** [IN/IN]; 1204,

Heritaje, Hiranandani Gardens, Powai, Mumbai 400 076, Maharashtra (IN). **SURVE, Manohar** [IN/IN]; Raghuvansh, Ambrai Karjat, Dist.: Raigad 410 201, Maharashtra (IN). **BIRARI, Dilip** [IN/IN]; Vijay Park B-20/604, Ghodbundar Road, Thane (West) 400 607, Maharashtra (IN).

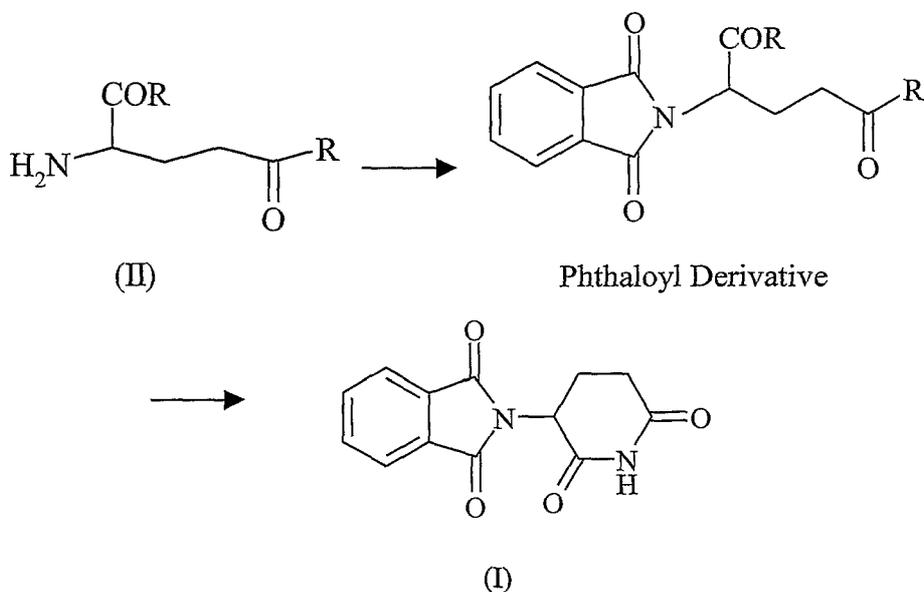
(74) Agents: **COTTRILL, Emily, Elizabeth, Helen** et al.; A.A. Thornton & Co., 235 High Holborn, London WC1V 7LE (GB).

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(54) Title: PROCESSES FOR THE PREPARATION OF THALIDOMIDE



(57) Abstract: The present invention provides a process for the preparation of thalidomide (I) comprising: i) reacting a compound of formula (II), where one of R represents -OH or -NH<sub>2</sub> and the other of R represents -NH<sub>2</sub> or -OH, respectively, with a phthaloylating agent in the presence of a base and a non-polar organic solvent to obtain a phthaloyl derivative where R have the same meanings as above; and ii) dehydrating the phthaloyl derivative using a dehydrating agent selected from an acid anhydride, an acid halide, an ion exchange resin or a molecular sieve to obtain thalidomide (I).

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## PROCESSES FOR THE PREPARATION OF THALIDOMIDE

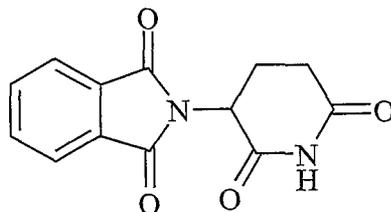
### Technical Field of the Invention

The present invention relates to simple and novel processes for the preparation of 2-(2,6-dioxo-3-piperdiny)-1H-isoindole-1,3-(2H)-dione or its pharmaceutically acceptable salts.

### Background of the Invention

2-(2,6-dioxo-3-piperdiny)-1H-isoindole-1,3-(2H)-dione is commonly known as thalidomide. Thalidomide is represented by the following formula (I).

10



(I)

Thalidomide was first disclosed in 1957 for use as an antiemetic in pregnant women. Even today thalidomide is of great importance because of its use in various types of diseases such as cancer, leprosy, rheumatoid arthritis, AIDS and Crohn's disease. Thalidomide is also used as immunomodulator.

GB768821 discloses a process for the preparation of thalidomide which involves reacting N-phthalyl glutamic acid or N-phthalyl glutamic acid anhydride with urea or thiourea or dry gaseous ammonia in the presence or absence of solvent. The reaction is carried out at higher temperature, for example 170 - 180°C. The yield of the reaction is about 60-70%. However, the processes disclosed in GB768821 involve violent evolution of carbon dioxide or carbon disulphide and ammonia which is dangerous, difficult to manage and also not environment friendly.

25

EP1004581B discloses a process for the preparation of thalidomide in which N-phthaloylglutamine or N-phthaloylisoglutamine is cyclised with N,N'-carbonyldiimidazole by

heating them in anhydrous tetrahydrofuran and in the presence of an inorganic base such as sodium carbonate or sodium bicarbonate.

US20060211728 discloses a process for the preparation of thalidomide (example 1) which  
5 involves reaction of t-butoxycarbamate with carbodiimide in tetrahydrofuran (THF) to give an imide. This imide is then deprotected with trifluoroacetic acid in methylene dichloride (MDC) at room temperature to yield aminoglutarimide which on reaction with phthalic anhydride in refluxing THF in the presence of triethylamine gives thalidomide.

10 US20050272934 discloses a process for the preparation of thalidomide which involves reaction of glutamine with a phthaloylating agent to give N-phthaloylglutamine, which is converted to thalidomide by addition of a condensing agent like carbonyl diimidazole or thionyl chloride in the presence of polar aprotic solvent. However, carbonyl diimidazole is very costly and thionyl chloride is corrosive, so the process disclosed in US20050272934  
15 is unsuitable for industrial scale-up. Furthermore, polar aprotic solvents as used in the process generally have a high boiling point and are difficult to remove completely from the final product at an industrial level. Still further, in the case of the use of pyridine as a solvent, the reaction mass is acidified with hydrochloric acid which is industrially not preferable. Yet further, pyridine is hazardous, hence not preferred industrially.

20

US20070173647 discloses the preparation of dicarboxylic imides by reaction of acid anhydride with urea in a high boiling solvent, specifically thalidomide is obtained by reaction of phthaloyl glutamic acid anhydride with urea in high boiling solvent.

25 Some of the reactions used in the prior art involve evolution of gases leading to foaming of the reaction mass which is dangerous and difficult to manage. Other reactions use costly reagents like carbonyl diimidazole or corrosive reagents like thionyl chloride. Some reactions are carried out at high temperatures which are not easy to achieve at industrial level and not environment friendly. Further, the use of urea or thiourea leads to an impure  
30 product due to thermal decomposition.

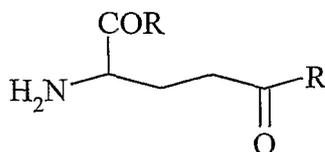
It has now surprisingly been found that thalidomide may be prepared by a simple reaction which avoids use of urea/thiourea and costly and/or corrosive reagents. The reaction is carried out at a moderate temperature which is environmentally friendly.

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### Summary of the Invention

It is an object of the present invention to provide a simple process for the preparation of thalidomide which may be carried out in one pot and which may involve no isolation of  
10 intermediates formed during the process.

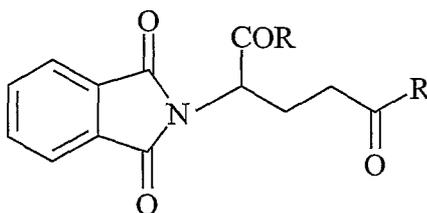
According to a first aspect of the present invention, there is provided a process for the preparation of thalidomide (I) comprising: i) reacting a compound of formula (II), where one of R represents  $-OH$  or  $-NH_2$  and the other of R represents  $-NH_2$  or  $-OH$ ,  
15 respectively,



(II)

with a phthaloylating agent in the presence of a base and a non-polar organic solvent to obtain a phthaloyl derivative where R have the same meanings as above,

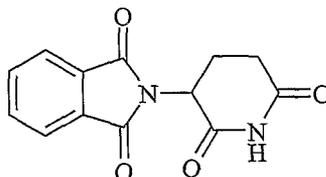
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Phthaloyl Derivative

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and ii) dehydrating the phthaloyl derivative using a dehydrating agent selected from an acid anhydride, an acid halide, an ion exchange resin or a molecular sieve, to obtain thalidomide (I).



(I)

5

The compound (II) may be glutamine  $\text{H}_2\text{NCH}(\text{CO}_2\text{H})\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$  or isoglutamine ( $\text{H}_2\text{NCH}(\text{CONH}_2)\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ).

10

Advantageously, steps (i) and (ii) are carried out without isolation of any of the intermediates formed in the process. Alternatively or in addition, the process is carried out in one pot. In an embodiment, the solvent from step (i) is distilled out partially before the addition of dehydrating agent.

15

Preferably, steps (i) and (ii) are carried out simultaneously, i.e. the compound of formula (II) is reacted with the phthaloylating agent in the presence of the base, non-polar organic solvent and dehydrating agent to obtain thalidomide.

20 In an embodiment, the phthaloylating agent is selected from the group consisting of phthalic acid, derivatives of phthalic acid (such as phthalic anhydride, N-carbethoxyphthalimide and phthaloyl chloride) and esters of phthalic acid (such as ethyl phthalate and dimethyl phthalate). Preferably, the phthaloylating agent is phthalic anhydride or N-carbethoxyphthalimide. In an embodiment, the phthaloylating agent is  
25 phthalic anhydride. In another embodiment, the phthaloylating agent is N-carbethoxyphthalimide.

In an embodiment, the base is an organic base, preferably an alkyl amine, more preferably a tertiary alkyl amines. Most preferably, the base is selected from triethyl amine, trimethyl amine and diisopropyl ethyl amine. Preferably, the base is triethylamine.

5 In an embodiment, the non-polar organic solvent is an aromatic hydrocarbon or a non-polar aprotic organic solvent. The solvent is preferably non-basic. The use of a base and a non-basic solvent according to the present invention, rather than the use of a basic solvent, is advantageous as it avoids the need for neutralization of the reaction mass. In US20050272934, particularly in Examples 1, 2, 3 and 9, basic solvents are used in the  
10 coupling step and this requires subsequent acidification with HCl. Such acidification is not required in the present process. This lends the process of the present invention further advantages as fewer steps typically result in a higher-yield product. Typically, the solvent is selected from toluene, xylene, n-heptane, diethyl benzene, chlorobenzene, bromobenzene, iodobenzene, mesitylene, diphenyl ether and nitrobenzene. Preferably,  
15 the solvent is toluene.

In an embodiment, step (i) is carried out with azeotropic removal of the water formed during the coupling. In other words, water is produced during the coupling step and this water is removed azeotropically as the reaction progresses.

20

In an embodiment, the dehydrating agent is selected from a dehydrating agent that is not N,N-carbonyldiimidazole nor thionyl chloride. Preferably, the dehydrating agent is an acid anhydride, an acid halide, an ion exchange resin or a molecular sieve. The acid anhydride or acid chloride may have the formula X-C(O)-Y, wherein X is C<sub>1</sub> to C<sub>6</sub> alkyl and Y is Cl, Br  
25 or OAc. Suitably, X is methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, pentyl or hexyl. Y may be Cl. Preferably, Y is OAc and X is methyl. Alternatively, Y is Cl and X is methyl.

More preferably, the dehydrating agent is an acid anhydride or an acid halide. The acid anhydride may be acetic anhydride, trifluoroacetic anhydride or isobutyric anhydride. The

acid halide may be acetyl chloride, acetyl bromide or propionyl chloride. Preferably, the dehydrating agent is acetic anhydride or acetyl chloride.

Most preferably, the non-polar organic solvent is toluene and the dehydrating agent is  
5 acetic anhydride.

The dehydration may be carried out in the presence or absence of a solvent. Typically, the dehydration is carried out in the presence of a solvent. The dehydration is suitably carried out in a polar aprotic solvent selected from N,N-dimethyl formamide, N-methyl  
10 pyrrolidone, dioxane, dimethyl acetamide, sulfolane, dimethyl sulphoxide or hexamethyl phosphoramidate.

After reaction of the dehydrating agent, the excess of dehydrating agent may be partially distilled out and the thalidomide isolated by crystallization. The crystallizing solvent may  
15 be selected from C<sub>1</sub>-C<sub>4</sub> alcohols, ketones and esters. For example, the crystallizing solvent may be selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, isobutanol, acetone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, n-butyl acetate and mixtures thereof.

20 Another advantage of the process of the present invention is that the thalidomide product does not require recrystallization. This is to be contrasted with the process disclosed in US20050272934, in which the thalidomide product is isolated as a solid and then recrystallised. Again, fewer steps in the present process typically result in a higher yield product. Therefore, in an embodiment, the process of the present invention does not  
25 require recrystallization of the thalidomide product.

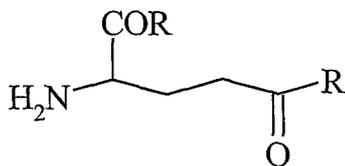
According to another aspect of the present invention, there is provided thalidomide prepared according to the process defined above. There is also provided a pharmaceutical composition comprising thalidomide prepared according to the process  
30 defined above together with one or more pharmaceutically acceptable excipients. Such

excipients and compositions are well known to those skilled in the art. According to yet another aspect of the present invention, there is provided the use of thalidomide prepared according to the process defined above in medicine, particularly in the treatment of cancer, leprosy, rheumatoid arthritis, AIDS and Crohn's disease. There is also provided a method  
 5 of treating cancer, leprosy, rheumatoid arthritis, AIDS and Crohn's disease comprising administering to a patient in need thereof a therapeutically effective amount of thalidomide prepared according to the process defined above.

### Detailed Description of the Invention

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In one embodiment of the present invention, thalidomide is prepared by the novel process in a single reactor which comprises reaction a compound of formula (II) with a phthaloylating agent to obtain a phthaloyl derivative of formula (II) and then converting the phthaloyl derivative to thalidomide, without isolating the intermediate phthaloyl derivative of  
 15 formula (II).



Wherein, R=-OH or -NH<sub>2</sub>

(II)

In the context of the present invention, the term "without isolation" means that the product being referred to as not being isolated is not isolated as a solid, for example it is not isolated from the reaction mass and dried to form a solid. Thus, "without isolation" may  
 20 mean that the product remains in solution and is then used directly in the next synthetic step, or it may mean that solvent is substantially removed from a solution of the product such that the product is present as a residue, but not as a solid.

The phthaloylating agent may be selected from the group consisting of phthalic acid,  
 25 derivatives of phthalic acid (such as phthalic anhydride, N-carbethoxyphthalimide and phthaloyl chloride) and esters of phthalic acid (such as ethyl phthalate and dimethyl

phthalate). The preferred phthaloylating agents are phthalic anhydride and N-carbethoxyphthalimide.

In another embodiment of the present invention, the reaction of the compound of formula  
5 (II) with the phthaloylating agent is carried out in a non-polar organic solvent selected from either aromatic hydrocarbons which may or may not be substituted or an aprotic organic solvent. The solvents may be selected from the group consisting of toluene, xylene, n-heptane, diethyl benzene, chlorobenzene, bromobenzene, iodobenzene, mesitylene, diphenyl ether and nitrobenzene. The preferred solvent is toluene.

10

In yet another embodiment of the present invention, the reaction of the compound of formula (II) with the phthaloylating agent is carried out in the presence of a base, particularly in the presence of an organic base, more particularly alkyl amines and further more particularly tertiary alkyl amines such as, but not limited to, triethyl amine, trimethyl  
15 amine, diisopropyl ethyl amine.

In another embodiment of the present invention, the conversion of the phthaloyl derivative of compound of formula (II) to thalidomide is carried out in the presence of a dehydrating agent such as an acid anhydride, an acid halide, an ion exchange resin or a molecular  
20 sieve. The acid anhydride may be acetic anhydride, trifluoroacetic anhydride or isobutyric anhydride. The acid halide may be acetyl chloride, acetyl bromide or propionyl chloride. The preferred dehydrating agents are acetic anhydride and acetyl chloride.

The thalidomide obtained may be further isolated using a suitable crystallizing solvent.

25

In another embodiment of the present invention, the solvent from step (i) is distilled out partially before the addition of dehydrating agent. Further, the dehydrating agent may be added with or without a suitable solvent. After reaction of the dehydrating agent, the excess of dehydrating agent may be distilled out and then a suitable crystallizing solvent  
30 may be added to the reaction mass. In an embodiment, the reaction mass is refluxed for

up to 2 hours, or up to 3 hours, preferably for around half an hour. The reaction mass may then be cooled to a temperature ranging from 10°C to 30°C, preferably from 15°C to 20°C.

Typically, the solvent is a polar aprotic solvent which may be selected from the group  
5 consisting of N,N-dimethyl formamide (DMF), N-methyl pyrrolidone, dioxane, dimethyl acetamide, sulfolane, dimethyl sulphoxide and hexamethyl phosphoramide.

The crystallizing solvent may be selected from C<sub>1</sub>-C<sub>4</sub> alcohols, ketones and esters. For example, the crystallizing solvent may be selected from the group consisting of methanol,  
10 ethanol, isopropanol, n-butanol, isobutanol, acetone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, n-butyl acetate and mixtures thereof.

The compound of formula (II) and phthalic anhydride may be reacted at a temperature ranging from about 20°C to about 50°C, preferably from about 20°C to about 30°C. After  
15 addition of the base, the temperature of reaction mass may be increased for example up to around 140°C, preferably up to a temperature ranging from about 105°C to about 110°C. Typically, the reaction mass is refluxed until reaction completion. After reaction completion, the temperature of the reaction mass may be lowered for example up to a temperature of about 50°C. After addition of the dehydrating agent, the temperature of the reaction mass  
20 may be increased for example up to a temperature of around 140°C, preferably up to about 105°C to about 110°C, typically under stirring.

The molar ratio of compound of formula (II) to phthalic anhydride may range from 1:1 to 1:1.5, preferably from 1:1 to 1:1.3.

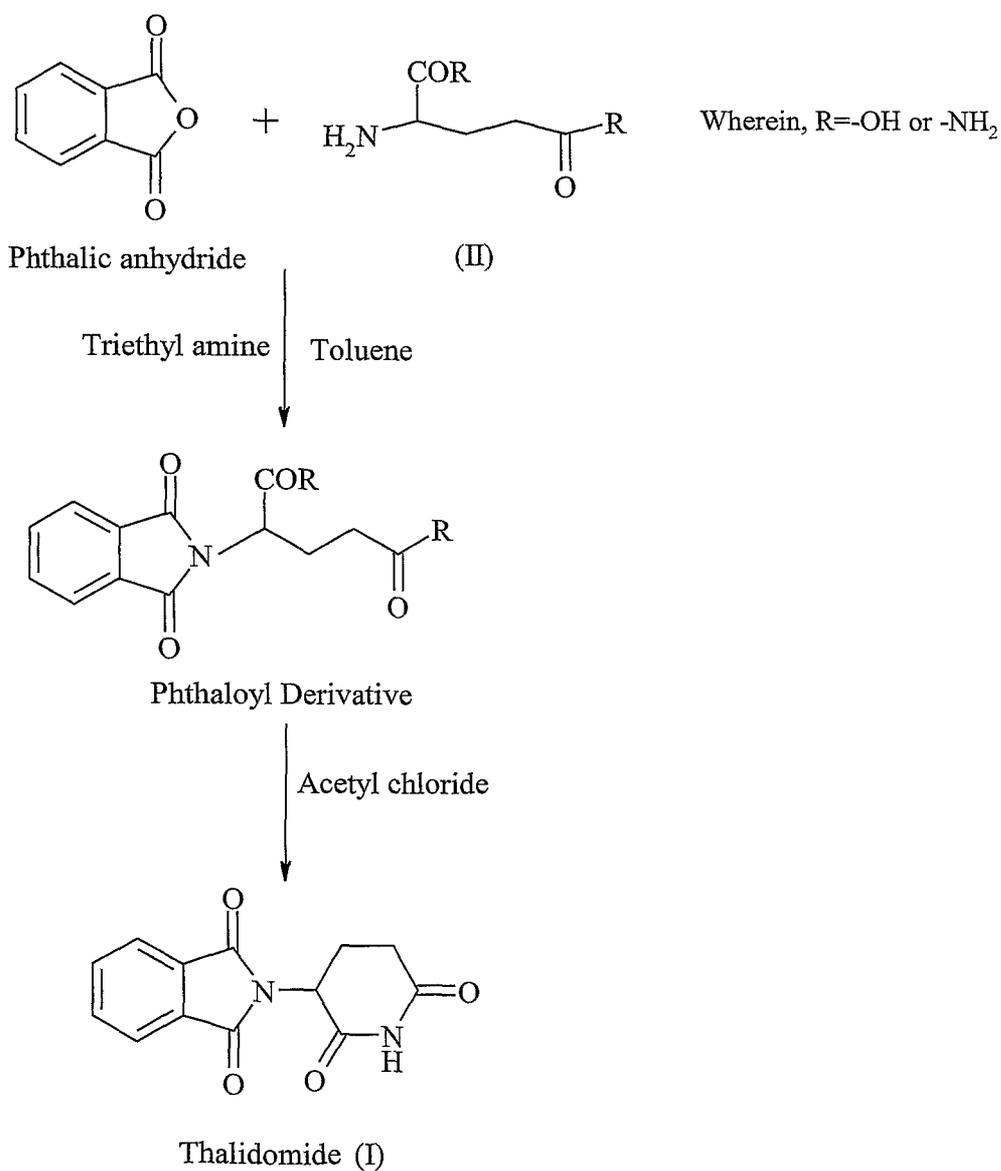
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The molar ratio of compound of formula (II) to organic base can range from 1:1 to 1:1.5, preferably from 1:1 to 1:1.3.

The molar ratio of compound of formula (II) to dehydrating agent may range from 1:1 to  
30 1:5, preferably from 1:1 to 1:3.

In an embodiment, the process of the present invention may be represented as shown below in reaction Scheme A:

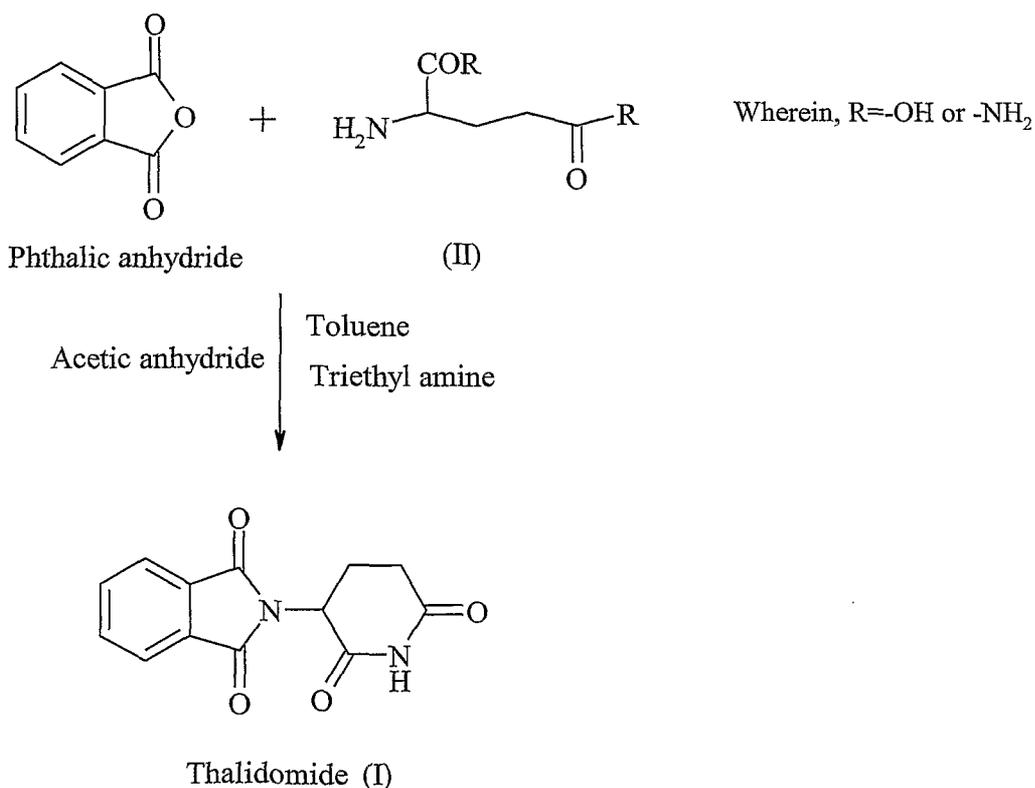
**SCHEME A**



In the most preferred embodiment of the present invention, thalidomide is prepared in a single step whereby the reaction of compound of formula (II) with phthaloylating agent in the presence of a base and further conversion of phthaloyl derivative of compound of formula (II) to thalidomide using a dehydrating agent are carried out simultaneously. In other words, steps (i) and (ii) are combined. In a particularly preferred embodiment, the process may be represented by scheme B.

Another advantage of the processes of present invention is that the reactions are carried out in a single reaction vessel without isolation of the intermediate formed in the process. Thus the yield is higher and the processing time is lower.

### SCHEME B



The present invention is now further illustrated by the following examples, which do not, in any way, limit the scope of the invention.

**Example 1**

- 5 L-glutamine (100g) and phthalic anhydride (140g) were suspended in toluene (1 liter) in a flask provided with a dean stark water separator. Triethyl amine (100 ml) was added to the flask. The contents of the flask were heated gradually to 110°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, the reaction mass was cooled to 50-60°C and acetic anhydride (200 ml) was added
- 10 thereto slowly. The resulting suspension was heated at 110°C, maintained for about three hours and cooled to 25-30°C to obtain a solid. The solid was filtered and dried at 50-55°C to obtain thalidomide (80 g).

**Example 2**

- 15 L-isoglutamine (100g) and phthalic anhydride (120g) were suspended in toluene (1 liter) in a flask provided with a dean stark water separator. Triethyl amine (120 ml) was added to the flask. The contents of the flask were heated gradually to 110°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, the reaction mass was cooled to 50-60°C and acetic anhydride (200ml) was added thereto
- 20 slowly. The resulting suspension was heated at 110°C, maintained for about three hours and cooled to 25-30°C to obtain a solid. The solid was filtered and dried at 50-55°C to obtain thalidomide (75g).

**Example 3**

- 25 L-glutamine (100g) and phthalic anhydride (135g) were suspended in toluene (1 liter) in a flask provided with a dean stark water separator. Triethyl amine (135ml) was added to the flask. The contents of the flask were heated gradually to 110°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, the reaction mass was cooled to 50-60°C and acetyl chloride (200ml) was added thereto
- 30 slowly. The resulting suspension was heated at 110°C, maintained for about three hours

and cooled to 25-30°C to obtain a solid. The solid was filtered and dried at 50-55°C to obtain thalidomide (65g).

#### Example 4

5 L-isoglutamine (100g) and phthalic anhydride (140g) were suspended in toluene (1 liter) in a flask provided with a dean stark water separator. Triethyl amine (135ml) was added to the flask. The contents of the flask were heated gradually to 110°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, the reaction mass was cooled to 50-60°C and acetyl chloride (200ml) was added slowly to  
10 the reaction mass. The resulting suspension was heated at 110°C, maintained for about three hours and cooled to 25-30°C to obtain a solid. The solid was filtered and dried at 50-55°C to obtain thalidomide (68g).

#### Example 5

15 L-glutamine (100g) and phthalic anhydride (140g) were suspended in xylene (1 liter) in a flask provided with a dean stark water separator followed by triethyl amine (130ml). The contents of the flask were heated gradually to 140°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, the reaction mass was cooled to 50-60°C and acetic anhydride (200ml) was added thereto slowly. The  
20 resulting suspension was heated at 110°C, maintained for about three hours and cooled to 25-30°C to obtain a solid. The solid was filtered and dried at 50-55°C to obtain thalidomide (73g).

#### Example 6

25 L-isoglutamine (100g) and phthalic anhydride (140g) were suspended in xylene (1 liter) in a flask provided with a dean stark water separator followed by triethyl amine (100ml). The contents of the flask were heated gradually to 140°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, the reaction mass was cooled to 50-60°C and acetic anhydride (200ml) was added thereto slowly. The  
30 resulting suspension was heated at 110°C, maintained for about three hours and cooled to

25-30°C to obtain a solid. The solid was filtered and dried at 50-55°C to obtain thalidomide (65 g).

**Example 7**

5 L-glutamine (100g) and phthalic anhydride (125g) suspended in chlorobenzene (1 liter) in a flask provided with a dean stark water separator followed by triethyl amine (135ml). The contents of the flask were heated gradually to 110°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, the reaction mass was cooled to 50-60°C and acetic anhydride (200ml) was added thereto slowly. The  
10 resulting suspension was heated to 110°C, maintained for about three hours and cooled to 25-30°C to obtain a solid. The solid was filtered and dried at 50-55°C to obtain thalidomide (72g).

**Example 8**

15 L-isoglutamine (100g) and phthalic anhydride (140g) suspended in chlorobenzene (1 liter) in a flask provided with a dean stark water separator followed by triethyl amine (135ml). The contents of the flask were heated gradually to 110°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, the reaction mass was cooled to 50-60°C and acetyl chloride (200ml) was added thereto slowly. The  
20 resulting suspension was heated to 110°C, maintained for about three hours and cooled to 25-30°C to obtain a solid. The solid was filtered and dried at 50-55°C to obtain thalidomide (75g).

**Example 9**

25 L-glutamine (100g) and phthalic anhydride (125g) were suspended in toluene (1 liter) in a flask provided with a dean stark water separator. Triethyl amine (100ml) was added to the flask. The contents of the flask were heated gradually to 110°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, toluene was distilled out under vacuum. Acetic anhydride (200ml) was added thereto  
30 slowly. The reaction mass was heated at 120°C and maintained for two hours. Acetic

anhydride was distilled out under vacuum to obtain a residue. Denatured alcohol (200ml) was added to the residue, refluxed for about half an hour and cooled to 15-20°C to obtain a solid. The solid was filtered and dried under vacuum to obtain thalidomide (65g).

#### 5 Example 10

L-glutamine (100g) and phthalic anhydride (135g) were suspended in toluene (1 liter) in a flask provided with a dean stark water separator. Triethyl amine (100ml) was added to the flask. The contents of the flask were heated gradually to 110°C. The water generated during the course of reaction was separated azeotropically. After completion of reaction, 10 toluene was distilled out under vacuum. Acetyl chloride (200ml) was added slowly to the flask followed by N,N-dimethyl formamide (200ml). The temperature of the reaction mass was raised to 50°C and maintained for 2 hours. Acetyl chloride was distilled out under vacuum to obtain a residue. Denatured alcohol (200ml) was added to the residue, refluxed for about half an hour and cooled to 15-20°C to obtain a solid. The solid was filtered and 15 dried under vacuum to obtain thalidomide (55g).

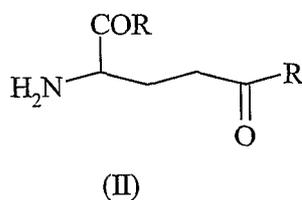
#### Example 11

L-glutamine (10g) and phthalic anhydride (10g) were suspended in toluene (100ml) in a flask followed by triethyl amine (10ml) and acetic anhydride (20ml). The contents of the 20 flask were heated gradually to 110°C, refluxed until completion of the reaction and cooled to 25-30°C to obtain a solid. The solid was filtered and dried under vacuum to obtain thalidomide (7.4g).

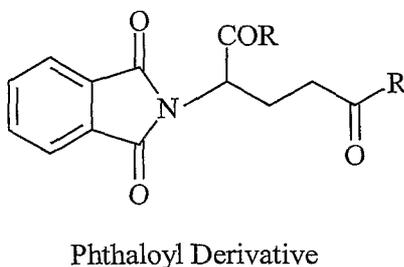
It will be appreciated that the invention may be modified within the scope of the appended 25 claims.

**CLAIMS**

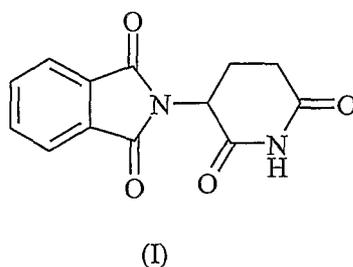
1. A process for the preparation of thalidomide (I) comprising: (i) reacting a compound of formula (II), where one of R represents –OH or –NH<sub>2</sub> and the other of R represents –NH<sub>2</sub> or –OH, respectively,



- with a phthaloylating agent in the presence of a base and a non-polar organic solvent to obtain a phthaloyl derivative where R have the same meanings as above,



- and (ii) dehydrating the phthaloyl derivative using a dehydrating agent selected from an acid anhydride, an acid halide, an ion exchange resin or a molecular sieve, to obtain thalidomide (I).



2. A process according to claim 1, wherein steps (i) and (ii) are carried out without isolation of any of the intermediates formed in the process.
- 5 3. A process according to claim 1 or 2, wherein the process is carried out in one pot.
4. A process according to claim 1, 2 or 3, wherein steps (i) and (ii) are carried out simultaneously.
- 10 5. A process according to any preceding claim, wherein the non-polar organic solvent is an aromatic hydrocarbon or a non-polar aprotic organic solvent.
6. A process according to claim 5, wherein the non-polar organic solvent is selected from toluene, xylene, n-heptane, diethyl benzene, chlorobenzene, bromobenzene,  
15 iodobenzene, mesitylene, diphenyl ether and nitrobenzene.
7. A process according to any preceding claim, wherein step (i) is carried out with azeotropic removal of water.
- 20 8. A process according to any preceding claim, wherein the phthaloylating agent is selected from the group consisting of phthalic acid, derivatives of phthalic acid and esters of phthalic acid.
9. A process according to any preceding claim, wherein the base is an alkyl amine.
- 25 10. A process according to claim 9, wherein the dehydrating agent is an acid anhydride or an acid halide.
11. A process according to any preceding claim, wherein the non-polar organic solvent  
30 is toluene and the dehydrating agent is acetic anhydride.

12. A process according to any preceding claim, wherein the dehydration is carried out in the presence or absence of a solvent.

5 13. A process according to claim 12, wherein the dehydration is carried out in a polar aprotic solvent selected from N,N-dimethyl formamide, N-methyl pyrrolidone, dioxane, dimethyl acetamide, sulfolane, dimethyl sulphoxide or hexamethyl phosphoramide.

14. A process according to any preceding claim, wherein the thalidomide is isolated by  
10 addition to the reaction mass of a crystallization solvent selected from a C<sub>1</sub>-C<sub>4</sub> alcohol, a ketone and an ester.

15. A process for the preparation of thalidomide substantially as herein described with reference to the examples.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/004290

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
C07D

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

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

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KING F E ET AL: "SYNTHESES FROM PHTHALIMIDO-ACIDS. PART VII. OXAZOLONES AND OTHER INTERMEDIATES IN THE SYNTHESIS OF PHTHALYLPEPTIDES, AND AN INVESTIGATION OF MALEIC ACID DERIVATIVES OF AMINO-ACIDS" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL SOCIETY. LETCHWORTH.; GB, 1 January 1957 (1957-01-01), pages 873-880, XP009054486 ISSN: 0368-1769	1-15
Y	----- page 878	1-15
Y	EP 1 602 654 A (ANTIBIOTICOS SPA [IT]) 7 December 2005 (2005-12-07) cited in the application sentences 1-4 ----- -/--	1-15

 Further documents are listed in the continuation of Box C. See patent family annex.

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\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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\*Z\* document member of the same patent family

Date of the actual completion of the international search

20 February 2009

Date of mailing of the international search report

04/03/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Bader, Karl Günther

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/004290

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	XIANG, DONG ET AL: "New synthetic route of R-orS-thalidomide" HUAXUE YANJIU YU YINGYONG , 18(11), 1349-1352 CODEN: HYYIFM; ISSN: 1004-1656, 2006, XP009112427 page 1350  -----	1-15

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/004290

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			JP	2005343895 A	15-12-2005
			US	2005272934 A1	08-12-2005

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