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(54) **PROCESS FOR THE PREPARATION OF INDOMETHACIN**

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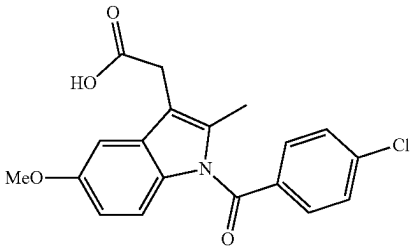
(57) **ABSTRACT**

An improved process for the preparation of Indomethacin of formula (I):

(I)




is provided by means of the precipitation, crystallization, re-crystallization or re-slurry of the intermediate 4-chloro-N-(4-methoxyphenyl)benzohydrazide in a mixture containing tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol.

# PROCESS FOR THE PREPARATION OF INDOMETHACIN

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of priority from European Patent Application Serial No. EP24158915.9, filed on 21 Feb. 2024, the contents of which are incorporated herein by reference.

## TECHNICAL FIELD

**[0002]** The present invention refers to an improved process for the preparation of Indomethacin.

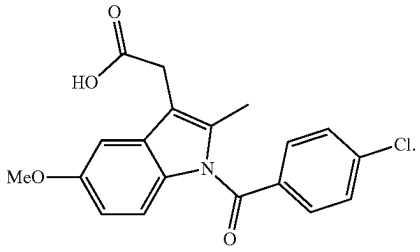
## BACKGROUND OF THE INVENTION

**[0003]** Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling from inflammation. It works by inhibiting the production of prostaglandins, endogenous signaling molecules known to cause these symptoms.

**[0004]** Indomethacin was discovered and approved for medical use in the early 1960s. It is on the World Health Organization's List of Essential Medicines.

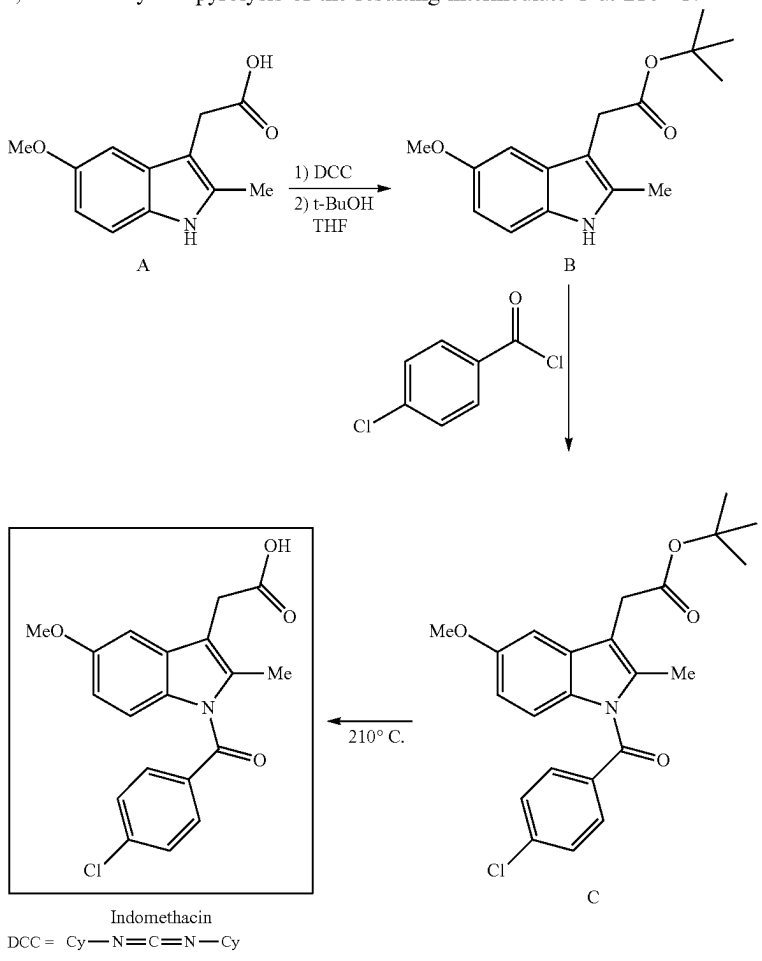
**[0005]** Indomethacin is an indole-3-acetic acid wherein the indole ring is substituted at positions 1, 2 and 5 by p-chlorobenzoyl, methyl, and methoxy groups, respectively. Its chemical name is 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid and has the following chemical formula (I):

(I)



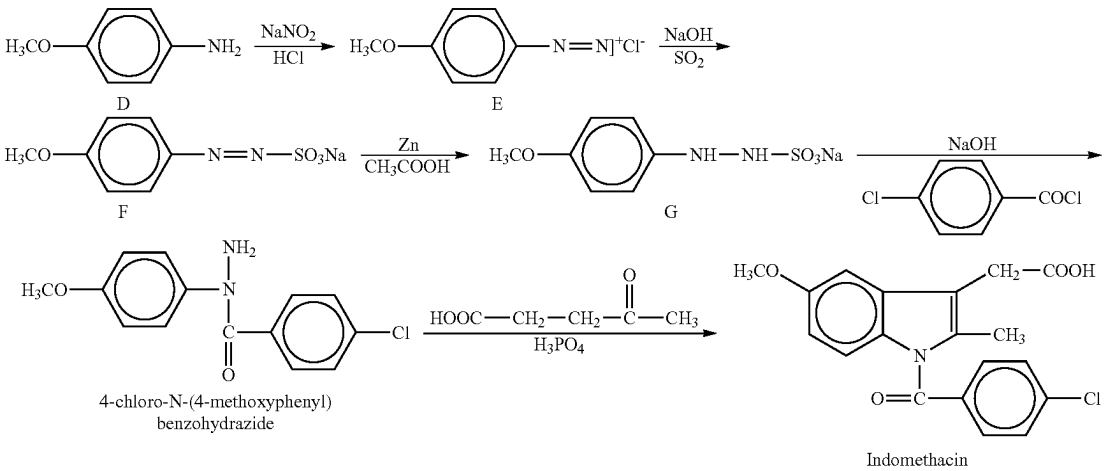

**[0006]** Indomethacin can be prepared according to several synthetic processes described in the literature.

**[0007]** The first synthesis of Indomethacin is described for example in J. Am. Chem. Soc. 1963, pages 488-489. The route of synthesis is attached in the following page. The starting material 5-methoxy-2-methylindole-3-acetic acid A is converted into its anhydride by reaction with dicyclohexylcarbodiimide. The latter is then treated with zinc chloride and t-butanol to give t-butyl-5-methoxy-2-methyl-3-indolylacetate B. Indomethacin is then obtained by acylation of the t-butyl ester with p-chlorobenzoyl chloride followed by pyrolysis of the resulting intermediate C at 210° C.




DCC = Cy—N=C=N—Cy

**[0008]** A new route of synthesis towards Indomethacin was later developed (J. Pharm. Biomed. Anal. 1998, 17, pages 409-413), comprising the following steps:

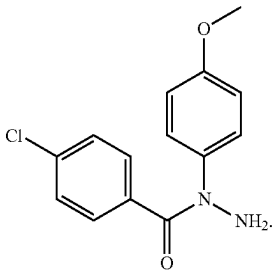



**[0009]** According to this new method, p-anisidine D is reacted with sodium nitrite to give the corresponding diazonium salt E, which is in turn converted into the diazensulfonate F with sulfur dioxide under basic conditions. The following reduction with zinc in acetic acid produces the hydrazine sulfonate G. By reaction with p-chlorobenzoyl chloride and concomitant desulfonation the intermediate 4-chloro-N-(4-methoxy phenyl)benzohydrazide is then obtained. This intermediate is finally reacted with levulinic acid (or 4-oxopentanoic acid) in the presence of phosphoric acid to achieve Indomethacin. This route of synthesis has many advantages with respect to the previous synthetic approach, such as higher yields.

**[0010]** Other processes later developed for the preparation of Indomethacin, reported for example in J. Pharm. Biomed. Anal. 2000, 24, 19-24, in Bioorg. Med. Chem. 2001, 9,745-762 or in Org. Letters 2004, 6, 79-82, have in common the intermediate 4-chloro-N-(4-methoxyphenyl)benzo hydrazide as final intermediate for the preparation of Indomethacin.

**[0011]** Modern synthetic approaches for the industrial manufacturing of Indomethacin, therefore, are based on the key intermediate 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II):

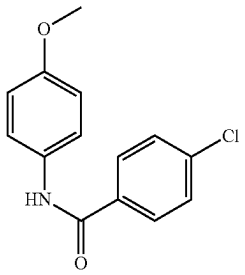
(II)



**[0012]** Since in all the synthetic routes where said intermediate is employed it is the last one before the obtainment of the final product Indomethacin, it clearly follows that its purity can affect final product impurity profile. For this reason, regulatory guidelines are nowadays strongly recommending developing manufacturing processes for Active Pharmaceutical Ingredients (APIs) in which the impurities are suitably controlled before the final synthetic step.

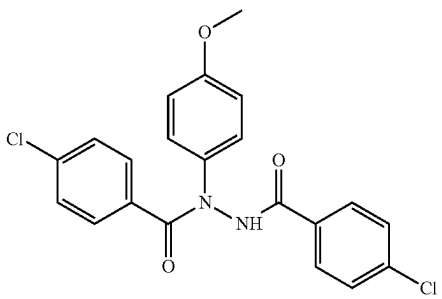
**[0013]** Among the several organic impurities specified for Indomethacin in the European Pharmacopoeia (European Pharmacopoeia 11.0, pages 3077-3079), 4-chloro-N-(4-methoxyphenyl)benzamide of formula (III):

(III)



**[0014]** is identified as Impurity C and 4-chloro-N'-(4-chlorobenzoyl)-N-(4-methoxyphenyl)benzo hydrazide of formula (IV):

(IV)



**[0015]** is identified as Impurity F. Both the impurities are typical process impurities generated in the synthetic process, which are normally found in the key intermediate 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II) within the range 1%-15% A/A % as determined by HPLC.

**[0016]** Such a variability on the impurity content of the key intermediate of formula (II) represents an evident issue in terms of reproducibility and control of the key process intermediate quality and, consequently, of the final product Indomethacin.

**[0017]** Impurities of formula (III) and formula (IV), in fact, together with other unspecified organic impurities eventually found in intermediate of formula (II), can be carried forward to the final API Indomethacin when intermediate of formula (II) is converted into Indomethacin, thus affecting final product impurity profile.

**[0018]** Prior art methods described for the preparation of Indomethacin through the key intermediate benzohydrazide of formula (II) do not provide an adequate control on process impurities. Impurity of formula (III) and impurity of formula (IV), in fact, are typically found in the intermediate of formula (II) ranging from 1% to 15% A/A % as determined by HPLC.

**[0019]** Thus, there is a need for a process for preparing Indomethacin characterized by a proper control of organic impurities content.

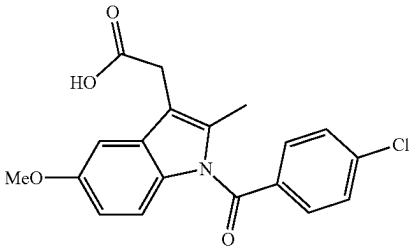
## SUMMARY OF THE INVENTION

**[0020]** The problem addressed by the present invention is therefore that of providing a process for the preparation of Indomethacin, which allows to control Indomethacin impurity content, in particular the content of impurity of formula (III) and impurity of formula (IV).

**[0021]** This problem is solved by a process for the precipitation, crystallization, re-crystallization or re-slurry of intermediate of formula (II) as outlined in the annexed claims, whose definitions are integral part of the present description.

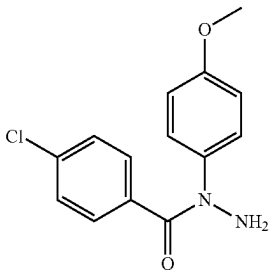
**[0022]** Particularly, the present invention provides a process for the preparation of Indomethacin of formula (I):

(I)




**[0023]** by means of precipitation, crystallization, re-crystallization or re-slurry of intermediate of formula (II):

(II)




**[0024]** in a mixture comprising tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol, followed by conversion of the obtained compound of formula (II) to give Indomethacin.

**[0025]** As a further aspect, the invention provides a process for the preparation of intermediate of formula (II) characterized by high purity as determined by HPLC.

**[0026]** As a further aspect, the present invention provides a process for the purging of process impurities of formula (III) and formula (IV) from intermediate of formula (II).

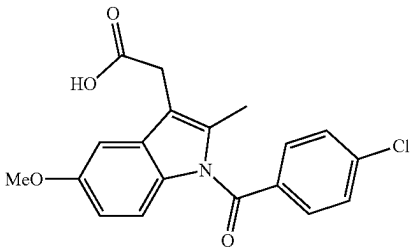
**[0027]** As another aspect, it is provided a process to prepare intermediate of formula (II) having impurity (III) content below 0.15% A/A % as determined by HPLC and having impurity (IV) content below 0.15% A/A % as determined by HPLC.

**[0028]** Further features and advantages of the processes according to the invention will result from the description hereafter reported of examples of realization of the invention, provided as an indication of the invention.

## DETAILED DESCRIPTION OF THE INVENTION

**[0029]** The present invention is related to a process for the preparation of Indomethacin of formula (I):

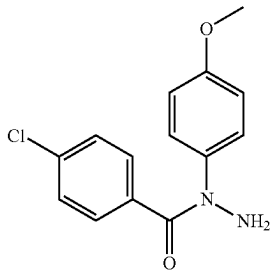
(I)



**[0030]** comprising the following steps:

**[0031]** i) precipitation, crystallization, re-crystallization or re-slurry of the compound 4-chloro-N-(4-methoxy phenyl)benzohydrazide of formula (II):

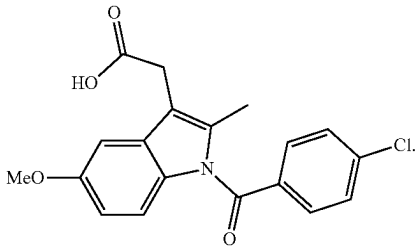
(II)



**[0032]** in a mixture comprising tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol;

**[0033]** ii) conversion of compound of formula (II) obtained in step i) to give Indomethacin of formula (I):

(I)



**[0034]** It was surprinsingly found, in fact, that by means of precipitation, crystallization, re-crystallization or re-slurry of intermediate of formula (II) in a mixture comprising tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol, the quality of compound of formula (II) is significantly improved.

**[0035]** In particular, it was surprinsingly found that the content of impurity of formula (III) and the content of impurity of formula (IV) in compound of formula (II) is drastically lowered.

**[0036]** It follows that, by means of precipitation, crystallization, re-crystallization or re-slurry of intermediate of formula (II) in a mixture comprising tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol, the quality of intermediate (II) and hence the quality of Indomethacin can be controlled.

**[0037]** By precipitation or crystallization it is intended the physical process of phase transformation of a dissolved substance into an insoluble solid, which remains suspended in the mixture. For promoting the precipitation or crystallization of a compound from a solution various methods are available, for example concentrating the solution until compound saturation is realized, cooling down said solution to lower compound solubility, adding a solvent in which the compound is poorly soluble or insoluble or seeding said solution with a small amount of the compound (seed). The solid obtained is then usually isolated by filtration or centrifugation.

**[0038]** Suspension means a solid material suspended in a solvent or solution, i.e. mixture of a solid with a solvent, which is liquid.

**[0039]** Solution means a liquid mixture in which the minor components (the solute) is dissolved and uniformly distributed within the major component (the solvent).

**[0040]** By re-crystallization it is intended that a solid compound is dissolved in a solvent and then precipitated for example by cooling the solution and/or adding another solvent. The solid obtained is then usually isolated by filtration or centrifugation.

**[0041]** By re-slurry it is intended that a solid compound is suspended in a solvent or in mixture of solvents. The solid obtained is then usually isolated by filtration or centrifugation.

**[0042]** According to a preferred embodiment of the process of the present invention, the term $C_1$-$C_4$ linear or branched alkyl alcohol, a component of the above mentioned mixture, means one alkyl alcohol selected in the group comprising: Methanol; Ethanol; 1-Propanol (i.e. Propanol); 2-Propanol (i.e. Isopropanol); 1-Butanol (i.e. Butanol); 2-Butanol (i.e. sec-Butanol); 2-methyl-1-Propanol (i.e. iso-Butanol); 2-methyl-2-Propanol (i.e. tert-Butanol).

**[0043]** According to a more preferred embodiment of the process of the present invention, the alkyl alcohol is isopropanol.

**[0044]** According to a preferred embodiment of the process of the present invention, the ratio between tetrahydrofuran and the $C_1$-$C_4$ linear or branched alkyl alcohol is comprised in the range from 4:1 to 1:4 v/v.

**[0045]** According to a more preferred embodiment of the process of the present invention, the ratio between tetrahydrofuran and the $C_1$-$C_4$ linear or branched alkyl alcohol is comprised in the range from 2:1 to 1:2 v/v.

**[0046]** According to a even more preferred embodiment of the process of the present invention, the ratio between tetrahydrofuran and the $C_1$-$C_4$ linear or branched alkyl alcohol is 1:1 v/v.

**[0047]** As intended herein, the expression v/v is the abbreviation of volume per volume, thus, for example, the proportion of two solvents within a mixture as measured by the volume occupied by each solvent. A mixture of tetrahydrofuran/isopropanol 2/1 v/v means, for example, 2 Liters of tetrahydrofuran per 1 Liter of isopropanol.

**[0048]** According to a preferred embodiment of the process of the present invention for preparing Indomethacin (I), in step i) the following steps are comprised:

**[0049]** a) charging 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II) and tetrahydrofuran;

**[0050]** b) heating the mixture of step a) until complete dissolution of the compound of formula (II);

**[0051]** c) cooling down the mixture of step b) to a temperature comprised in the range from 35° C. to 60° C. over a period comprised in the range from 30 minutes to 2 hours;

**[0052]** d) dosing the $C_1$-$C_4$ linear or branched alkyl alcohol into the mixture of step c) over a period comprised in the range from 30 minutes to 3 hours at a temperature comprised in the range from 35° C. to 60° C.;

**[0053]** e) stirring the mixture of step d) for a period comprised in the range from 30 minutes to 3 hours at a temperature comprised in the range from 35° C. to 60° C.;

**[0054]** f) cooling down the mixture of step e) to a temperature comprised in the range from −15° C. to 30° C. over a period comprised in the range from 30 minutes to 5 hours;

**[0055]** g) stirring the mixture of step f) at a temperature comprised in the range from −15° C. to 30° C. for a period comprised in the range from 30 minutes to 5 hours;

**[0056]** h) isolating the solid obtained in step g) by filtration or centrifugation to obtain 4-chloro-N-(4-methoxyphenyl)benzo hydrazide of formula (I).

**[0057]** According to a preferred embodiment of the process of the present invention, in step a) tetrahydrofuran is charged from 1 volume to 10 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II).

**[0058]** According to a more preferred embodiment of the process of the present invention, in step a) tetrahydrofuran is charged from 1 volume to 5 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II).

**[0059]** According to a even more preferred embodiment of the process of the present invention, in step a) tetrahydrofuran is charged from 1 volume to 2 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzo hydrazide of formula (II)

**[0060]** The term "volume" means volume of solvent per unit of product, thus, for example, 1 volume is 1 Liter per 1 Kilo, or 1 mL per 1 gram, or 1 microliter per 1 milligram. Thus, 10 volumes means for example 10 liters per 1 Kilogram of substance.

**[0061]** According to a preferred embodiment of the process of the present invention, in step c) the mixture is cooled down to a temperature comprised in the range from 49° C. to 51° C. over 1 hour.

**[0062]** According to a preferred embodiment of the process of the present invention, in step d) the alcohol is dosed from 1 volume to 10 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II).

**[0063]** According to a more preferred embodiment of the process of the present invention, in step d) the alcohol is dosed from 1 volume to 5 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II).

**[0064]** According to a even more preferred embodiment of the process of the present invention, in step d) the alcohol is dosed from 1 volume to 2 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzo hydrazide of formula (II).

**[0065]** According to a preferred embodiment of the process of the present invention, in step d) the alcohol is dosed into the mixture over 1 hour at a temperature comprised in the range from 49° C. to 51° C.

**[0066]** According to a preferred embodiment of the process of the present invention, in step e) the mixture is stirred for 1 hour at a temperature comprised in the range from 49° C. to 51° C.

**[0067]** According to a preferred embodiment of the process of the present invention, in step f) the mixture is cooled down to a temperature comprised in the range from 4° C. to 6° C. over 2 hours.

**[0068]** According to a preferred embodiment of the process of the present invention, in step g) the mixture is stirred at a temperature comprised in the range from 4° C. to 6° C. for 1 hour.

**[0069]** According to a more preferred embodiment of the process of the present invention, in step c) the mixture is cooled down to a temperature comprised in the range from 49° C. to 51° C. over 1 hour, in step d) the alcohol is dosed into the mixture over 1 hour at a temperature comprised in the range from 49° C. to 51° C., in step e) the mixture is stirred for 1 hour at a temperature comprised in the range from 49° C. to 51° C., in step f) the mixture is cooled down to a temperature comprised in the range from 4° C. to 6° C. over 2 hours and in step g) the mixture is stirred at a temperature comprised in the range from 4° C. to 6° C. for 1 hour.

**[0070]** According to a preferred embodiment of the process of the present invention for preparing Indomethacin (I), in step i) the following steps are comprised:

**[0071]** a1) charging 4-chloro-N-(4-methoxyphenyl) benzohydrazide of formula (I), tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol;

**[0072]** b1) heating the mixture of step a1) to a temperature comprised in the range from 30° C. to 70° C.;

**[0073]** c1) stirring the mixture of step b1) at a temperature comprised in the range from 30° C. to 70° C. for a period comprised in the range from 1 hour to 5 hours;

**[0074]** d1) cooling down the mixture of step c1) to a temperature comprised in the range from 15° C. to 35° C. over a period comprised in the range from 10 minutes to 3 hours;

**[0075]** e1) stirring the mixture of step d1) at a temperature comprised in the range from 15° C. to 35° C. for a period comprised in the range from 10 minutes to 5 hours;

**[0076]** f1) isolating the solid obtained in step e1) by filtration or centrifugation to obtain 4-chloro-N-(4-methoxyphenyl)benzo hydrazide of formula (I).

**[0077]** According to a preferred embodiment of the process of the present invention, in step a1) tetrahydrofuran is charged from 1 volume to 10 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II) and the alcohol is charged from 1 volume to 10 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II).

**[0078]** According to a more preferred embodiment of the process of the present invention, in step a1) tetrahydrofuran is charged from 1 volume to 5 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II) and the alcohol is charged from 1 volume to 10 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II).

**[0079]** According to a even more preferred embodiment of the process of the present invention, in step a) tetrahydrofuran is charged from 1 volume to 2 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzo hydrazide of formula (II) and the alcohol is charged from 1 volume to 10 volumes with respect to 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II).

**[0080]** According to a preferred embodiment of the process of the present invention, in step b1) and step c1) the temperature is comprised in the range from 50° C. to 55° C.

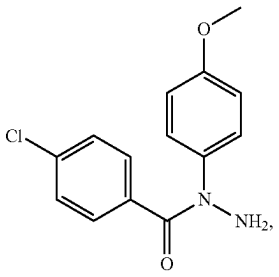
**[0081]** According to a preferred embodiment of the process of the present invention, in step d1) the mixture is cooled down to a temperature comprised in the range from 20° C. to 25° C. over 2 hours and in step e1) the mixture is stirred at a temperature comprised in the range from 20° C. to 25° C. for 1 hour.

**[0082]** According to a preferred embodiment of the process of the present invention, in step b1) and step c1) the temperature is comprised in the range from 50° C. to 55° C., in step d1) the mixture is cooled down to a temperature comprised in the range from 20° C. to 25° C. over 2 hours and in step e1) the mixture is stirred at a temperature comprised in the range from 20° C. to 25° C. for 1 hour.

**[0083]** According to a preferred embodiment of the process of the present invention, step i) is repeated more than one time.

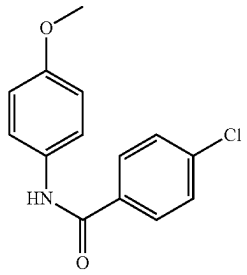
**[0084]** According to a preferred embodiment of the process of the present invention the compound 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II):

(II)



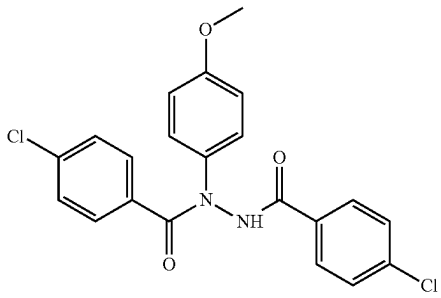
**[0085]** obtained in step i) has a content of impurity 4-chloro-N-(4-methoxyphenyl)benzamide of formula (III):

(III)



**[0086]** not higher than 0.15% A/A % as determined by HPLC, and a content of impurity 4-chloro-N'-(4-chlorobenzoyl)-N-(4-methoxyphenyl)benzo hydrazide of formula (IV):

(IV)

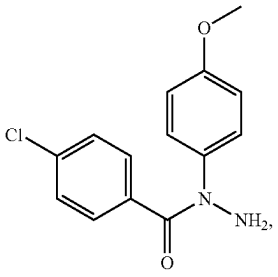


**[0087]** not higher than 0.15% A/A % as determined by HPLC.

**[0088]** As known by a person skilled in the art, in a HPLC chromatogram each peak represents one of the components found in the compound analyzed (sample). The area under each peak corresponds to the concentration of the corresponding component in the sample. By A/A % it is thus intended the concentration of each component as a percent of the total.

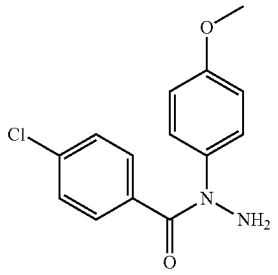
**[0089]** The present invention is also addressed to a process for the preparation of the compound 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II):

(II)



**[0090]** by precipitation, crystallization, re-crystallization or re-slurry of the compound 4-chloro-N-(4-methoxy phenyl)benzohydrazide of formula (II):

(II)



**[0091]** in a mixture comprising tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol.

**[0092]** According to preferred embodiments of the present invention, the process for the preparation of compound of formula (II) is carried out applying one or more of the features described in the paragraphs above for step i).

**[0093]** Obviously and optionally, step i) of the process of the present invention can be re-applied on compound (II) to reach the desired purity of compound of formula (II) and/or Indomethacin of formula (I), specifically to reach the desired amount of impurity of formula (III) and impurity of formula (IV) in compound of formula (II) and/or Indomethacin of formula (I).

**[0094]** All the features and preferred embodiments of the process of the present invention given above can be combined in each possible combination to carry out the claimed process.

## EXPERIMENTAL SECTION

**[0095]** The starting material 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II) can be prepared according to well-known prior art methods, or for example, as

described in J. Pharm. Biomed. Anal. 1998, 17, pages 409-413, or can be purchased on the market.

**[0096]** Room temperature (RT) means a temperature that is comprised in a range from 20 to 25° C., it is defined as comfortable temperature range indoors.

**[0097]** As intended herein, drying the wet material under vacuum means to heat the material to a given temperature for a given time while applying a reduced pressure. This operation is performed to remove residual solvents from the product.

Example 1: Re-Crystallization of Compound of Formula (II) in a Mixture Tetrahydrofuran/Methanol 1:1 v/v

**[0098]** In a round bottom flask equipped with a half-moon stirrer were charged: 20 g of 4-chloro-N-(4-methoxyphenyl) benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 5.85% A/A % by HPLC and a content of impurity of formula (IV) of 11.36% A/A % by HPLC, 30 mL of methanol and 30 mL of tetrahydrofuran. The mixture was heated to T=50° C. and kept stirring at this temperature for 1 h. Thereafter, the mixture was cooled to RT over 2 h and the resulting slurry was filtered. The wet solid was dried under vacuum at T=80° C. for 12h. 11.2 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 1.56% A/A % by HPLC and a content of impurity of formula (IV) of 2.55% A/A % by HPLC.

Example 2: Re-Crystallization of Compound of Formula (II) in a Mixture Tetrahydrofuran/Ethanol 2:1 v/v

**[0099]** In a round bottom flask equipped with a half-moon stirrer were charged: 20 g of 4-chloro-N-(4-methoxyphenyl) benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 5.85% A/A % by HPLC and a content of impurity of formula (IV) of 11.36% A/A % by HPLC, 20 ml of ethanol and 40 mL of tetrahydrofuran. The mixture was heated to dissolution (T=55° C.) and kept stirring at this temperature for 1 h. Thereafter, the mixture was cooled to RT and stirred at this temperature for 1 h. The slurry was then filtered, washing the cake with 10 ml of ethanol. The wet solid was dried under vacuum at T=55° C. and 11.8 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.38% A/A % by HPLC and a content of impurity of formula (IV) of 0.76% A/A % by HPLC.

Example 3: Re-Crystallization of Compound of Formula (II) in a Mixture Tetrahydrofuran/Isopropanol 1:1 v/v

**[0100]** In a round bottom flask equipped with a half-moon stirrer were charged: 100 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 5.43% A/A % by HPLC and a content of impurity of formula (IV) of 11.39% A/A % by HPLC and 200 mL of tetrahydrofuran. The mixture was heated to dissolution (T=66° C.) and kept stirring at this temperature for 20 min. The mixture was cooled down to T=41° C. over 1 h. Thereafter, 100 ml of isopropanol were dosed over 30 min keeping the temperature within the range 41-41.5° C. The mixture was then heated to T=54-55° C. and 100 ml of isopropanol were added maintaining this temperature. After stirring at T=55° C. for 1 h, the mixture was cooled to T=21° C. over 2 h and then stirred at this temperature for 75 min. The slurry was then filtered, washing the cake with 2×100 ml of isopropanol. The wet solid was dried under vacuum at T=80° C. for 10 h and 68.9 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.59% A/A % by HPLC and a content of impurity of formula (IV) of 0.40% A/A % by HPLC.

Example 4: Re-Slurry of Compound of Formula (II) in a Mixture Tetrahydrofuran/Isopropanol 1:1 v/v

**[0101]** In a round bottom flask equipped with a half-moon stirrer were charged: 40 g of 4-chloro-N-(4-methoxyphenyl) benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 5.43% A/A % by HPLC and a content of impurity of formula (IV) of 11.39% A/A % by HPLC and 80 mL of tetrahydrofuran. After 15 min stirring at RT, 80 mL of isopropanol were added. The mixture was heated to T=51° C. and the resulting suspension was kept stirring at this temperature for 1 h. Thereafter, the mixture was cooled to RT over 2 h and stirred at this temperature for 1 h. The slurry was then filtered, washing the cake with 40 mL of isopropanol. The wet solid was dried under vacuum at T=80° C. for 10 h and 26.7 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.62% A/A % by HPLC and a content of impurity of formula (IV) of 0.13% A/A % by HPLC.

Example 5: Re-Slurry of Compound of Formula (II) in a Mixture Tetrahydrofuran/Isopropanol 1:1 v/v

**[0102]** In a round bottom flask equipped with a half-moon stirrer were charged: 200 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 1.48% A/A % by HPLC and a content of impurity of formula (IV) of 11.08% A/A % by HPLC and 400 mL of tetrahydrofuran. After 15 min stirring at RT, 400 ml of isopropanol were added. The mixture was heated to T=53° C. and the resulting suspension was kept stirring at this temperature for 1 h. Thereafter, the mixture was cooled to T=22° C. over 2 h and stirred at this temperature for 65 min. The slurry was then filtered, washing the cake with 2×200 ml of isopropanol. The wet solid was dried under vacuum at T=80° C. for 9.5h and 147 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.10% A/A % by HPLC and a content of impurity of formula (IV) of 0.12% A/A % by HPLC.

Example 6: Re-Crystallization of Compound of Formula (II) in a Mixture Tetrahydrofuran/Isopropanol 2:3 v/v

**[0103]** In a 400 mL reactor equipped with an anchor stirrer were charged: 30 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 1.61% A/A % by HPLC and a content of impurity of formula (IV) of 1.13% A/A % by HPLC and 60 mL of tetrahydrofuran. The mixture was heated to T=70° C. until complete dissolution of the solid, then the mixture was cooled to T=50° C. over 1 h and 90 mL of isopropanol were dosed over 90 min keeping this

temperature. After stirring at T=50° C. for 30 min, the mixture was cooled to T=−10° C. over 180 min and then stirred at this temperature for 1 h. The slurry was then filtered, and the wet solid was dried under vacuum at T=80° C. for 12h. 27.1 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.06% A/A % by HPLC and a content of impurity of formula (IV) of 0.10% A/A % by HPLC.

Example 7: Re-Crystallization of Compound of Formula (II) in a Mixture Tetrahydrofuran/Isopropanol 2:3 v/v

**[0104]** In a 400 mL reactor equipped with an anchor stirrer were charged: 30 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 1.61% A/A % by HPLC and a content of impurity of formula (IV) of 1.13% A/A % by HPLC and 60 mL of tetrahydrofuran. The mixture was heated to T=70° C. until complete dissolution of the solid, then the mixture was cooled to T=50° C. over 1 h and 90 mL of isopropanol were dosed over 30 min keeping this temperature. After stirring at T=50° C. for 90 min, the mixture was cooled to T=−10° C. over 180 min and then stirred at this temperature for 1 h. The slurry was then filtered, and the wet solid was dried under vacuum at T=80° C. for 12h. 28.8 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.06% A/A % by HPLC and a content of impurity of formula (IV) of 0.15% A/A % by HPLC.

Example 8: Re-Crystallization of Compound of Formula (II) in a Mixture Tetrahydrofuran/Isopropanol 2:1 v/v

**[0105]** In a 400 mL reactor equipped with an anchor stirrer were charged: 30 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 1.61% A/A % by HPLC and a content of impurity of formula (IV) of 1.13% A/A % by HPLC and 60 mL of tetrahydrofuran. The mixture was heated to T=70° C. until complete dissolution of the solid, then the mixture was cooled to T=50° C. over 1 h and 30 mL of isopropanol were dosed over 30 min keeping this temperature. After stirring at T=50° C. for 90 min, the mixture was cooled to T=−10° C. over 60 min and then stirred at this temperature for 1 h. The slurry was then filtered, and the wet solid was dried under vacuum at T=80° C. for 12h. 26.5 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.09% A/A % by HPLC and a content of impurity of formula (IV) of 0.12% A/A % by HPLC.

Example 9: Re-Crystallization of Compound of Formula (II) in a Mixture Tetrahydrofuran/Isopropanol 2:3 v/v

**[0106]** In a 400 mL reactor equipped with an anchor stirrer were charged: 30 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 1.61% A/A % by HPLC and a content of impurity of formula (IV) of 1.13% A/A % by HPLC and 60 mL of tetrahydrofuran. The mixture was heated to T=70° C. until complete dissolution of the solid, then the mixture was cooled to T=50° C. over 1 h and 90 mL of isopropanol were dosed over 90 min keeping this temperature. After stirring at T=50° C. for 30 min, the mixture was cooled to T=20° C. over 60 min and then stirred at this temperature for 1 h. The slurry was then filtered, and the wet solid was dried under vacuum at T=80° C. for 12h. 27.7 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.08% A/A % by HPLC and a content of impurity of formula (IV) of 0.14% A/A % by HPLC.

Example 10: Re-Crystallization of Compound of Formula (II) in a Mixture Tetrahydrofuran/Isopropanol 1:1 v/v

**[0107]** In a 400 mL reactor equipped with an anchor stirrer were charged: 30 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 1.61% A/A % by HPLC and a content of impurity of formula (IV) of 1.13% A/A % by HPLC and 60 mL of tetrahydrofuran. The mixture was heated to T=70° C. until complete dissolution of the solid, then the mixture was cooled to T=50° C. over 1 h and 60 mL of isopropanol were dosed over 60 min keeping this temperature. After stirring at T=50° C. for 60 min, the mixture was cooled to T=5° C. over 120 min and then stirred at this temperature for 1 h. The slurry was then filtered, and the wet solid was dried under vacuum at T=80° C. for 12h. 25.6 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 0.09% A/A % by HPLC and a content of impurity of formula (IV) of 0.12% A/A % by HPLC.

Example 11: Comparative Example (not of Invention). Re-Crystallization of Compound of Formula (II) in Isopropanol

**[0108]** In a round bottom flask equipped with an half-moon stirrer were charged: 5 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 5.85% A/A % by HPLC and a content of impurity of formula (IV) of 11.36% A/A % by HPLC and 20 mL of isopropanol. The mixture was heated to reflux until complete dissolution of the solid and the mixture was stirred at this temperature for 45 min. After cooling down to RT over 120 min, the mixture was stirred at this temperature for further 2 h. The slurry was then filtered, and the wet solid was dried under vacuum at T=60° C. for 11h. 4.5 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 5.65% A/A % by HPLC and a content of impurity of formula (IV) of 8.19% A/A % by HPLC.

Example 12: Comparative Example (not of Invention). Re-Crystallization of Compound of Formula (II) in Tetrahydrofuran

**[0109]** In a round bottom flask equipped with an half-moon stirrer were charged: 5 g of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (compound of formula (II)), characterized by a content of impurity of formula (III) of 5.85% A/A % by HPLC and a content of impurity of formula (IV) of 11.36% A/A % by HPLC and 20 mL of tetrahydrofuran. The mixture was heated to T=60° C. until complete dissolution of the solid and the mixture was stirred at this temperature for 30 min. After cooling down to RT over 120 min, the mixture was stirred at this temperature for further 90 min. The slurry was then filtered, and the wet solid was

dried under vacuum at T=80° C. for 8h. 2.7 g of compound (II) were obtained, characterized by a content of impurity of formula (III) of 2.73% A/A % by HPLC and a content of impurity of formula (IV) of 5.16% A/A % by HPLC.

Example 13: Table Comparing the Results of the Experiments Reported Above

| | Starting material Compound (II) | | | | Product Compound (II) | |
|---|---|---|---|---|---|---|
| Example no | Imp. (III) (HPLC A/A %) | Imp. (IV) (HPLC A/A %) | Type of experiment | Solvent | Imp. (III) (HPLC A/A %) | Imp. (IV) (HPLC A/A %) |
| Example 1 | 5.85 | 11.36 | Recrystallization | THF/MeOH 1:1 | 1.56 | 2.55 |
| Example 2 | 5.85 | 11.36 | Recrystallization | THF/EtOH 2:1 | 0.38 | 0.76 |
| Example 3 | 5.43 | 11.39 | Recrystallization | THF/IPA 1:1 | 0.59 | 0.40 |
| Example 4 | 5.43 | 11.39 | Reslurry | THF/IPA 1:1 | 0.62 | 0.13 |
| Example 5 | 1.48 | 11.08 | Reslurry | THF/IPA 1:1 | 0.10 | 0.12 |
| Example 6 | 1.61 | 1.13 | Recrystallization | THF/IPA 2:3 | 0.06 | 0.10 |
| Example 7 | 1.61 | 1.13 | Recrystallization | THF/IPA 2:3 | 0.06 | 0.15 |
| Example 8 | 1.61 | 1.13 | Recrystallization | THF/IPA 2:1 | 0.09 | 0.12 |
| Example 9 | 1.61 | 1.13 | Recrystallization | THF/IPA 2:3 | 0.08 | 0.14 |
| Example 10 | 1.61 | 1.13 | Recrystallization | THF/IPA 1:1 | 0.09 | 0.12 |
| Example 11 (Comparative Ex) | 5.85 | 11.36 | Recrystallization | IPA | 5.65 | 8.19 |
| Example 12 (Comparative Ex) | 5.85 | 11.36 | Recrystallization | THF | 2.73 | 5.16 |

**[0110]** In the table above, tetrahydrofuran is reported as THF, methanol as MeOH, ethanol as EtOH and isopropanol as IPA.

**[0111]** The results of the Table above clearly show that using a single solvent, such as isopropanol or tetrahydrofuran (refer to Example 11 and Example 12) the rejection of impurity of formula (III) and impurity of formula (IV) is not very effective. On the contrary, when combining tetrahydrofuran and an alcohol as a solvent mixture, a very efficient impurities rejection is obtained. Such a Table clearly shows an unexpected synergic effect by combining said tetrahydrofuran and an alcohol.

Example 14: Preparation of Indometacin (Compound of Formula (I)), Starting from 4-Chloro-N-(4-Methoxyphenyl)Benzohydrazide (Compound of Formula (I)) Obtained from a Re-Crystallization or Re-Slurry Process of Compound of Formula (II) in a Mixture Comprising Tetrahydrofuran and a $C_1$-$C_4$ Linear or Branched Alkyl Alcohol

**[0112]** In a 1000 mL reactor equipped with an anchor stirrer were charged: 50 g of 4-chloro-N-(4-methoxyphenyl) benzohydrazide (compound of formula (II)) obtained following the procedure of Example 5) and 300 mL of toluene. The mixture was heated to T=75° C. until complete dissolution of the solid, then the solvent was evaporated under vacuum until reaching 150 mL of residual volume. The residue was taken up with 150 mL of toluene and, keeping the temperature within T=65-68° C., 25 g of levulinic acid were dosed over the mixture. After 2h stirring at T=65-68° C., 55.8 mL of phosphoric acid pre-heated to T=38-42° C. were dosed over 30 min while heating the mixture to T=100° C. After stirring at T=100° C. for 60 min, the mixture was cooled to T=75° C. and 30 ml of water were added. After 30 min at this temperature, the biphasic mixture was allowed to settle and the phases were separated. The aqueous layer was extracted at T=75° C. with 100 ml of toluene and then again with 30 mL of toluene. The combined organic phases were washed at T=75° C. with water (3×10 mL). Maintaining T=75° C., 1.9 g of charcoal and 0.3 g of dicalite were charged over the organic solution. After 15 min stirring at this temperature, the mixture was filtered over a dicalite pad washing with 37 mL of toluene. The resulting solution was concentrated under vacuum to 120 mL and then cooled down to T=20° C. over 6 h. The resulting slurry was filtered, washing the cake with toluene (20 mL). The wet solid was dried under vacuum at T=65° C. for 14h. 49.6 g of compound (I) were obtained, characterized by a content of impurity of formula (III) of 0.03% A/A % by HPLC and a content of impurity of formula (IV) of 0.11% A/A % by HPLC.

Example 15: Analytical Method for Determining the Chemical Purity of 4-chloro-N-(4-methoxyphenyl)benzohydrazide (Compound of Formula (II)), Via HPLC

**[0113]** Eclipse plus C8, 100×4.6 mm, 1.8 μm, or equivalent;

**[0114]** Temp. Column: 55° C.;

**[0115]** Mobile Phase A: $H_3PO_4$ 0.1%/Acetonitrile 85/15 v/v;

**[0116]** Mobile Phase B: $H_3PO_4$ 0.1%/Methanol/Acetonitrile 20/15/65 v/v;

**[0117]** Gradient

| Time (min) | % A | % B |
|---|---|---|
| 0 | 100 | 0 |
| 4.0 | 65 | 35 |
| 6.5 | 50 | 50 |
| 10.5 | 0 | 100 |
| 11.0 | 0 | 100 |

**[0118]** Flow: 2.0 mL/min;

**[0119]** UV Detector: 235 nm;

**[0120]** Injection Volume: 3 μL;

**[0121]** Analysis Time: 11 min;

**[0122]** Post-run Time: 2.5 min

**[0123]** Diluent: Acetonitrile

Example 16: Analytical Method for Determining the Chemical Purity of Crude Indomethacin (Compound of Formula (I)), Via HPLC

**[0124]** Colum: EclipseXDB C18, 50×4.6 mm, 1.8 μm, or equivalent;

**[0125]** Temp. Column: 80° C.;

**[0126]** Mobile Phase A: $H_3PO_4$ 0.1% solution in water

**[0127]** Mobile Phase B: $H_3PO_4$ 0.1% in Acetonitrile

**[0128]** Gradient

| Time (min) | % A | % B |
|---|---|---|
| 0 | 70 | 30 |
| 2.5 | 20 | 80 |
| 5.0 | 20 | 80 |

**[0129]** Analysis Time: 5 min;

**[0130]** Post-run Time 2.5 min

**[0131]** Flow: 1.0 mL/min;

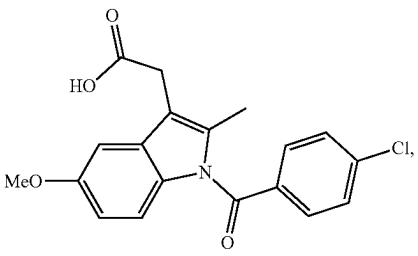
**[0132]** UV Detector: 235 nm;

**[0133]** Injection Volume: 2 μL;

**[0134]** Diluent: Acetonitrile.

**1**. A process for preparation of the Indomethacin compound of formula (I):

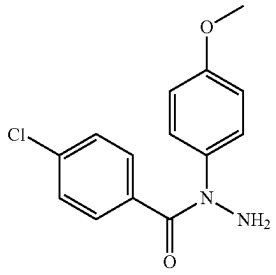
(I)




comprising:

i) precipitating, crystallizing, re-crystallizing or re-slurrying of the compound 4-chloro-N-(4-methoxy phenyl)benzohydrazide of formula (II):

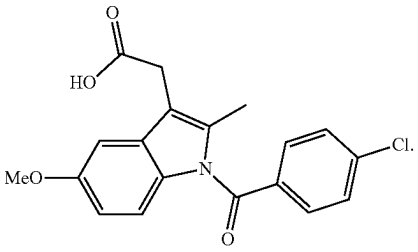
(II)




in a mixture comprising tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol; and

ii) converting the compound of formula (II) to give Indomethacin compound of formula (I):

(I)




**2**. The process of claim **1**, wherein the $C_1$-$C_4$ alkyl alcohol is isopropanol.

**3**. The process of claim **1**, wherein the ratio of the tetrahydrofuran to the $C_1$-$C_4$ linear or branched alkyl alcohol is from 4:1 to 1:4 v/v.

**4**. The process of claim **3**, wherein the ratio of the tetrahydrofuran to the $C_1$-$C_4$ linear or branched alkyl alcohol is from 2:1 to 1:2 v/v.

**5**. The process of claim **4**, wherein the ratio of the tetrahydrofuran to the $C_1$-$C_4$ linear or branched alkyl alcohol is 1:1 v/v.

**6**. The process of claim **1**, wherein step i) comprises:

a) charging 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II) and tetrahydrofuran;

b) heating the mixture of step a) until complete dissolution of the compound of formula (II);

c) cooling the mixture of step b) to a temperature of from 35° C. to 60° C. over a period of from 30 minutes to 2 hours;

d) dosing the $C_1$-$C_4$ linear or branched alkyl alcohol into the mixture of step c) over a period of from 30 minutes to 3 hours at a temperature of from 35° C. to 60° C.;

e) stirring the mixture of step d) for a period of from 30 minutes to 3 hours at a temperature of from 35° C. to 60° C.;

f) cooling down the mixture of step e) to a temperature of from 15° C. to 30° C. over a period of from 30 minutes to 5 hours;

g) stirring the mixture of step f) at a temperature of from −15° C. to 30° C. for a period of from 30 minutes to 5 hours; and

h) isolating the solid obtained in step g) by filtration or centrifugation to provide 4-chloro-N-(4-methoxyphenyl)benzo hydrazide of formula (II).

**7**. The process of claim **6**, wherein in step c) the mixture is cooled to a temperature of from 49° C. to 51° C. over 1 hour.

**8**. The process of claim **6**, wherein in step d) the alcohol is dosed into the mixture over 1 hour at a temperature of from 49° C. to 51° C.

**9**. The process of claim **6**, wherein in step e) the mixture is stirred for 1 hour at a temperature of from 49° C. to 51° C., in step f) the mixture is cooled to a temperature of from 4° C. to 6° C. over 2 hours and in step g) the mixture is stirred at a temperature of from 4° C. to 6° C. for 1 hour.

**10**. The process of claim **1**, wherein step i) comprises:

a1) charging 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II), tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol;

b1) heating the mixture of step a1) to a temperature of from 30° C. to 70° C.;

c1) stirring the mixture of step b1) at a temperature of from 30° C. to 70° C. for a period of from 1 hour to 5 hours;

d1) cooling the mixture of step c1) to a temperature of from 15° C. to 35° C. over a period of from 10 minutes to 3 hours;

e1 stirring the mixture of step d1) at a temperature of from 15° C. to 35° C. for a period of from 10 minutes to 5 hours; and

f1) isolating the solid obtained in step e1) by filtration or centrifugation to provide 4-chloro-N-(4-methoxyphenyl)benzo hydrazide of formula (II).

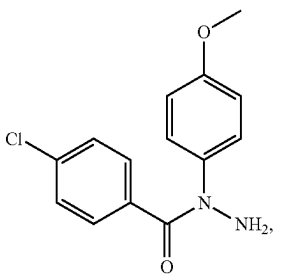
**11**. The process of claim **9**, wherein in step b1) and step c1) the temperature is of from 50° C. to 55° C.

**12**. The process of claim **10** wherein in step d1) the mixture is cooled to a temperature of from 20° C. to 25° C. over 2 hours and in step e1) the mixture is stirred at a temperature of from 20° C. to 25° C. for 1 hour.

**13**. The process of claim **1**, wherein step i) is repeated more than one time.

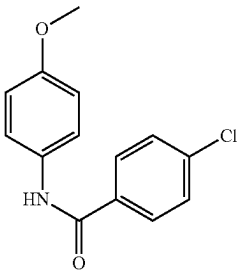
**14**. The process of claim **1**, wherein the compound 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II):

(II)



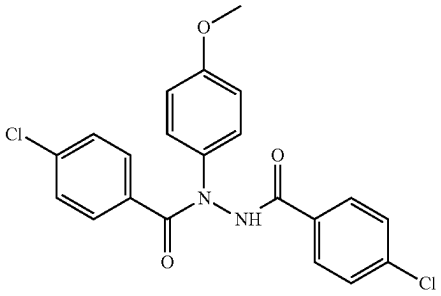

obtained in step i) has a content of impurity 4-chloro-N-(4-methoxyphenyl)benzamide of formula (III):

(III)




not higher than 0.15% A/A % as determined by HPLC, and a content of impurity 4-chloro-N'-(4-chlorobenzoyl)-N-(4-methoxyphenyl)benzo hydrazide of formula (IV):

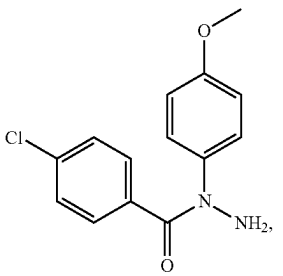
(IV)




not higher than 0.15% A/A % as determined by HPLC.

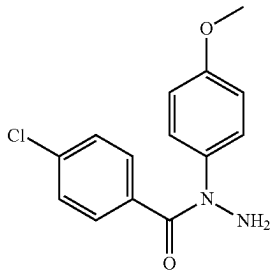
**15**. A process for the preparation of the compound 4-chloro-N-(4-methoxyphenyl)benzohydrazide of formula (II):

(II)



comprising precipitating, crystallizing, recrystallizing or re-slurrying of the compound 4-chloro-N-(4-methoxy phenyl)benzohydrazide of formula (II):

(II)




in a mixture comprising tetrahydrofuran and a $C_1$-$C_4$ linear or branched alkyl alcohol.

* * * * *