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(54) **Title**: A PROCESS FOR THE PREPARATION OF N-[2-[(ACETYLTHIO) METHYL]-1-OXO-3-PHENYLPROPYL] GLYCINE PHENYL METHYL ESTER AND INTERMEDIATES THEREOF

(57) **Abstract**: The present invention relates to a process for the preparation of N-[2-[(acetylthio) methyl]-1-oxo-3-phenylpropyl] glycine phenyl methyl ester and intermediates thereof. More particularly the present invention relates to a process for the preparation of intermediate compound 2-(benzyl acrylolyl amino) acetic acid benzyl ester.

A PROCESS FOR THE PREPARATION OF N-[2-[(ACETYLTHIO) METHYL]-1-OXO-3-PHENYLPROPYL] GLYCINE PHENYL METHYL ESTER AND INTERMEDIATES THEREOF

BACKGROUND OF THE INVENTION

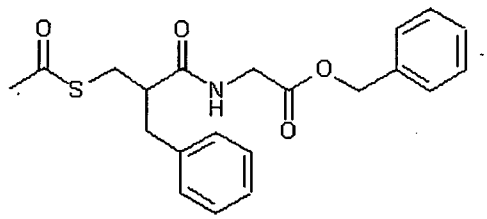
1. Technical Field

The present invention relates to a process for the preparation of N-[2-[(acetylthio) methyl]-1-oxo-3-phenylpropyl] glycine phenyl methyl ester and intermediates thereof.

More particularly the present invention relates to a process for the preparation of intermediate compound 2-(benzyl acrylolyl amino) acetic acid benzyl ester.

2. Description of the Related Art

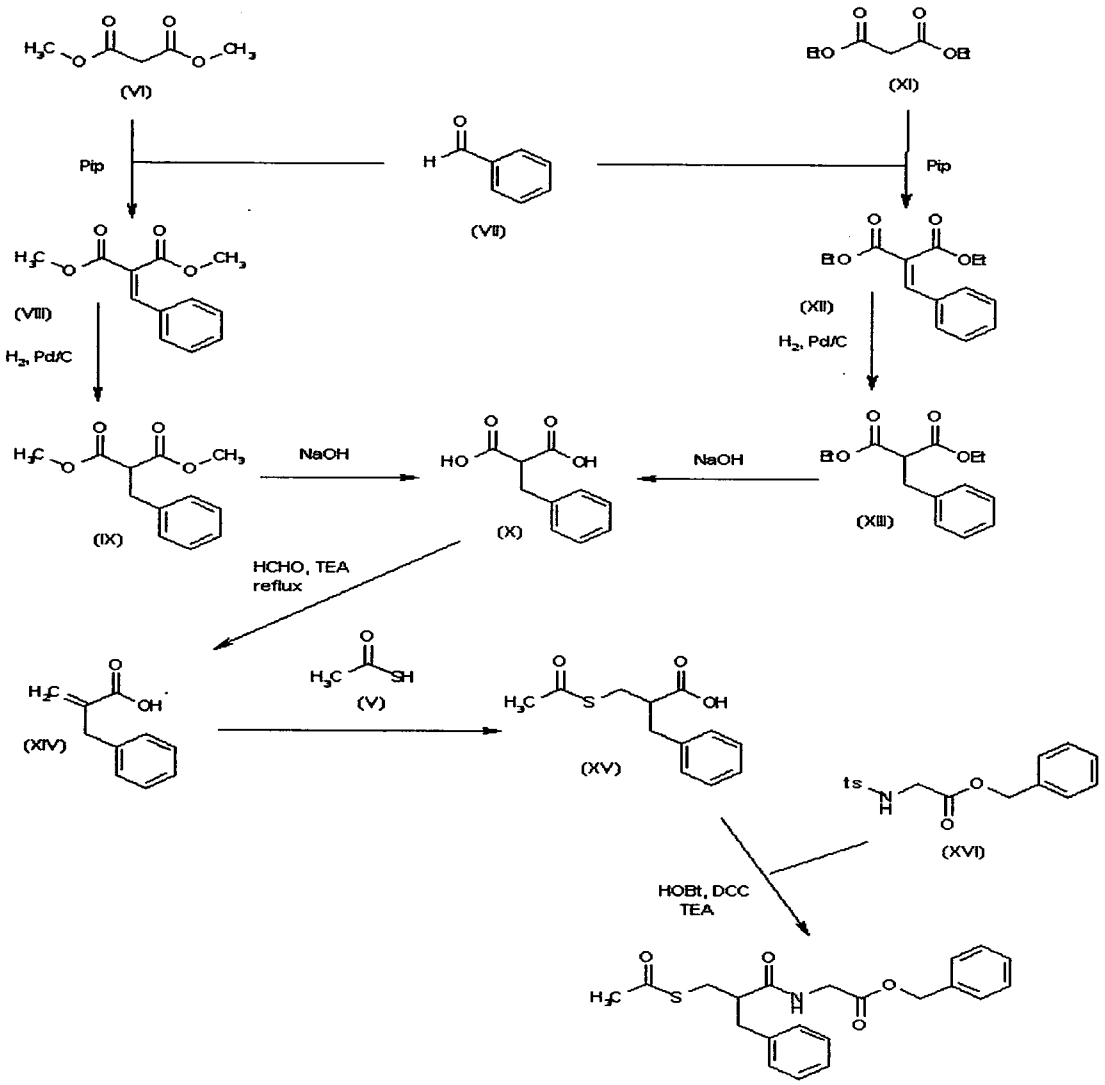
Racecadotril is a neutral endopeptidase inhibitor used as antidiarrheal in the treatment of chronic cardiac insufficiency and is available under the brand names Hidrasec and Tiorfan. Racecadotril is chemically known as N-[2-[(acetylthio) methyl]-1-oxo-3-phenylpropyl] glycine phenyl methyl ester. (herein after referred by its generic name racecadotril) and represented by the formula (I).



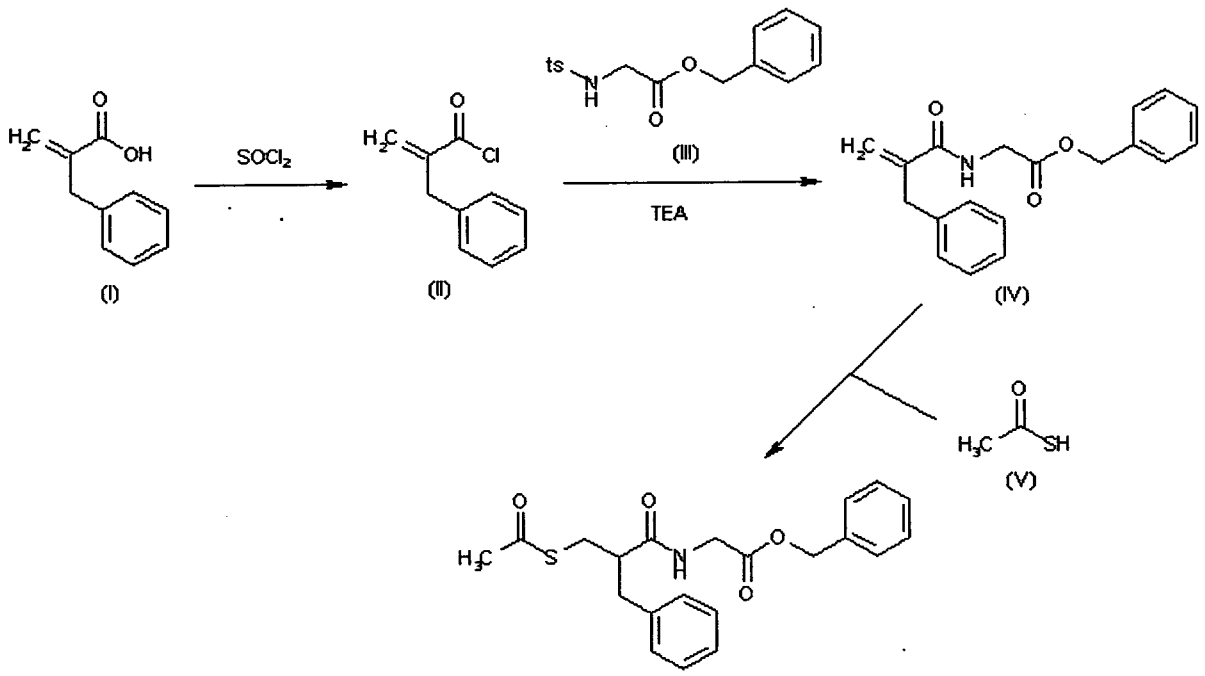
(I)

U.S. Patent No. US 4,513,009 describes amino acid derivatives including racecadotril, a pharmaceutical composition and a method of treatment.

The US'009 patent also discloses a process for the preparation of racecadotril which is illustrated by below scheme:



U.S. Patent No. US 6,835,851 B2 discloses a process for the preparation of racecadotril which is illustrated by scheme below:



The processes described above involves expensive reagents such as hydroxyl benzotriazole (HOBT) and dicyclohexyl amine carbodiimide (DCC) and hazardous reagent like thionyl chloride thus rendering the processes expensive and not applicable on industrial scale.

Hence there is a need in the art for an improved process for the preparation of racecadotril and its intermediates, which avoids the use of hazardous and expensive reagents, while enhancing the desired product racecadotril with high yield and purity.

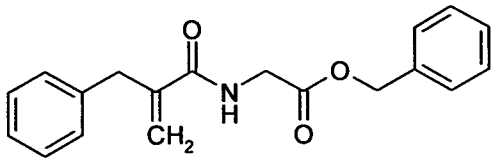
The process of present invention is simple, cost effective, eco-friendly, reproducible, robust and is well suited on commercial scale.

SUMMARY OF THE INVENTION

The present invention relates to a process for the preparation of N-[2-[(acetylthio) methyl]-1-oxo-3-phenylpropyl] glycine phenyl methyl ester and intermediates thereof.

More particularly the present invention relates to a process for the preparation of intermediate compound 2-(benzyl acrylolyl amino) acetic acid benzyl ester.

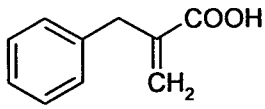
In an aspect, the present invention relates to a process for the preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester of formula (Ia)



(Ia)

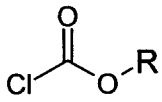
comprising :

a) reacting the compound 2-benzyl acrylic acid of formula V



V

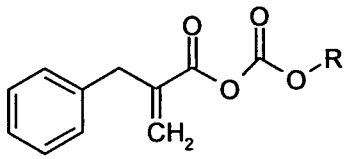
with the compound alkyl chloro formate of formula IV



IV

Where R is C1-C6 alkyl branched or straight chain or aryl.

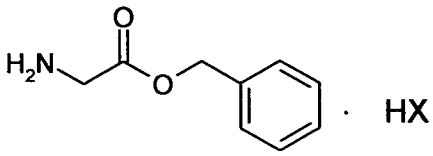
in the presence of suitable base and an organic solvent to give the compound 2-benzylacrylic (alkyl carbonic) anhydride of formula III which is optionally isolated



III

Where R is same as defined above.

b) reacting the compound of formula III with the compound glycine benzyl ester or a salt thereof of formula II



II

Wherein HX is acid addition salts, such as those made with hydrochloric, hydrobromic, hydroiodic, methylsulfonic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic,

lactic pyruvic, malonic, succinic, maleic, fumaric, maleic, tartaric, citric, benzoic, carbonic cinnamic, mandelic, methanesulfonic, ethanesulfonic, benezenesulfonic, hydroxyethanesulfonic, p-toluene sulfonic, cyclohexanesulfamic, salicyclic, p- aminosalicylic, 2-phenoxybenzoic, and 2-acetoxy benzoic acid

to give the compound of formula (Ia).

BRIEF DESCRIPTION OF THE DRAWING

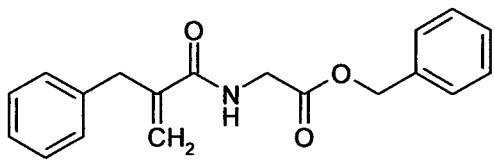
Fig. 1: is a schematic representation of an embodiment of the process of present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a process for the preparation of N-[2-[(acetylthio) methyl]-1-oxo-3-phenylpropyl] glycine phenyl methyl ester and intermediates thereof.

More particularly the present invention relates to a process for the preparation of intermediate compound 2-(benzyl acrylolyl amino) acetic acid benzyl ester.

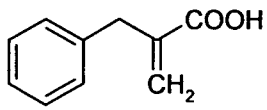
In an embodiment of the present invention, there is provided a process for the preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester of formula (Ia)



(Ia)

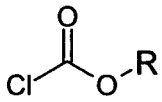
comprising :

a) reacting the compound 2-benzyl acrylic acid of formula V



V

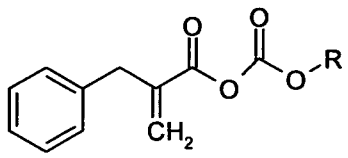
with the compound alkyl chloro formate of formula IV



IV

Where R is C1-C6 alkyl branched or straight chain or aryl.

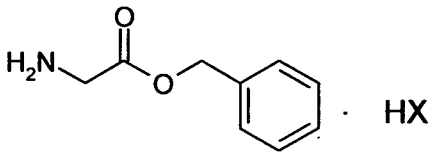
in the presence of suitable base and an organic solvent to give the compound 2-benzylacrylic (alkyl carbonic) anhydride of formula III which is optionally isolated



III

Where R is same as defined above.

b) reacting the compound of formula III with the compound glycine benzyl ester or a salt thereof of formula II



II

Wherein HX is is acid addition salts, such as those made with hydrochloric, hydrobromic, hydroiodic, methylsulfonic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic pyruvic, malonic, succinic, maleic, fumaric, maleic, tartaric, citric, benzoic, carbonic cinnamic, mandelic, methanesulfonic, ethanesulfonic, benezenesulfonic, hydroxyethanesulfonic, p-toluene sulfonic, cyclohexanesulfamic, salicyclic, p- aminosalicylic, 2-phenoxybenzoic, and 2-acetoxy benzoic acid

to give the compound of formula (Ia).

The suitable base that can be used in step a) include inorganic or organic base. Inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, ammonia and the like; and the organic bases such as triethylamine, tripropylamine, pyridine, dimethyl amino pyridine, diisopropylamine, diisopropylethylamine and the like, or mixture thereof, preferably triethylamine.

The organic solvents that can be used in step a) is selected from the group consisting of halogenated solvents such as dichloromethane, ethylene dichloride , chloroform, chlorobenzene, and the like; hydrocarbon solvents such as toluene, xylene, cyclohexane, n-hexane and the like; esters such as ethyl acetate, isopropyl acetate and the like: or mixtures thereof in various proportions without limitation. Preferably, dichloromethane is being used.

The reaction temperature and time should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. The reaction temperature is from about -20°C to about 40°C. Preferably at about -5°C to about 10 °C. The

time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent(s) employed. The time period is from about 1 hour to about 10 hours, preferably from about 1 hour to 5 hours.

The molar equivalent of base used can be from about 0.5 mole to about 10 moles on weight of the compound of formula V taken. Preferably, 1 mole is being used.

The molar equivalent of formula IV used can be from about 0.5 mole to about 5 moles on weight of the compound of formula V taken. Preferably, 1 mole is being used.

In step b) the compound of formula II is being used in acid addition salt form that can be organic or inorganic acid salt namely hydrobromic acid salt, iodic acid salt, hydrogen sulfate salt, besylate salt, paratoluene sulfonate salt, mesylate salt, tartarate salt and the like. Preferably paratoluene sulfonate is being prepared.

The R groups in the compounds of formula III and IV can be C_1-C_6 alkyl straight chain or branched or aryl namely methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, allyl, cyclohexyl, benzyl, phenyl, para nitro phenyl etc. preferably the R- group is ethyl.

The preferable compounds suitable for the preparation of compounds of formula III and IV include but are limited to ethyl chloro formate, benzyl chloro formate, isobutyl chloro formate, allyl chloro formate, phenyl chloro formate, paranitro phenyl chloro formate or mixtures thereof. Preferably ethyl chloro formate.

The reaction temperature is from about -20°C to about 40°C. preferably at about -5°C to about 10 °C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent(s) employed. The time period is from about 1 hour to about 10 hours, preferably from about 1 hour to 5 hours.

The intermediate compound of formula III is optionally isolated as and when needed.

After completion of the reaction, isolation of the desired compound from the reaction mixture can be carried out by common operation, but in consideration of the physical properties of the desired compound, crystallization, extraction, washing, column chromatography, etc. may be combined.

Optionally the processes of present invention can be carried out by one pot synthesis.

The intermediate compounds can be optionally purified by recrystallisation, using a solvent or mixture of solvents; or by converting into their corresponding acid addition salt and then processed back to the respective free base or free acid compounds.

Advantageously, the process of present invention provides the intermediates with higher yields and purities thus leading to higher yields and purities of final product.

A process according to the present invention by using the intermediates prepared by the processes of present invention preferably yields racecadotril (I) substantially pure form. Thus the racecadotril obtained by the process of present invention has purity at least about 98 area % by HPLC , preferably at least about 99 area%. More preferably at least about 99.5 area % by HPLC.

The intermediate compound of formula (Ia) obtained by the above described process of present invention can be further converted into Racecadotril of formula I by processes described in the art. Illustratively, by the process described in U.S. Patent No. US 6,835,851 B2.

The present invention provides a simple, ecofriendly, inexpensive, reproducible, robust processes for preparation intermediates of racecadotril, which forthwith are viably adaptable on a commercial scale.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention.

It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

Example -1 : Preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester (Ia) using ethyl chloro formate

50gms of 2-benzyl acrylic acid, 500ml. of dichloromethane and 34.3 gms of triethylamine were charged in a clean and dry 1 lit. 4 neck R.B. flask. The reaction mass was cooled to about -5° C and 36.84 gms of ethylchloroformate was added drop-wise at about -5° C and stirred for about 30min. at the same temperature . After completion of the reaction, 104.03gr. of glycine benzyl ester p-tosylate, 34.3gr. of triethylamine and 200ml. of dichloromethane were added at -5° C and stirred for 1 hr 30min. at the same temperature. After completion of reaction, the reaction mass was brought to about 25 °C and stirred for 30min.

The reaction mass was washed with 250ml. of water followed by 250ml. of 4% sodium bicarbonate solution and again with 250ml. of water. The organic layer was separated and washed with 4 gms of carbon. The resulted reaction solution was distilled ordinarily and then finally under vacuum. Then charged 75ml. of isopropyl alcohol and distilled under vacuum upto 80°C to obtain 2-(benzylacryloyl amino)acetic acid benzyl ester as the residue.

Wt: 104gr.

To the 104gr. of residue, added 104ml. of isopropyl alcohol and 104ml. of n-hexane at ambient temperature. The resulted solution was cooled to 0-5°C and stirred for 30min. at the same temperature. The resulted solution was filtered and washed with 50ml. of n-hexane to obtain the 2-(benzylacryloyl amino)acetic acid benzyl ester as a pure solid.

Yield: 50-53gr. Purity by HPLC: 99.8%.

Example-2: Preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester (Ia) using benzyl chloro formate

The process is performed in the similar manner as described in the above Ex 1 by replacing ethyl chloro formate with benzyl chloro formate.

Yield: 10gms. (%Yield: 42%); Purity by HPLC: 98.3%.

Example-3: Preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester (Ia) using isobutyl chloro formate

The process is performed in the similar manner as described in the above Ex 1 by replacing ethyl chloro formate with isobutyl chloro formate .

Yield: 9.8gms. (%Yield: 41%); Purity by HPLC: 99.1%.

Example-4: Preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester (Ia) using allyl chloro formate

The process is performed in the similar manner as described in the above Ex 1 by replacing ethyl chloro formate with allyl chloro formate.

Yield: 11gms. (% Yield: 46%); Purity by HPLC: 98.5%.

Example-5: Preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester (Ia) using phenyl chloro formate

The process is performed in the similar manner as described in the above Ex 1 by replacing ethyl chloroformate with phenyl chloro formate.

Yield: 20.5gms (%Yield: 43%); Purity by HPLC: 98.7%.

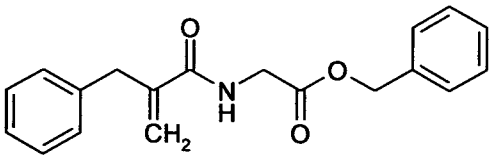
Example-6: Preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester (Ia) using p-nitro phenyl chloroformate

The process is performed in the similar manner as described in the above Ex 1 by replacing ethyl chloro formate with p-nitro phenyl chloro formate.

Yield : 10.5 gms (%Yield: 44%); Purity by HPLC: 99.3%

We Claim:

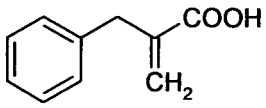
1) A process for the preparation of 2-(benzyl acrylolyl amino) acetic acid benzyl ester of formula (Ia)



(Ia)

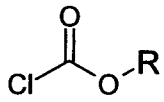
comprising :

a) reacting the compound 2-benzyl acrylic acid of formula V



V

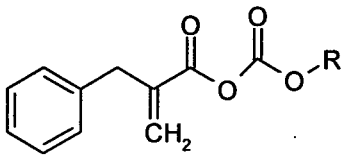
with the compound alkyl chloro formate of formula IV



IV

Where R is C_1-C_6 alkyl branched or straight chain or aryl.

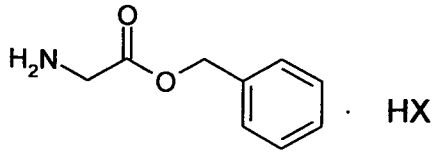
in the presence of suitable base and an organic solvent to give the compound 2-benzylacrylic (alkyl carbonic) anhydride of formula III which is optionally isolated



III

Where R is same as defined above.

b) reacting the compound of formula III with the compound glycine benzyl ester or a salt thereof of formula II



II

Wherein HX is is acid addition salts, such as those made with hydrochloric, hydrobromic, hydroiodic, methylsulfonic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic pyruvic, malonic, succinic, maleic, fumaric, maleic, tartaric, citric, benzoic, carbonic cinnamic, mandelic, methanesulfonic, ethanesulfonic, benezenesulfonic, hydroxyethanesulfonic, p-toluene sulfonic, cyclohexanesulfamic, salicyclic, p-aminosalicylic, 2-phenoxybenzoic, and 2-acetoxy benzoic acid
to give the compound of formula (Ia).

2) The process of claim 1, wherein the suitable base that can be used in step a) is selected from the group consisting of inorganic bases like as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, ammonia, organic bases like triethylamine, tripropylamine, pyridine, dimethyl amino pyridine, diisopropylamine, diisopropylethylamine or mixture thereof, preferably triethylamine.

3) The process of claim1, wherein the organic solvents that can be used in step a) is selected from the group consisting of halogenated solvents like dichloromethane, ethylene dichloride chloroform, chlorobenzene, hydrocarbon solvents like toluene, xylene, cyclohexane, n-hexane and the like; esters such as ethyl acetate, isopropyl acetate and the like: or mixtures thereof in various proportions without limitation. Preferably, dichloromethane is being used.

4) The process of claim 1, wherein the molar equivalent of base used is from about 0.25 mole to about 10 moles on weight of the compound of formula V taken, preferably, 1 mole is being used.

5) The process of claim 1, wherein the molar equivalent of formula IV used is from about 0.25 mole to about 5 moles on weight of the compound of formula V taken, preferably, 1 mole is being used.

6) A process of claim 1, wherein organic solvent is selected form the group consisting of alcohols like methanol, ethanol, propanol, isopropanol, butanol, esters like ethyl acetate, methyl acetate, n-butyl acetate, chlorinated solvents like methylene dichloride. ethylene dichloride, chloroform; aprotic polar solvents dimethyl formamide, dimethyl

acetamide and dimethyl sulfoxide, preferably dimethyl sulfoxide.

7) A process of claim 1, wherein reaction steps are carried out at temperatures from about – 20°C to about 40°C, preferably from about -5°C to about 10°C.

8) Racecadotril (I) of preceding claims has a purity of at least about 98 area % by HPLC.

9) Racecadotril (I) of claim 8, has a purity of at least about 99 area % by HPLC.

10) Racecadotril (I) of preceding claims has less than about 0.1 area % of individual impurity and 0.5 area % of total impurities by HPLC .

Symed labs limited **Fig. 1 of 1**

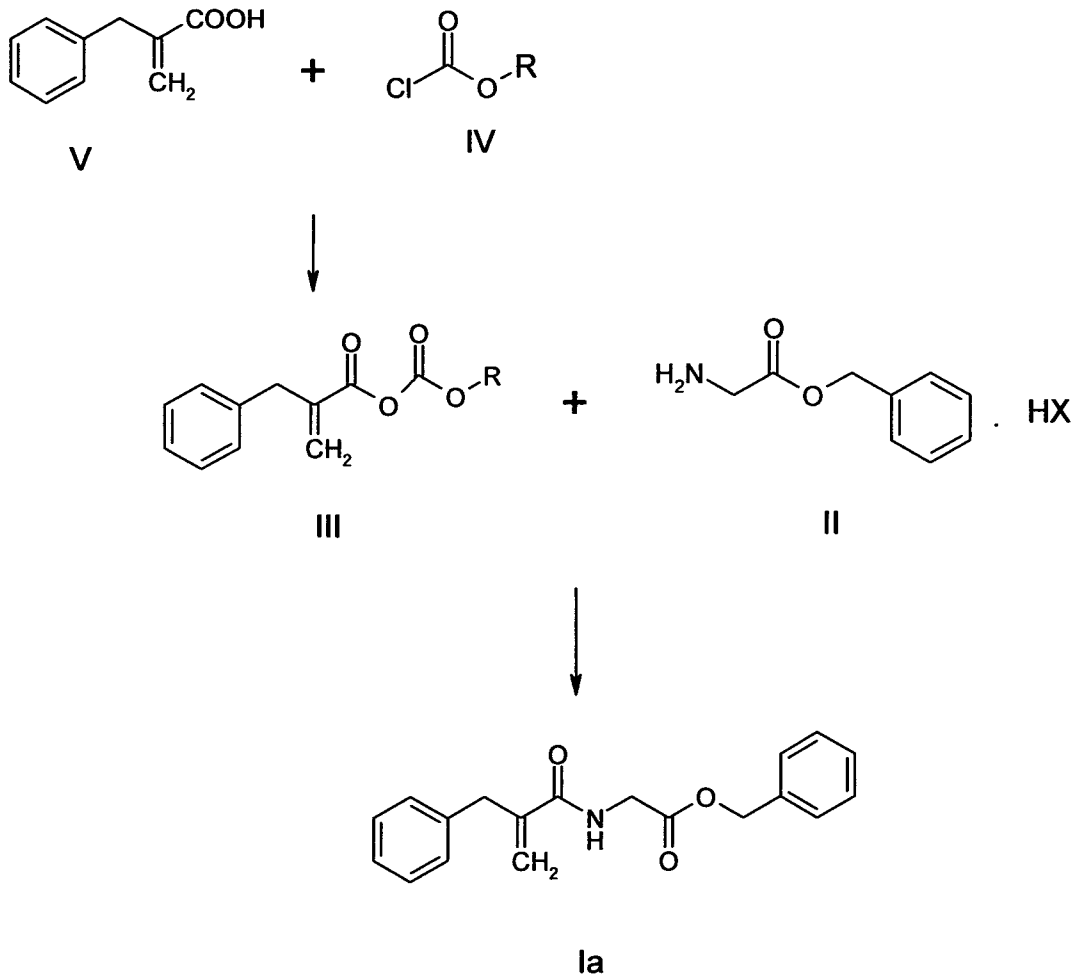


Fig 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 11/00132

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/34; A61K 31/275 (2011.01)
USPC - 514/528-529
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)
USPC - 514/528-529

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/506-507, 510 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, EPAB, JPAB); Google (Google Scholar, Google Patents)
Search Terms Used: 2-(benzyl acrylolyl amino) acetic acid benzyl ester, 2-(benzyl acryloyl amino) acetic acid benzyl ester, acetorphan, racecadotril, 2-benzyl acrylic acid, 2-benzylacrylic acid, acrylic acid, chloroformate, chloro formate, chloro-formate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/0055645 A1 (MONTEIL et al.) 09 May 2002 (09.05.2002) para [0004]-[0005], [0007]-[0008], [0013]-[0014], [0031]-[0032], [0037]-[0038], [0040]-[0041], [0043]-[0046], [0050]-[0051]	1-7
Y	US 6,610,880 B1 (OVERKAMP et al.) 26 August 2003 (26.08.2003) col 5, ln 1-7; col 6, ln 1-7, ln 60-67; col 7, ln 1-7, ln 21-32, ln 40-43	1-7
Y	US 2002/0077481 A1 (KARPF et al.) 20 June 2002 (20.06.2002) para [0010], [0024], [0027], [0029]	1-7
Y	US 2,736,728 A (PIOCH) 28 February 1956 (28.02.1956) col 2, ln 13-16	1-7

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"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
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2011 (30.08.2011)	0 6 SEP 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 11/00132

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-10
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.