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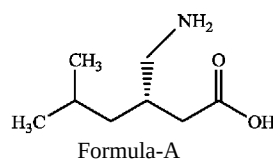
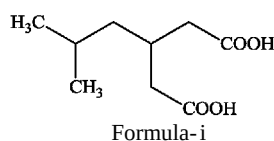
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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF PREGABALIN



(57) Abstract: The present invention relates to an improved process for the preparation of 3-isobutyl glutaric acid compound of formula-1 which is used as the key intermediate in the preparation of Pregabalin compound of formula-A. The present invention also relates to an improved process for the preparation of (S)-3-(aminomethyl)-5-methylhexanoic acid compound of formula-A.



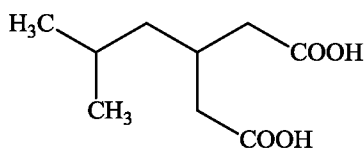
An improved process for the preparation of Pregabalin

Related Applications:

This application claims priority to Indian patent application number 201841012866 filed on April 04, 2018; the disclosure of which are incorporated herein by reference in its entirety.

Field of the invention:

The present invention relates to an improved process for the preparation of 3-isobutylglutaric acid compound of formula-1 which is used as the key intermediate in the preparation of Pregabalin.

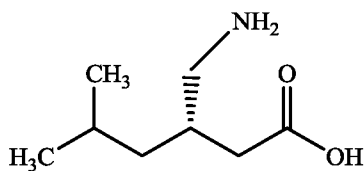


Formula-1

The present invention also relates to an improved process for the preparation of (S)-3-(aminomethyl)-5-methylhexanoic acid compound of formula-A.

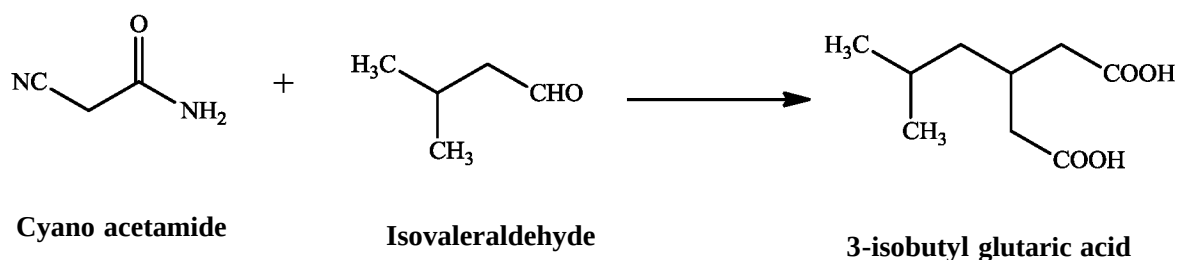
Background of the invention:

Pregabalin is also known as γ -amino butyric acid or (S)-3-isobutyl GABA or (S)-3-(aminomethyl)-5-methylhexanoic acid. Pregabalin has been found to activate GAD (L-glutamic acid decarboxylase). (S)-pregabalin has a dose dependent protective effect on seizure, and is a CNS-active compound. (S)-pregabalin is useful in anticonvulsant therapy, due to its activation of GAD, promoting the production of GABA, one of the brain's major inhibitory neurotransmitters, which is released at 30 percent of the brain's synapses. (S)-pregabalin has analgesic, anticonvulsant, and anxiolytic activity. (S)-pregabalin is marketed under the trade name LYRICA®.



Formula-A

Preparation of 3-isobutylglutaric acid compound of formula-1 is well disclosed in the prior art literature as follows:



The prior literature i.e., *Organic Process Research & Development* 1997, 1, 26-38; Indian patent publication 2889/MUM/2012 discloses the preparation of 3-isobutylglutaric acid using cyano acetamide/cyanoethyl ester, isovaleraldehyde and diethyl malonate. The above acetamide route is largely left unexplored for commercial applications.

In spite of the different synthetic routes known in the prior art there is a need to develop an improved process for the preparation of 3-isobutylglutaric acid in turn pregabalin from the said intermediate which is advantageous over prior art and which is simple, eco-friendly and commercially viable.

The inventors of the present invention directed the efforts towards the development of an improved process for the preparation of 3-isobutylglutaric acid using cyano acetic acid without using diethyl malonate, which is simple, economically advantageous, eco-friendly and easily scalable. The said process involves shorter reaction time, improvement in yields, use of small volumes of solvent, easy handling on commercial scale and non-hazardous reaction conditions which makes the process commercially adaptable and economically acceptable.

The present invention also provides the conversion of 3-isobutylglutaric acid into pregabalin.

Brief description of the invention:

The first embodiment of the present invention is to provide an improved process for the preparation of 3-isobutylglutaric acid compound of formula- 1.

The second embodiment of the present invention is to provide an alternative process for the preparation of 3-isobutylglutaric acid compound of formula- 1.

The third embodiment of present invention is to provide an improved process for the preparation of 3-isobutylglutaric acid compound of formula-1.

The fourth embodiment of present invention is to provide an improved process for the preparation of Pregabalin compound of formula-A.

The fifth embodiment of present invention is to provide an improved process for the preparation of Pregabalin compound of formula-A.

The sixth embodiment of present invention is to provide a process for the recovery of dimethyl 3-isobutylpentanedioate compound of formula-3.

The seventh embodiment of present invention is to provide another process for the recovery of dimethyl 3-isobutylpentanedioate compound of formula-3.

The eighth embodiment of the present invention is to provide an improved process for the preparation of compound of formula-A.

Detailed description of the invention:

As used herein the term “suitable solvent” used in the present invention refers to “hydrocarbon solvents” such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; “ether solvents” such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; “ester solvents” such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; “polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; “chloro solvents” such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; “ketone solvents” such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; “nitrile solvents” such as acetonitrile, propionitrile, isobutyronitrile and the like; “alcoholic solvents” such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, 1, 2-ethoxyethanol, diethylene glycol, 1,

2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; “polar solvents” such as water or mixtures thereof.

As used herein the present invention the term “suitable base” refers to inorganic bases and organic bases; inorganic base is selected from “alkali metal carbonates” such as sodium carbonate, potassium carbonate, lithium carbonate and the like; “alkali metal bicarbonates” such as sodium bicarbonate, potassium bicarbonate and the like; “alkali metal hydroxides” such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride, lithium hydride and the like; alkali metal amides such as sodium amide, potassium amide, lithium amide and the like; and organic bases like dimethylamine, diethylamine, diisopropyl amine, diisopropylethylamine, diisobutylamine, triethylamine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), 2,6-lutidine, lithium diisopropylamide; “alkali metal alkoxides” such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like; organosilicon bases such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) or mixtures thereof.

The term “acid” used in the present invention refers to inorganic acids selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid etc; organic acids such as acetic acid, maleic acid, malic acid, tartaric acid, oxalic acid, trifluoroacetic acid, methane sulfonic acid, p-toluene sulfonic acid; chiral acids such as S-(+) mandelic acid, R-(-) mandelic acid, L-(+)tartaric acid, D-(-)tartaric acid, L-malic acid, D-malic acid, D-maleic acid, (-)-naproxen, (-i)-naproxen, (1R)-(-)-camphor sulfonic acid, (1S)- (+)-camphor sulfonic acid, (1R)-(+)-bromocamphor-10-sulfonic acid, (1S)-(-)- bromocamphor-10-sulfonic acid, (-)-Dibenzoyl-L-tartaric acid, (-)-Dibenzoyl-L- tartaricacid monohydrate, (+)-Dibenzoyl-D -tartaric acid, (-t)-Dibenzoyl-D -tartaric acid monohydrate, (+)-dipara-tolyl-D-tartaric acid, (-)-dipara-tolyl-L-tartaricacid, L(-)- pyroglutamic acid, L(+)-pyroglutamic acid, (-)-lactic acid, L-lysine, D-lysine etc., and like.

The first embodiment of the present invention provides an improved process for the preparation of 3-isobutylglutaric acid compound of formula- 1, comprising:

- a) reacting the cyano acetic acid or its salts with isovaleraldehyde in presence of a suitable base in as suitable solvent at a suitable temperature to provide 2,4-dicyano-3-isobutylpentanedioic acid,
- b) adding a suitable acid to the obtained reaction mixture in step-a),
- c) heating the reaction mixture to a suitable temperature,
- d) stirring the reaction mixture,
- e) cooling the reaction mixture,
- f) extracting the reaction mixture using a suitable water immiscible solvent,
- g) distilling off the solvent from the organic layer obtained in step-f) to get the compound of formula- 1,
- h) optionally purifying the compound of formula- 1 obtained in step-g).

Wherein in step-a) the suitable solvent is selected from polar solvents such as water or mixture of water with an organic solvent; wherein organic solvent is selected from alcohol solvents, ether solvents, polar aprotic solvents and like; the suitable base is selected from inorganic or organic bases; preferably inorganic bases; the suitable temperature is about 0 to 30°C;

in step-b) the suitable acid is selected from organic or inorganic acids; preferably inorganic acids;

in step-c) the suitable temperature is about 30°C to reflux temperature of the solvent used;

in step-f) the suitable water immiscible solvent is selected from chloro solvents, hydrocarbon solvents, ether solvents and ester solvents and the like.

The second embodiment of the present invention provides an improved process for the preparation of 3-isobutylglutaric acid compound of formula- 1, comprising:

- a) reacting the cyano acetic acid or its salts with isovaleraldehyde in presence of a suitable base in as suitable solvent at a suitable temperature to provide 2,4-dicyano-3-isobutylpentanedioic acid,
- b) adding a suitable acid to the obtained reaction mixture in step-a),
- c) heating the reaction mixture to a suitable temperature,
- d) stirring the reaction mixture,
- e) cooling the reaction mixture to below 40°C,

- f) optionally adding a suitable solvent to the reaction mixture,
- g) optionally further cooling the reaction mixture obtained in step-e) or step-f),
- h) filtering the solid obtained in step-g) to get the compound of formula- 1,
- i) optionally purifying the compound of formula- 1 obtained in step-h).

Wherein in step-a) the suitable solvent is selected from polar solvents such as water or mixture of water with an organic solvent; wherein organic solvent is selected from alcohol solvents, ether solvents, polar aprotic solvents and like; the suitable base is selected from inorganic or organic bases; preferably inorganic bases; the suitable temperature is about 0 to 30°C;

in step-b) the suitable acid is selected from organic or inorganic acids; preferably inorganic acids;

in step-c) the suitable temperature is about 30° to reflux temperature of the solvent used;

in step-f) the suitable solvent is selected from hydrocarbon solvents.

In the above embodiments usage of bases such as sodium hydroxide solution, potassium hydroxide solution and like are cheaper. The reaction proceeds rapidly under the conditions at elevated temperatures i.e., between about 0°C to about 30°C. And further the hydrolysis is carried out at about 35°C to reflux temperature of the solvent used.

The third embodiment of present invention provides an improved process for the preparation of 3-isobutyl glutaric acid compound of formula- 1 comprising:

- a) reacting cyano acetic acid or its salts with isovaleraldehyde in presence of an inorganic base in a solvent to obtain 2,4-dicyano-3-isobutylpentanedioic acid,
- b) treating the mixture obtained in step-a) with an acid to provide 3-isobutyl glutaric acid compound of formula- 1.

The fourth embodiment of present invention provides an improved process for the preparation of Pregabalin compound of formula-A comprising:

- a) reacting cyano acetic acid or its salts with isovaleraldehyde in presence of an inorganic base in a solvent to obtain 2,4-dicyano-3-isobutylpentanedioic acid,
- b) treating the mixture obtained in step-a) with an acid to provide 3-isobutyl glutaric acid compound of formula- 1,
- c) converting the compound of formula- 1 into Pregabalin compound of formula-A.

Solvent in third and fourth embodiments is selected from as water, organic solvent or mixtures thereof; wherein organic solvent is selected from alcohol solvents, ether solvents, polar aprotic solvents and like; the inorganic base is selected from alkali base; more preferably alkali base is selected from sodium hydroxide, potassium hydroxide and the like; suitable acid is selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid and the like.

The 2,4-dicyano-3-isobutylpentanedioic acid formed in the above aspects can be further converted into compound of formula-1 without isolating the same from the reaction mixture. It is advantageous in commercial scale in getting the high yields.

In an aspect of the step-a) of the third and fourth embodiment, the reaction is carried out with 2 moles of cyanoacetic acid per 1 mole of isovaleraldehyde in presence aqueous alkaline basic solution at basic pH. The reaction is provided without any side reactions and is completed within shorter time period to provide 2,4-dicyano-3-isobutylpentanedioic acid which on in-situ hydrolysis using acid provided 3-isobutylglutaric acid with high yields i.e., 90% or above. This kind of higher yield is not reported in prior art for the preparation of 3-isobutylglutaric acid. The reaction proceeds rapidly under the conditions at temperatures between about 0°C to about 30°C. And further the hydrolysis is carried out at about 35°C to reflux temperature of the solvent used.

Salts of cyanoacetic acid can be also used in the above reaction. The cyanoacetic salts were prepared by reacting chloroacetic salts with alkyl cyanides. In a variant 70% to 99% of aqueous cyano acetic acid is used in the present invention.

The fifth embodiment of present invention provides an improved process for the preparation of Pregabalin compound of formula-A comprises:

- a) reacting the cyano acetic acid or its salts with isovaleraldehyde in presence of an inorganic base in a solvent to provide 2,4-dicyano-3-isobutylpentanedioic acid,
- b) treating the mixture obtained in step-a) with an acid to provide 3-isobutyl glutaric acid compound of formula-1,
- c) treating the compound of formula-1 with an acid selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid and the like in methanol to obtain dimethyl 3-isobutylpentanedioate compound

of formula-3,

d) converting the compound of formula-3 into pregabalin compound of formula-A.

Solvent, inorganic base and acid in step-a) and step-b) are same as defined in the third embodiment.

In the literature reference *journal of American chemical society* 1993, 115, 77-81 describes esterification using methanol and trimethyl silyl chloride. Sulfuric acid is 50 times cheaper than Trimethyl silyl chloride. Hence Trimethyl silyl chloride is not recommended for industrial scale development or large scale production.

Journal of Applied Microbiology 2013, 115(5), 1127-1133 describes the esterification using methanol and thionyl chloride. Thionyl chloride is also costlier than sulfuric acid. Thionyl chloride is a colorless to yellow fuming liquid with a suffocating pungent odor, lachrymator, highly corrosive and toxic. Long-term inhalation of low concentrations or short-term inhalation of high concentrations has adverse health effects. Thionyl chloride also requires lengthy workup process for the removal of unreacted thionyl chloride.

WO2009158343A1 herein after described as WO'343 describes preparation of Pregabalin from 3-isobutyl glutaric acid by enzymatic process. All the contents of the publication are herein by reference.

2719/CHE/2009 describes preparation of Pregabalin from dimethyl 3-isobutylpentanedioate by the enzymatic process. All the contents of the publication are herein by reference.

None of these references provide any recovery process of dimethyl 3-isobutylpentanedioate compound of formula-3. Present application provides simple, efficient process, recovery of unreacted intermediates and process impurities which are further converted to useful intermediates. The recovery and reutilization of the intermediates, further reduces the cost of production and makes the present process was more advantageous and economical compared to the prior art.

The sixth embodiment of present invention provides a process for the recovery of dimethyl 3-isobutylpentanedioate compound of formula-3 comprising; treating monoacid compound of formula-6, diacid compound of formula-1, dimethyl 3-isobutylpentanedioate compound of formula-3 or mixtures thereof with an acid selected from hydrochloric acid,

nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid in methanol to provide dimethyl 3-isobutylpentanedioate compound of formula-3.

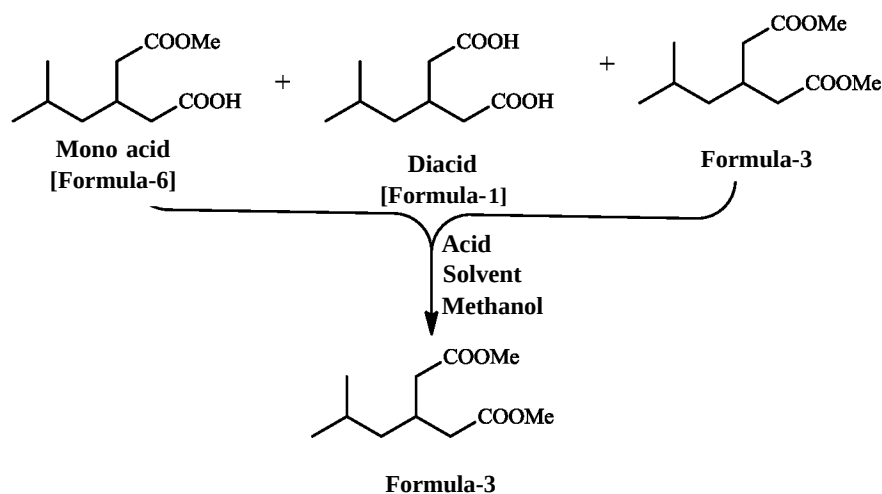
In an aspect of the sixth embodiment, wherein monoacid compound of formula-6, diacid compound of formula-1, dimethyl 3-isobutylpentanedioate compound of formula-3 or mixture thereof used as input are obtained as bi-products or as left over residues from the extracts or filtered mother liquors obtained in the preparation of dimethyl 3-isobutylpentanedioate compound of formula-3.

In further aspect of the sixth embodiment, further comprising converting the recovered dimethyl 3-isobutylpentanedioate compound of formula-3 into Pregabalin compound of formula-A.

Further aspect of the sixth embodiment, the left over residue from the extracts comprising; treating the aqueous layer obtained in the preparation of dimethyl 3-isobutylpentanedioate compound of formula-3 in an water immiscible organic solvent with an acid and distilling off the solvent from the organic layer to provide the residue contained the mixture of monoacid compound of formula-6, diacid compound of formula-1 and dimethyl 3-isobutylpentanedioate compound of formula-3.

Water immiscible solvents selected from ether solvents, hydrocarbon solvents, ester solvents, chloro solvents and like; acid in step-a) and step-b) is selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, acetic acid and like.

As per the recovery process the present inventors converted the monoacid compound of formula-6 and diacid compound of formula-1 into dimethyl 3-isobutylpentanedioate compound of formula-3 as per the following scheme and the recovered dimethyl 3-isobutylpentanedioate compound of formula-3 is may reutilized in the preparation of Pregabalin compound of formula-A which is very advantageous and is most useful in the reduction of cost of production of Pregabalin.



Scheme- 1

Recovery process of the present invention provides recovery of undesired intermediate compounds from left over extracts obtained during the preparation of dimethyl 3-isobutylpentanedioate compound of formula-3. Those undesired intermediates are converted to desired dimethyl 3-isobutylpentanedioate compound of formula-3 which substantially reduced cost of production and makes process economically and environmentally suitable in an industrial scale.

The seventh embodiment of present invention provides another process for the recovery of dimethyl 3-isobutylpentanedioate compound of formula-3 comprising:

- a) converting (R)-3-(carbamoylmethyl)-5-methylhexanoic acid compound of formula-5, 3-isobutyl glutaric acid formula- 1 or mixtures thereof to 3-isobutyl glutaric acid compound of formula- 1 by treating with an aqueous acid,
- b) treating the compound of formula-1 obtained in step-a) with an acid selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid and the like in methanol to provide dimethyl 3-isobutylpentanedioate compound of formula-3.

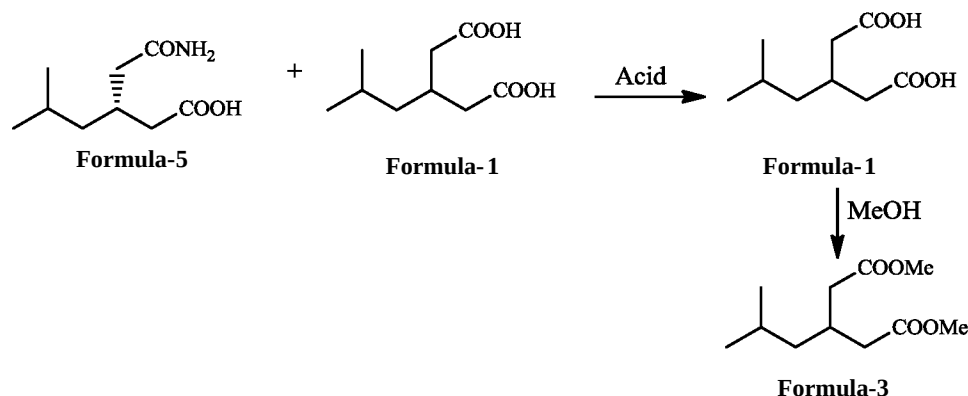
The acid in aqueous acid of step-a) is selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid or mixtures thereof.

In an aspect of the seventh embodiment, wherein (R)-3-(carbamoylmethyl)-5-

methylhexanoic acid, 3-isobutyl giutaric acid or mixtures thereof used as input are filtered mother liquors obtained in the preparation of (R)-3-(carbamoylmethyl)-5-methylhexanoic acid compound of formula-5.

Further aspect of the seventh embodiment, further comprising converting the recovered dimethyl 3-isobutylpentanedioate compound of formula-3 into Pregabalin compound of formula-A.

Further aspect of the seventh embodiment the recovery can be done, for example, by neutralizing the filtrate, extracting with an organic solvent and evaporating the combined extracts. The obtained mixture of (R)-3-(carbamoylmethyl)-5-methylhexanoic acid compound of formula-5 and 3-isobutyl giutaric acid compound of formula-1 is treated with an acid to provide pure 3-isobutyl giutaric acid compound of formula-1; wherein the acid is selected from inorganic acids and organic acids. Further 3-isobutyl giutaric acid compound of formula-1 is converted to diester compound of formula-3 as per the following scheme.



Scheme-2

The eighth embodiment of the present invention provides an improved process for the preparation of Pregabalin compound of formula-A comprising:

- treating dimethyl 3-isobutylpentanedioate compound of formula-3 with whole cell mass in presence of a buffer in a solvent to provide (S)-3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid compound of formula-4,
- converting the compound of formula-4 into (R)-3-(carbamoylmethyl)-5-methylhexanoic acid compound of formula-5,
- converting the compound of formula-5 into Pregabalin compound of formula-A.

In an aspect of step-a) of eighth embodiment, the whole cell mass is E.Coli expressing Lipase B derived from Candida Antarctica; the solvent is selected from water, organic solvents or mixtures thereof; the buffer is selected from potassium phosphate buffer, dipotassium hydrogen phosphate buffer, sodium phosphate buffer, Tris-HCl buffer; the reaction is carried out at about 25°C to 35°C.

The hydrolysis of dimethyl 3-isobutylpentanedioate compound of formula-3 is done in presence of enzyme in basic buffer, thus providing required isomer of hydrolyzed product i.e., (S)-3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid. The suitable enzyme that is capable of performing a stereo selective hydrolysis reaction of dimethyl 3-isobutylpentanedioate compound of formula-3 to provide (S)-3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid in high enantiomeric excess is lipase B from Candida Antarctica (Cal B).

It is known in literature that i.e., WO2009158343A1, the dimethyl 3-isobutylpentanedioate compound of formula-3 hydrolysis reaction, when performed at temperature of about -3°C to 10°C gives optimal optical purity of (S)-3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid ester required for producing next intermediate. However, low temperature reaction takes 70 - 90 hrs for completion of the reaction there by making the overall process inefficient, not commercially viable.

Typically, the enzymes are produced using recombinant DNA technology in bacterial host like E. Coli after cloning the required gene into host cell expression system. The over expressed enzyme within the host cell is subjected to further process to obtain crude enzyme powder or in some cases the whole cell can be used in reaction process. It is herein referred to whole cell mass.

In an aspect of the step-a) of eighth embodiment the process in the enzyme is used as in the form of whole cell mass in combination in presence of buffered medium is for conducting hydrolysis reaction. It is most advantageous by reducing time and cost. Further, in this case it may provide advantage in terms enantio selectivity due to intrinsic physico-chemical differences between isomers.

Owing to the usage of whole cell mass in an efficient manner in the process of present invention it leads to better results in terms of enantio selectivity of the hydrolysis step. It reduces the burden of isolating pure & specific enzyme from the whole cell mass for using it

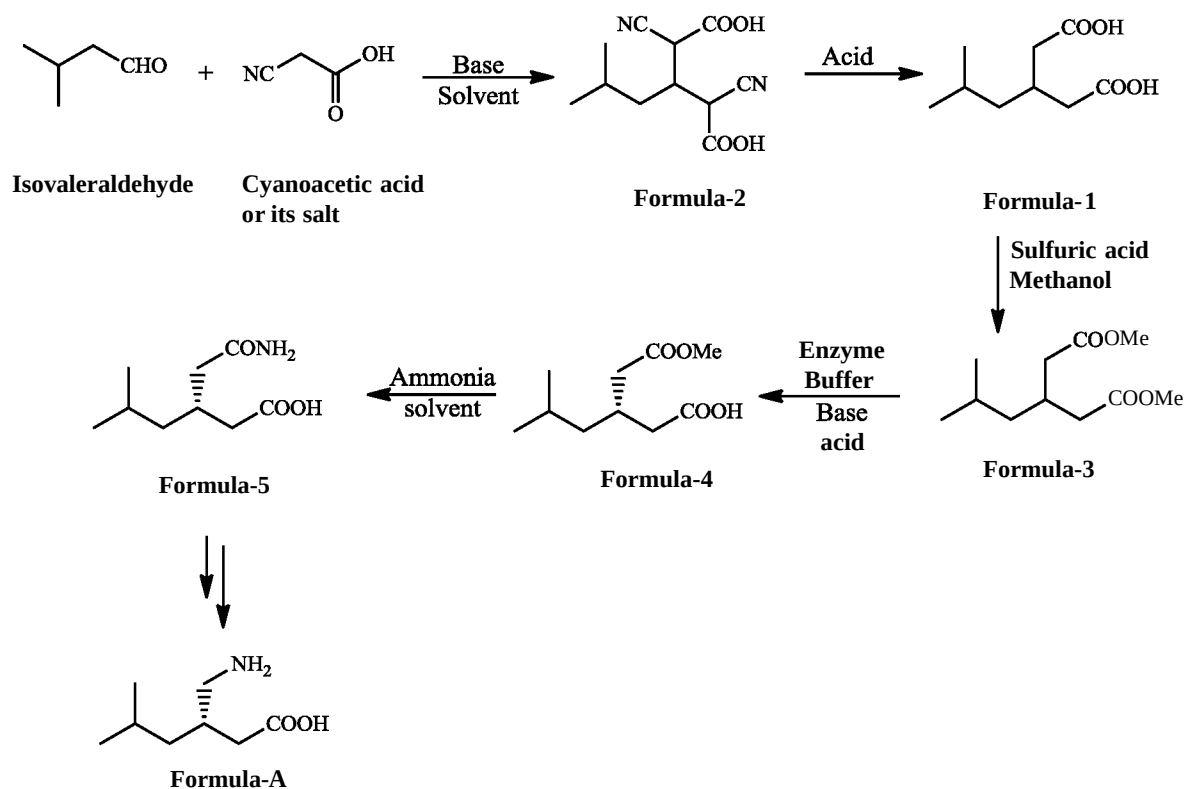
in the said hydrolysis step. This in turn helped in defining simply, economical & commercially viable process for Pregabalin compound of formula-A.

Further aspect of the eighth embodiment, the resulting compound of formula-4 and formula-5 have a chiral purity of about >95% or about >96% or about >97% or about >98% or about >99% or about >99.5% or about >99.9% (ee) or 100% as measured by Chiral HPLC method.

In turn the Pregabalin prepared from the compound of formula-4 or formula-5 obtained according to the present invention has a chiral purity of >98% or >99% or >99.5% or >99.9% (ee) or 100% as measured by Chiral HPLC method.

The chiral HPLC method that can be used to measure chiral purity in the present invention can be easily derived by a person skilled in the art from the known method reported in the art.

The 3-isobutylglutaric acid compound of formula-1 and/or dimethyl 3-isobutyl pentanedioate compound of formula-3 prepared according to the present invention is further converted into Pregabalin compound of formula-A as following scheme:



Scheme-3

The best mode of carrying out the present invention was illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be construed as limitation in the scope of the invention.

Examples:**Example-1: Preparation of 3-isobutylglutaric acid**

The mixture of water (114 ml) and 70% cyano acetic acid (286 g) was cooled to 10-15°C. Slowly added the aqueous sodium hydroxide solution (116 g of sodium hydroxide in 114 ml of water) to the reaction mixture at 10-15°C and stirred for 5 minutes at the same temperature. 100 g of isovaleraldehyde was added to the reaction mixture at 10-15°C and stirred the reaction mixture for 6 hours at the same temperature. Hydrochloric acid (800 ml) was added to the reaction mixture at 10-15°C. Heated the reaction mixture to reflux and stirred it for 10 hours at the same temperature. Cooled the reaction mixture to 25-30°C and toluene was added to the reaction mixture. Separated both the organic and aqueous layers and the aqueous layer was extracted with toluene. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 200 g (91.5%).

Example-2: Preparation of dimethyl 3-isobutylpentanedioate

A mixture of 3-isobutylglutaric acid (100 g) and methanol (200 ml) was heated to 40-45°C and sulphuric acid (10 g) was slowly added to this reaction mixture. Further heated the reaction mixture to reflux temperature and stirred it for 14 hours at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure. Cooled the reaction mixture to 25-30°C. Water and toluene were added to the reaction mixture and stirred for 30 minutes at 25-30°C. Separated the both organic and aqueous layers and the organic layer was washed with aqueous sodium carbonate solution. Distilled off the solvent completely from the organic layer to get the title compound. Yield: 100 g.

Example-3: Preparation of dimethyl 3-isobutylpentanedioate

Cooled the mixture of isobutyl glutaric acid (200 g) and methanol (500 ml) to 10-15°C. Sulphuric acid (50 g) was slowly added to the reaction mixture at 10-15°C. Heated the reaction mixture to 65-70°C and stirred for 2 hours at the same temperature. Distilled off the

solvent completely from the reaction mixture under reduced pressure. Water and dichloromethane were added to the obtained residue at 25-30°C and adjusted the pH of the reaction mixture using aqueous sodium carbonate solution. Stirred the reaction mixture for 15 minutes at 25-30°C and separated the both organic and aqueous layers. Organic layer was washed with aqueous sodium bicarbonate solution and followed by with water. Distilled off the solvent completely from the organic layer to get the title compound. Yield: 162 g.

Example-4: Preparation of (S)-3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid

Dissolved di potassium phosphate (13.1 g) in water (750 ml) at 25-30°C, neutralized the reaction mixture using hydrochloric acid and cooled the reaction mixture to 10-15°C. Enzyme CAL-B 7L (15 g) followed by dimethyl 3-isobutylpentanedioate (100 g) were slowly added to the reaction mixture at 10-15°C and stirred for 7 hours at the same temperature. The reaction mixture was acidified using hydrochloric acid at 10-15°C and toluene was added to the reaction mixture. Raised the temperature of the reaction mixture to 25-30°C and stirred for 30 minutes at the same temperature. Separated the both organic and aqueous layers, filtered the organic layer over the hyflow bed and washed with toluene. The organic layer was washed with water and distilled off solvent completely from the organic layer to get the title compound. Yield: 92 g.

Example-5: Preparation of (S)-3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid

Dissolved potassium dihydrogen phosphate (10.8 g) in water (475 ml) at 25-30°C, neutralized the reaction mixture using aqueous sodium hydroxide solution and cooled the reaction mixture to 0-5°C. Addzyme CAL-B 7L (20 g) followed by dimethyl 3-isobutylpentanedioate (100 g) were slowly added to the reaction mixture at 0-5°C and stirred for 95 hours at the same temperature. The reaction mixture was acidified using hydrochloric acid at 0-5°C and ethyl acetate was added to the reaction mixture. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 minutes at the same temperature. Separated the both organic and aqueous layers and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and dried over anhydrous sodium sulphate. Distilled off the solvent completely from the organic layer and co-distilled with dichloromethane to get the title compound. Yield: 92 g.

Example-6: Preparation of (R)-3-(2-amino-2-oxoethyl)-5-methylhexanoic acid

The mixture of (S)-3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid (100 g) and 25% aqueous ammonia (600 ml) was stirred for 3 days at 25-30°C. Heated the reaction mixture to 85-90°C and stirred for 3 hours at same temperature. Cooled the reaction mixture to 15-20°C and acidified the reaction mixture using hydrochloric acid. Cooled the reaction mixture to 0-5°C and stirred for 2 hours at the same temperature. Filtered the solid, washed with water and dried to get title compound. Yield: 75 g.

Example-7: Preparation of (R)-3-(2-amino-2-oxoethyl)-5-methylhexanoic acid compound of formula-5

(S)-3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid (80 g), methanol (800 ml) and calcium chloride (54 g) were charged into autoclave and cooled the reaction mixture to 15-20°C. 4.5 kg of ammonia gas pressure was passed into the reaction mixture at the same temperature. Heated the reaction mixture to 55-60°C and stirred the reaction mixture for 12 hours at the same temperature. Cooled the reaction mixture to 40-45°C and distilled off solvent completely from the reaction mixture. Water was added to the obtained residue and acidified using hydrochloric acid at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 45 minutes at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound. Yield: 60 g. Chiral purity: 94.11%, S-isomer: 5.89%.

Example-8: Purification of (R)-3-(2-amino-2-oxoethyl)-5-methylhexanoic acid

A mixture of (R)-3-(2-amino-2-oxoethyl)-5-methylhexanoic acid (20 g), ethyl acetate (9 ml) and water (2.5 ml) was heated to 60-65°C and stirred for 45 minutes at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 60 minutes at the same temperature. Filtered the solid, washed with ethyl acetate and dried to get the title compound. Yield: 16.6 g. Chiral Purity: 99.45%, S-isomer: 0.05%.

Example-9: Preparation of (S)-3-(aminomethyl)-5-methylhexanoic acid

(R)-3-(2-amino-2-oxoethyl)-5-methylhexanoic acid (100 g) was slowly added to the pre-cooled solution of sodium hydroxide (60 g) in water (100 ml) at 0-5°C and stirred for 10 minutes at the same temperature. To this reaction mixture sodium hypochlorite solution (350 ml) was added at 0-5°C and stirred for 30 minutes at the same temperature. Raised the temperature of the reaction mixture to 25-30°C, further heated to 80-85°C and stirred it for

45 minutes at the same temperature. Cooled the reaction mixture to 25-30°C and adjusted the pH of the reaction mixture using hydrochloric acid and stirred for 20 minutes at same temperature. Slowly heated the reaction mixture to 80-85°C and stirred for 1 hour at the same temperature. Slowly cooled the reaction mixture to 25-30°C and further cooled to 0-5°C and stirred for 2 hours at the same temperature. Filtered the solid, washed with methanol and dried to get the title compound. Yield: 65 g.

Example-10: Preparation of 3-isobutylglutaric acid

Cooled the mixture of 2-cyanoacetamide (500 g) and water (4000 ml) to 6-12°C. Isovaleraldehyde (130 g) followed by morpholine (10 g) was slowly added to the above reaction mixture at 6-12°C and stirred the reaction mixture for 2 hours at the same temperature. To this reaction mixture isovaleraldehyde (130 g) followed by morpholine (5 g) was added at 6-12°C and stirred for 18 hours at the same temperature. To this reaction mixture concentrated hydrochloric acid (2500 ml) was added and heated the reaction mixture to 105-110°C and stirred for 18 hours at the same temperature. Cooled the reaction mixture to 25-30°C and cyclohexane (1000 ml) was added. Further cooled the reaction mixture to 10-15°C and stirred for 3 hours at the same temperature. Filtered the solid, washed with cyclohexane and dried to get the title compound. Yield: 480 g.

Example-11: Preparation of dimethyl 3-isobutylpentanedioate

The mixture of water (100 ml) and 70% aqueous cyano acetic acid (290 g) was cooled to 10-15°C. Aqueous sodium hydroxide solution (116 g of sodium hydroxide in 100 ml of water) and isovaleraldehyde (100 g) were slowly added to the reaction mixture at 10-15°C and stirred for 8 hours at the same temperature. Concentrated hydrochloric acid (800 ml) was added to the reaction mixture at 10-15°C, heated to reflux and stirred it for 17 hours at the same temperature. Cooled the reaction mixture to 25-30°C, water and toluene were added to the reaction mixture. Separated both the organic and aqueous layers and the aqueous layer was extracted with toluene. Distilled off the solvent completely from the organic layer under reduced pressure to get 3-isobutyl glutaric acid as a residue. Methanol (400 ml) and sulfuric acid (20 g) were added to residue at 25-30°C and heated reaction mixture to 65-70°C and stirred for 8 hours at same temperature. Cooled the reaction mixture to 40-45°C and distill off solvent completely under reduced vacuum. Cooled the reaction mixture to 10-15°C, toluene

and water were added. Separated the both organic and aqueous layers and organic layer was washed with aqueous sodium carbonate solution. Combined the organic layers and washed with water. Distilled off the solvent completely from organic layer to get title compound.

Yield: 190 g

Example-12: Preparation of (R)-3-(carbamoylmethyl)-5-methylhexanoic acid

Neutralized the aqueous di potassium phosphate solution (22 g in water) using neutralized hydrochloric acid and cooled the mixture to below 15°C. CAL-B enzyme (25.5 g) followed by dimethyl 3-isobutylpentanedioate (170 g) were slowly added to the buffer solution at below 15°C and stirred for 80 hours at the same temperature by adjusting pH by using aqueous sodium hydroxide. Raised the temperature of the reaction mixture to 25-30°C and acidified using aqueous hydrochloric acid solution. Toluene was added to reaction mixture. Separated both organic and aqueous layers and aqueous layer was extracted with toluene. Combined the organic layers, filtered through hyflow bed and was washed with toluene. Obtained filtrate was washed with water. Ammonia (1020 ml) was added to the toluene layer at 25-30°C and stirred for 45 minutes at the same temperature. Separated both organic and aqueous layer and aqueous layer was kept aside for 85 hours at 25-30°C. Heated the reaction mixture to 85-90°C and stirred for 4 hours at the same temperature. Cooled the reaction mixture to 15-20°C and acidified using aqueous hydrochloric acid solution. Cooled the reaction mixture to 0-3°C and stirred for 3 hours at the same temperature. Filtered the solid, washed with water and dried to get the titled compound. Recrystallized the obtained compound using the mixture of ethyl acetate and water to get pure title compound.

Yield: 93 g, Purity by HPLC: 99.94%

Example-13: Preparation of (R)-3-(carbamoylmethyl)-5-methylhexanoic acid

Neutralized the aqueous di potassium phosphate solution (1.1 g in water) using neutralized hydrochloric acid and cooled the mixture to below 15°C. Whole cell mas (8.5 g) followed by dimethyl 3-isobutylpentanedioate (8.5 g) were slowly added to the buffer solution at below 15°C by maintaining pH. Raised the temperature of the reaction mixture to 25-30°C and stirred for 10 hours. Acidified the reaction mixture using aqueous hydrochloric acid solution and toluene was added to reaction mixture. Separated both organic and aqueous layers and aqueous layer was extracted with toluene. Combined the organic layers, filtered through

hyflow bed and was washed with toluene. Obtained filtrate was washed with water. Ammonia (51 ml) was added to the toluene layer at 25-30°C and stirred for 45 minutes at the same temperature. Separated both organic and aqueous layer and aqueous layer was kept aside for 85 hours at 25-30°C. Heated the reaction mixture to 85-90°C and stirred for 4 hours at the same temperature. Cooled the reaction mixture to 15-20°C and acidified using aqueous hydrochloric acid solution. Cooled the reaction mixture to 0-3°C and stirred for 3 hours at the same temperature. Filtered the solid, washed with water and dried to get the titled compound. Purity: 98.10% by chiral HPLC.

Recrystallized the obtained compound using the mixture of ethyl acetate and water to get pure title compound. Yield: 6 g, Purity: 100.0% by Chiral HPLC.

Example-14: Process for the recovery of dimethyl 3-isobutylpentanedioate

Treated the aqueous layer obtained in example-11 contained 3-isobutyl glutaric acid, 3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid and dimethyl 3-isobutylpentanedioate with hydrochloric acid at 25-30°C. Extracted the compound into toluene and distilled off solvent from the toluene layer to get compound contained 3-isobutyl glutaric acid, 3-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid and dimethyl 3-isobutylpentanedioate as residue. Methanol and sulfuric acid were added to residue, heated the reaction mixture to 65-70°C and stirred for 8 hours at same temperature. Cooled the reaction mixture to 40-45 °C and distilled off the solvent completely under reduced pressure. Toluene and water were added to the obtained compound. Separated the both organic and aqueous layer and organic layer was washed with aqueous sodium carbonate solution followed by with water. Distilled off the solvent completely from the organic layer to get title compound. Yield: 90%; HPLC purity: 95.59%.

Example-15: Process for the recovery of dimethyl 3-isobutylpentanedioate

The mixture of ethyl acetate and water mother liquor which was obtained by the recrystallization process in example- 12 contained 3-isobutyl glutaric acid impurity and (R)-3-(carbamoylmethyl)-5-methylhexanoic acid was washed with aqueous sodium chloride solution. Organic layer was distilled off under reduced pressure. Concentrated hydrochloric acid was added to the obtained residue. Heated the reaction mixture to 10-15°C and stirred 10 hours at the same temperature. Cooled the reaction mixture to 25-30°C and toluene was added to it. Separated both organic and aqueous layers and distilled off the solvent from the

organic layer to get 3-isobutyl glutaric acid as a residue. Methanol and sulfuric acid were added to the obtained residue and heated reaction mixture to 65-70°C and stirred for 8 hours at same temperature. Cooled the reaction mixture to 40-45°C and distilled off solvent completely under reduced pressure. Toluene and water were added to the obtained mass at 10-15°C. Separated the both organic and aqueous layers and organic layer was washed with aqueous sodium carbonate solution followed by with water. Distilled off solvent completely from organic layer to get the title compound. Yield: 70%; purity by HPLC 95.21%.

Example-16: Preparation of (S)-3-(aminomethyl)-5-methylhexanoic acid

Aqueous sodium hypochlorite solution (248 ml) was added to the pre-cooled solution of sodium hydroxide (32 g) in water (100 ml) at 0-5°C and stirred for 10 minutes at the same temperature. To this mixture (R)-3-(2-amino-2-oxoethyl)-5-methylhexanoic acid (50 g) was slowly added at -5°C to 0°C. Raised the temperature of the reaction mixture to 25-30°C, further heated to 40-45°C and stirred it for 1 hour at the same temperature. Cooled the reaction mixture to 25-30°C and adjusted the pH of the reaction mixture using hydrochloric acid and washed the mixture with toluene. Adjusted the pH of the aqueous layer to 6 to 7 by using aqueous sodium hydroxide solution. Cooled the mixture to 0-5°C and stirred for 2 hours at the same temperature. Filtered the solid, washed with methanol and dried to get the title compound. Yield: 30 g.

We Claim:

1. A process for the preparation of Pregabalin compound of formula-A comprising:
 - a) reacting cyano acetic acid or its salts with isovaleraldehyde in presence of an inorganic base in a solvent to obtain 2,4-dicyano-3-isobutylpentanedioic acid,
 - b) treating the mixture obtained in step-a) with an acid to provide 3-isobutyl glutaric acid compound of formula- 1,
 - c) converting the compound of formula- 1 into Pregabalin compound of formula-A.
2. A process for the preparation of Pregabalin compound of formula-A comprising:
 - a) reacting the cyano acetic acid or its salts with isovaleraldehyde in presence of an inorganic base in a solvent to provide 2,4-dicyano-3-isobutylpentanedioic acid,
 - b) treating the mixture obtained in step-a) with an acid to provide 3-isobutyl glutaric acid compound of formula- 1,
 - c) treating the compound of formula- 1 with an acid in methanol to obtain dimethyl 3-isobutylpentanedioate compound of formula-3,
 - d) converting the compound of formula-3 into Pregabalin compound of formula-A.
3. The process according to claims 1 or 2, the inorganic base is selected from alkali base; solvent is selected from water, organic solvent or mixtures thereof; wherein the organic solvent is selected from alcohol solvents, ether solvents, polar aprotic solvents and acid is selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid or mixtures thereof.
4. A process for the recovery of dimethyl 3-isobutylpentanedioate compound of formula-3 comprising; treating monoacid, diacid, dimethyl 3-isobutylpentanedioate or mixtures thereof with an acid selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid in methanol to provide dimethyl 3-isobutylpentanedioate compound of formula-3.

5. The process according to claim 4, wherein monoacid, diacid, dimethyl 3-isobutylpentanedioate or mixture thereof used as input are obtained as bi-products or as left over residues from the extracts or filtered mother liquors obtained in the preparation of dimethyl 3-isobutylpentanedioate compound of formula-3.
6. The process according to claim 4, further comprising converting the recovered dimethyl 3-isobutylpentanedioate compound of formula-3 into Pregabalin compound of formula-A.
7. A process for the recovery of dimethyl 3-isobutylpentanedioate compound of formula-3 comprising;
 - a) converting (R)-3-(carbamoylmethyl)-5-methylhexanoic acid compound of formula-5, 3-isobutyl glutaric acid compound of formula-1 or mixtures thereof to 3-isobutyl glutaric acid compound of formula-1 by treating with an aqueous acid,
 - b) treating the compound of formula-1 obtained in step-a) with an acid selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid in methanol to provide dimethyl 3-isobutylpentanedioate compound of formula-3.
8. The process according to claim 7, wherein (R)-3-(carbamoylmethyl)-5-methylhexanoic acid, 3-isobutyl glutaric acid or mixtures thereof used as input are filtered mother liquors obtained in the preparation of (R)-3-(carbamoylmethyl)-5-methylhexanoic acid compound of formula-5.
9. The process according to claim 7, wherein the acid in aqueous acid of step-a) is selected from hydrochloric acid, nitric acid, sulfuric acid, para-toluene sulfonic acid, HI, hydrobromic acid, phosphoric acid, acetic acid or mixtures thereof.

10. The process according to claim 7, further comprising converting the recovered dimethyl 3-isobutylpentanedioate compound of formula-3 into Pregabalin compound of formula-A.
11. A process for the preparation of Pregabalin compound of formula-A comprising:
 - a) treating the dimethyl 3-isobutylpentanedioate compound of formula-3 with whole cell mass in presence of a buffer in a solvent to provide the compound of formula-4,
 - b) converting the compound of formula-4 into compound of formula-5,
 - c) converting the compound of formula-5 into Pregabalin compound of formula-A.
12. The process according to claim 11, wherein the whole cell mass is E.Coli expressing Lipase B derived from Candida Antartica.
13. The process according to claim 11, wherein the solvent is selected from water, organic solvents or mixtures thereof is used in step-a).
14. The process according to claim 11, wherein the buffer is selected from potassium phosphate buffer, dipotassium hydrogen phosphate buffer, sodium phosphate buffer, Tris-HCl buffer is used in step-a).
15. The process according to claim 11, wherein the reaction is carried out at about 25°C to about 35°C.
16. The process according to claim 11, the compound of formula-4 obtained in step-a) having chiral purity of about >96% by chiral HPLC method.
17. The process according to claim 11, wherein the compound of formula-5 obtained in step-b) having chiral purity of about >97% by chiral HPLC method.
18. The process according to claim 11, wherein Pregabalin having chiral purity of about >99.5% by chiral HPLC method.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050279

A. CLASSIFICATION OF SUBJECT MATTER
C07C229/08, C12P13/00 Version=2019.01

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)

C07C, C12P

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 practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5616793 A (WARNER-LAMBERT COMPANY), 01 April 1997 (1997-04-01) the scheme I col.3 lines 57-67, col. lines 7-11; col. 4 lines 48-59; examples, claims 1, 3, 5 and 8	1-6
X	WO 2011/077463 A1 (MSN LABORATORIES LIMITED), 30 June 2011 (2011-06-30) page 2 lines 18-25; page 4 lines 25-30	7-10
Y	abstract, examples, page 4 lines 25-30 page 10 lines 20-23; examples 2, 12, claim 19	11-18
Y	WO 2009/158343 A1 (TEVA PHARMACEUTICAL INDUSTRIES, LTD.) 30 December 2009 (2009-12-30) page 6 para [0016], [0020], [0022]; page 7 para [0025], [0028]; examples 3-7; claims 1, 11-12 and 24-26	11-18

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

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"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

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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