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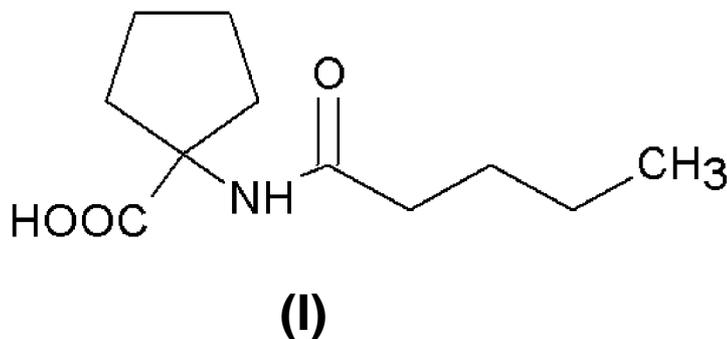
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(54) Title: AN IMPROVED PROCESS FOR PREPARING 1-(PENTANOYLAMINO)CYCLOPENTANECARBOXYLIC

ACID



(57) Abstract: The present invention relates to an improved process for preparing 1-(pentanoylamino)cyclopentanecarboxylic acid formula (I) which is useful intermediate for the preparation of Irbesartan.

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Description

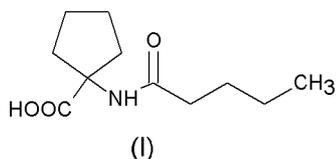
Title of Invention: AN IMPROVED PROCESS FOR PREPARING 1-(PENTANOYLAMINO)CYCLOPENTANECARBOXYLIC ACID

Field of the invention:

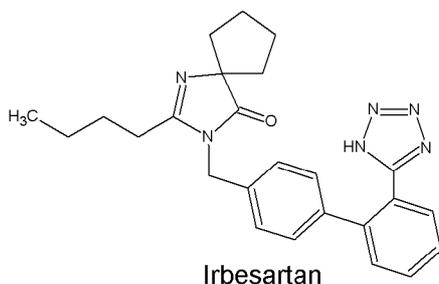
[1]

[2] The present invention relates to an improved process for preparing 1-(pentanoylamino)cyclopentanecarboxylic acid formula (I) which is useful in-
intermediate for the preparation of Irbesartan.

[3]



[4]



[5]

Background of the invention:

[6]

[7] The chemical name of Irbesartan is 1-Butyl-S-CP'-CIH-tetrazol-S-yOCIJ'-biphenyll-^yllmethyll-l^-diazaspiroK^non-l-en-4-one and formula is $C_{25}H_{28}N_6O$ and molecular weight is 428.53. The current pharmaceutical product containing this drug is being sold by Sanofi Synthelabo using the tradename AVAPRO, in the form of tablets.

[8]

[9] Irbesartan is useful in the treatment of diabetic nephropathy, heart failure therapy and hypertension. Irbesartan is angiotension II type I (AIIi)-receptor antagonist. Angiotension II is the principal pressor agent of the rennin-angiotension system and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotension II by selectively binding to the AT_1 angiotension II receptor.

[10]

[H] 1-(pentanoylamino)cyclopentanecarboxylic acid (I) is useful intermediate in the preparation of Irbesartan. The present invention provides an improved process for the preparation of this intermediate.

[12]

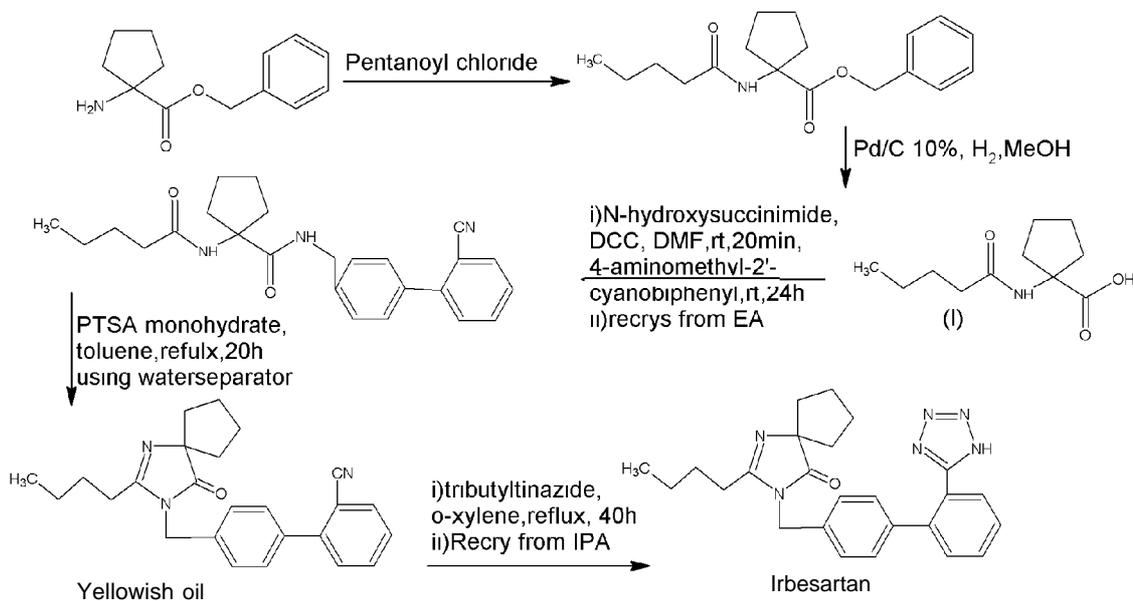
[13] US 5270317 disclose process for preparation of 1-Aminocyclopentanenitrile by reacting cyclopentanone with sodium cyanide in the presence of ammonium chloride in water and 20% aqueous ammonia.

[14]

[15] Canadian Patent No. 2050769 provides a process for the preparation of intermediate 1-(pentanoylamino)cyclopentanecarboxylic acid (I) and preparation of Irbesartan from this intermediate. The synthetic scheme is as given below.

[16]

[17]



[18]

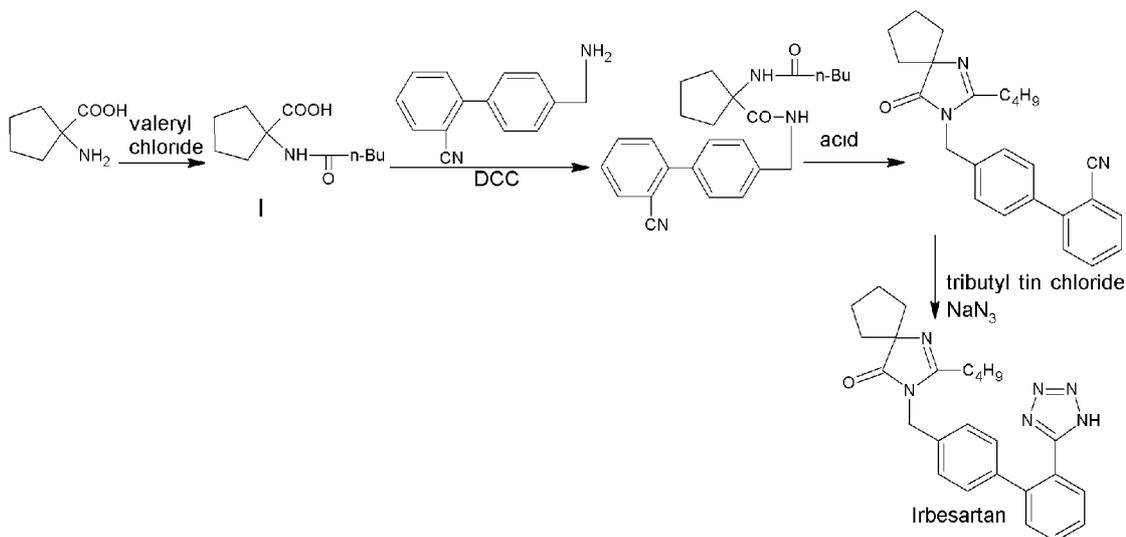
[19] This process comprises the steps of protecting carboxylic group present on cyclopentane ring which is deprotected in consecutive step by vigorous hydrogenation condition in autoclave which is operationally difficult at a large scale.

[20]

[21] WO2005 113518 discloses the process of preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I) and subsequently Irbesartan by condensing 1-amino-cyclopentanecarboxylic acid with valeroyl chloride in presence of inorganic or organic base to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I). This compound is further condensed with 2-(4-aminomethyl phenyl) benzonitrile using dicyclocarbodiimide (DCC) and 1-hydroxy benzotriazole as catalyst to give an open

chain intermediate which is then cyclized in the presence of an acid to give cyano derivative which in turn is converted to Irbesartan by treating it with tributyl tin chloride and sodium azide.

[22]



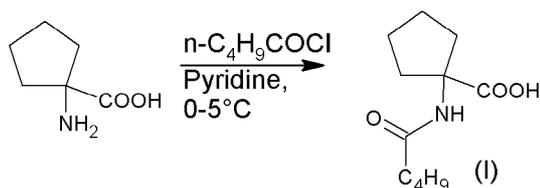
[23]

[24]

Farmaco-Ed. Sc.-vol XXI. FASC.9 discloses a process for preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I) according to the below given scheme.

[25]

[26]



[27]

[28]

In this process 1-amino cyclopentanecarboxylic acid is reacted with valeroyl chloride in the presence of pyridine to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I).

[29]

[30]

However, pyridine is hazardous reagent and it is not advisable to use at industrial scale because of environment concern. The reaction requires low temperature such as 0 to 5°C. Further, in this process dimer impurity forms which is difficult to remove after repeated crystallization.

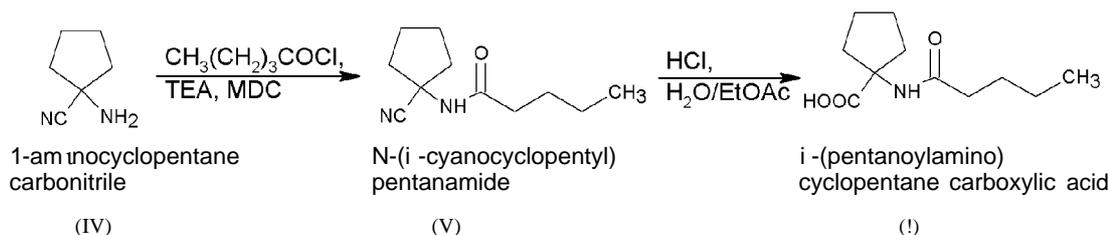
[31]

[32]

Synthetic Communication, 37: 2897-2905, 2007 discloses a process for preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I) according to the below given scheme.

[33]

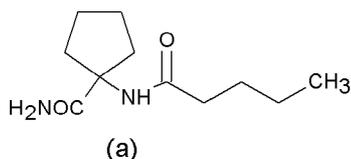
[34]



[35]

[36] In second step of this process, cyano group is first converted to amide to give amide intermediate (a)

[37]



[38]

[39]

[40] which is then further converted acid of formula (I). In the conversion of amide intermediate (a) to 1-(pentanoylamino)cyclopentanecarboxylic acid (I), there always remains 4 to 5% amide intermediate (a) unreacted. It leads to presence of unwanted 3-4% amide impurity in the final compound (I) which is difficult to remove after repeated crystallization. The prolonged duration of the reaction time and the excess amount of hydrochloric acid does not reduce the amount of amide intermediate (a) in the final compound (I).

[41]

[42] US Patent No. 7038060 also discloses the process of preparation of Irbesartan from 4-bromomethyl biphenyl 2'-(1H-tetrazol (2-triphenylmethyl) 5-yl) and Ethyl ester of 1-Valeramido cyclopentanecarboxylic acid in toluene in presence of base and PTC, and then hydrolyzing the protecting group. However this requires chromatographic purification.

[43]

[44] All the above patents/applications are incorporated herein as reference.

[45]

[46] It is therefore, a need to develop a process which not only overcomes the disadvantages of the prior art but also economical, operationally simple and industrially applicable.

[47]

[48] Present inventors have directed their research work towards developing a process for the preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I) which is devoid of the above disadvantages. The present inventors found that when N-

(1-cyanocyclopentyl)pentanamide (V) is hydrolyzed with hydrochloric acid alone, the unreacted amide intermediate (a) remains 4 to 5% in final compound (I). Whereas when it is hydrolyzed in the presence of combination of hydrochloric acid and acetic acid, the amount of unreacted amide intermediate (a) reduces to less than 0.5% in the final compound 1-(pentanoylamino)cyclopentanecarboxylic acid (I).

[49]

Summary of the invention:

[50]

[51] It is therefore an object of the present invention is to provide an improved process for the preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I).

[52]

[53] Another object of the present invention is to provide an improved process for the preparation of Irbesartan using 1-(pentanoylamino)cyclopentanecarboxylic acid (I).

[54]

[55] Another object of the present invention is to provide a process for preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I) which is simple and easy to handle at an industrial scale.

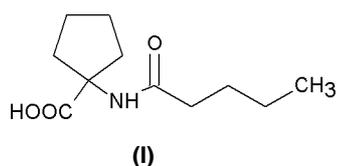
[56]

[57] Another object of the present invention is to provide a process for preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I) in which amide impurity (a) is less than 0.5%.

[58]

[59] Accordingly, present invention provides an improved process of preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid(I).

[60]

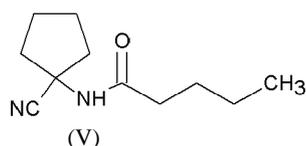


[61]

[62] comprising a step of reacting N-(1-cyanocyclopentyl)pentanamide (V)

[63]

[64]



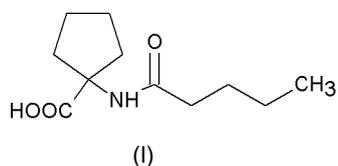
[65]

[66] with hydrochloric acid and acetic acid to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I).

[67]

[68] The present invention provides an improved process of preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I)

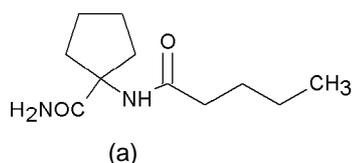
[69]



[70] having an amide impurity (a) less than 0.5%

[71]

[72]

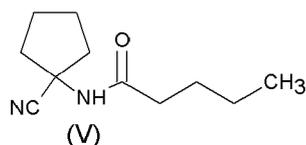


[73]

[74] comprising a step of reacting N-(1-cyanocyclopentyl)pentanamide (V)

[75]

[76]



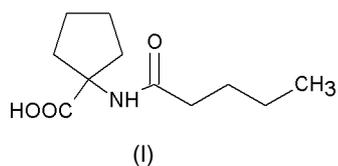
[77]

[78] with hydrochloric acid and acetic acid to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I)

[79]

[80] The present invention provides an improved process of preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I)

[81]

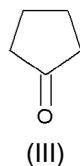


[82]

[83] comprising steps of:

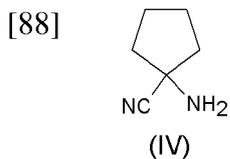
[84] (i) reacting cyclopentanone (III)

[85]



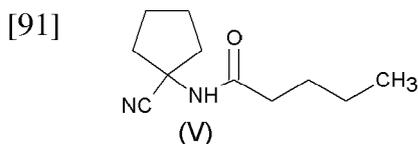
[86]

[87] with sodium cyanide in the presence of ammonium chloride and solvent dichloromethane to obtain 1-aminocyclopentane carbonitrile (IV)



[89]

[90] (ii) reacting 1-aminocyclopentane carbonitrile (IV) obtained in step (i) with valeroyl chloride in the presence of triethylamine and dichloromethane to obtain N-(1-cyanocyclopentyl)pentanamide (V)



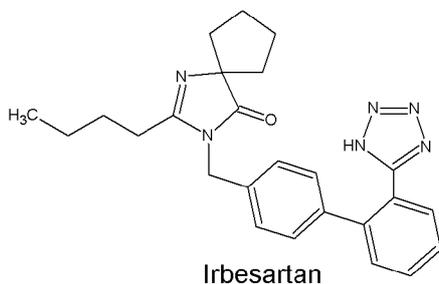
[92]

[93] (iii) reacting N-(1-cyanocyclopentyl)pentanamide (V) obtained in step (ii) with hydrochloric acid and acetic acid to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I).

[94]

[95] The present invention provides an improved process of preparation of Irbesartan

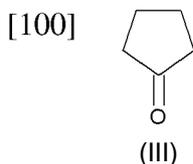
[96]



[97]

[98] comprising steps of:

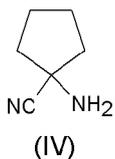
[99] (i) reacting cyclopentanone (III)



[101]

[102] with sodium cyanide in the presence of ammonium chloride and solvent dichloromethane to obtain 1-aminocyclopentane carbonitrile (IV)

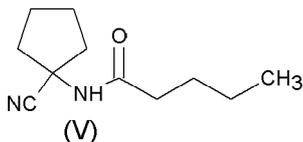
[103]



[104]

[105] (ii) reacting 1-aminocyclopentane carbonitrile (IV) obtained in step (i) with valeroyl chloride in the presence of triethylamine and dichloromethane to obtain N-(1-cyanocyclopentyl)pentanamide (V)

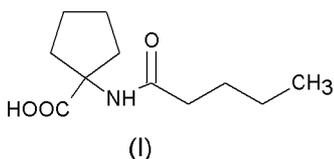
[106]



[107]

[108] (iii) reacting N-(1-cyanocyclopentyl)pentanamide (V) obtained in step (ii) with hydrochloric acid and acetic acid to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I)

[109]

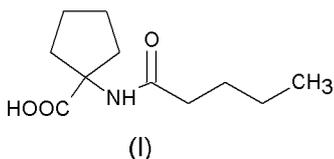


[HO]

Detailed description of the invention:

[111]

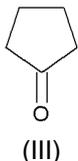
[112] The present invention provides an improved process of preparation of 1-(pentanoylamino)cyclopentanecarboxylic acid (I)



[113] comprising steps of:

[114] (i) reacting cyclopentanone (III)

[115]

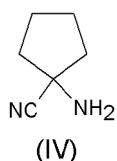


[116]

[117] with sodium cyanide in the presence of ammonium chloride and solvent dichloromethane to obtain 1-aminocyclopentane carbonitrile (IV)

[118]

[119]

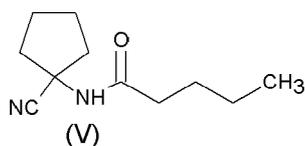


[120]

[121] (ii) reacting 1-aminocyclopentane carbonitrile (IV) obtained in step (i) with valeroyl chloride in the presence of triethylamine and dichloromethane to obtain N-(1-cyanocyclopentyl)pentanamide (V)

[122]

[123]



[124]

[125] (iii) reacting N-(1-cyanocyclopentyl)pentanamide (V) obtained in step (ii) with hydrochloric acid and acetic acid to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I).

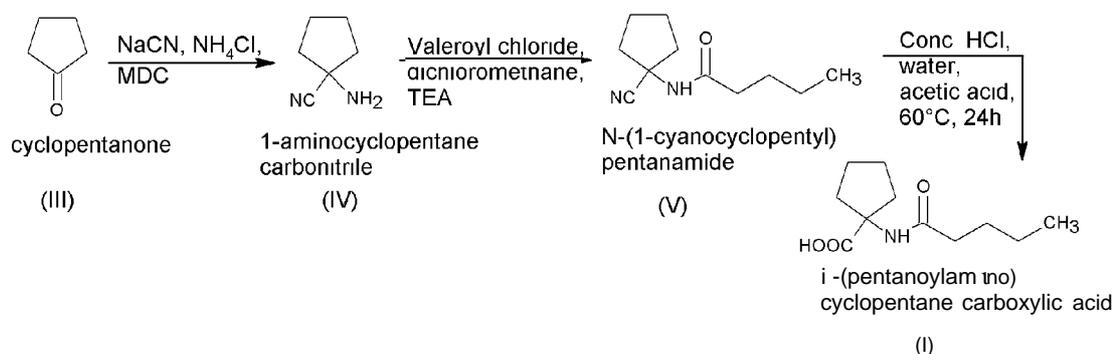
[126]

[127] The schematic representation of the present invention is as given below.

[128]

[129]

[130]



[131]

[132] sodium cyanide is dissolved in water. An aq. ammonium chloride solution and 20% aq. ammonia solution is added to the reaction mixture. Cyclopentanone in methanol is added to the reaction mixture and stirred for about one and a half hour. The mixture is heated at about 60°C for about 45 min. The reaction mixture is cooled to 25°C and extracted several times with dichloromethane. The combined dichloromethane is dried over sodium sulfate and concentrated under vacuum to give 1-aminocyclopentane carbonitrile (IV) in the form of oil.

[133]

[134] 1-aminocyclopentanone carbonitrile in dichloromethane is cooled at 10°C and triethylamine is added to it. Valeroyl chloride is added to the reaction mixture at about 5°C to about 10°C. The reaction mixture is stirred at the same temperature for about 2 hrs and then further stirred at room temperature for about 1 hrs. DM Water is charged to the reaction mixture and organic layer is separated. The organic layer is evaporated to get N-(1-cyanocyclopentyl)pentanamide (V) as oil. This oil is used for hydrolysis step.

[135]

[136] The oil obtained above is mixed with water, conc. hydrochloric acid and acetic acid and heated at about 60°C for about 24 hrs. The reaction mixture is cooled to room temperature and maintained for 1 hour. The solid product is filtered and washed with water. The product is suck dried and dried in oven under reduced pressure to give 1-(pentanoylamino) cyclopentanecarboxylic acid (I).

[137]

[138] 1-(pentanoylamino) cyclopentanecarboxylic acid (I) is converted to Irbesartan by the methods known in the art. 1-(pentanoylamino) cyclopentanecarboxylic acid (I) is reacted with 2-(4-aminomethyl phenyl) benzonitrile in the presence of DCC to give condensed intermediate. The corresponding intermediate is cyclized in presence of acid and then the formed cyano irbesartan is converted to Irbesartan by reacting it with sodium azide to form tetrazole moiety.

[139]

[140] The following examples illustrate the invention further. It should be understood, however, that the invention is not confined to the specific limitations set forth in the individual examples but rather to the scope of the appended claims.

[141]

[142] **Example-1**

[143] **Preparation of 1-aminocyclopentanone carbonitrile (IV)**

[144] 1.97 g of sodium cyanide are dissolved in 3.9 ml of water in a round-bottomed flask and a solution containing 2.33 g of ammonium chloride in 5.9 ml of water and 3.5 ml of 20% aqueous ammonia is added; finally, 3 g of cyclopentanone in 3.8 ml of methanol are added to the flask. After stirring for 1 and a half hours, the mixture is heated at 60°C for 45 minutes, heating is then stopped, stirring is continued for 45 minutes and the mixture is then cooled to 25°C. It is extracted several times with dichloromethane. The extracts are dried over sodium sulfate, filtered and concentrated under vacuum to give 1-aminocyclopentanone carbonitrile (IV) in the form of oil (4 g).

[145]

[146] **Example-2**

[147] **Preparation of N-(1-cyanocyclopentyl)pentanamide (V)**

[148] 1-aminocyclopentanecarbonitrile (30.0 g) in dichloromethane (180 ml) was cooled to 10°C. Triethyl amine (24 ml) was added to the reaction mixture and stirred. Valeroyl chloride (32.8 ml) was added at 5°C to 10°C and stirred at the same temperature for 2 hrs. The reaction mixture was further stirred at room temperature for 1 hour. DM Water was charged to the reaction mixture and organic layer was separated. The organic layer was evaporated to dryness to get N-(1-cyanocyclopentyl) pentanamide (V) as an oil (30.0g).

[149]

[150] **Example-3**

[151] **Preparation of 1-(pentanoylamino) cyclopentane carboxylic acid**

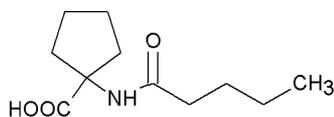
[152] N-(1-cyanocyclopentyl) pentanamide (V) (30.0 g) obtained in example-2 is mixed with reacts with cone. hydrochloric acid (30.0 ml), water (60.0 ml), acetic acid (10.0 ml) and heated at 60°C for about 24 hrs. The reaction mixture is cooled to room temperature and maintain for 1 hour. The solid product is filtered and washed with water. The product is suck dried and dried in oven under reduced pressure to give 1-(pentanoylamino) cyclopentanecarboxylic acid (I) (24.0 g).

[153] Purity by HPLC: 99%

Claims

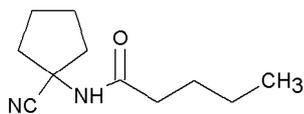
[Claim 1]

1. A process of preparation of
1-(pentanoylamino)cyclopentanecarboxylic acid (I)



(I)

comprising a step of reacting N-(1-cyanocyclopentyl)pentanamide (V)

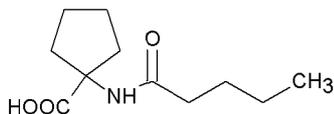


(V)

with hydrochloric acid and acetic acid to give
1-(pentanoylamino)cyclopentanecarboxylic acid (I).

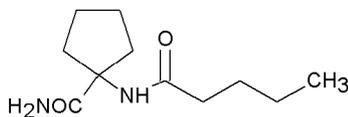
[Claim 2]

2. A process of preparation of
1-(pentanoylamino)cyclopentanecarboxylic acid (I)



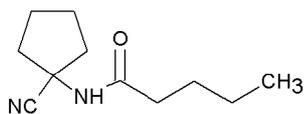
(I)

having an amide impurity (a) less than 0.5%



(a)

comprising a step of reacting N-(1-cyanocyclopentyl)pentanamide (V)

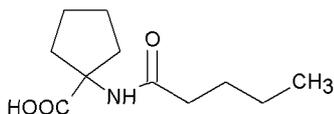


(V)

with hydrochloric acid and acetic acid to give
1-(pentanoylamino)cyclopentanecarboxylic acid (I).

[Claim 3]

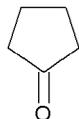
3. A process of preparation of
1-(pentanoylamino)cyclopentanecarboxylic acid (I)



(I)

comprising steps of:

(i) reacting cyclopentanone (III)



(III)

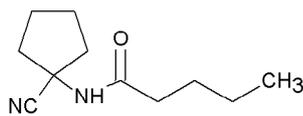
with sodium cyanide in the presence of ammonium chloride and solvent dichloromethane to obtain 1-aminocyclopentane carbonitrile

(IV)



(IV)

(ii) reacting 1-aminocyclopentane carbonitrile (IV) obtained in step (i) with valeroyl chloride in the presence of triethylamine and dichloromethane to obtain N-(1-cyanocyclopentyl)pentanamide (V)

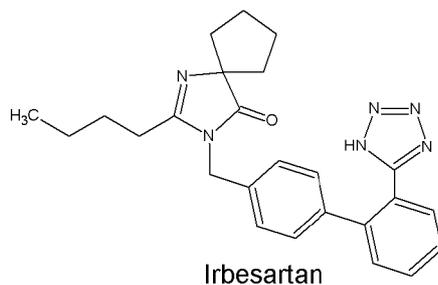


(V)

(iii) reacting N-(1-cyanocyclopentyl)pentanamide (V) obtained in step (ii) with hydrochloric acid and acetic acid to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I).

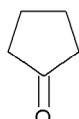
[Claim 4]

4. A process of preparation of Irbesartan



comprising steps of:

(i) reacting cyclopentanone (III)

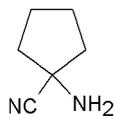


(III)

with sodium cyanide in the presence of ammonium chloride and

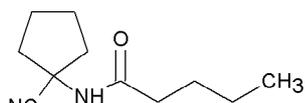
solvent dichloromethane to obtain 1-aminocyclopentane carbonitrile

(IV)



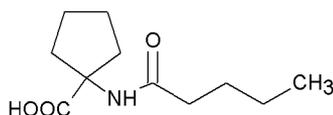
(IV)

(ii) reacting 1-aminocyclopentane carbonitrile (IV) obtained in step (i) with valeroyl chloride in the presence of triethylamine and dichloromethane to obtain N-(1-cyanocyclopentyl)pentanamide (V)



(V)

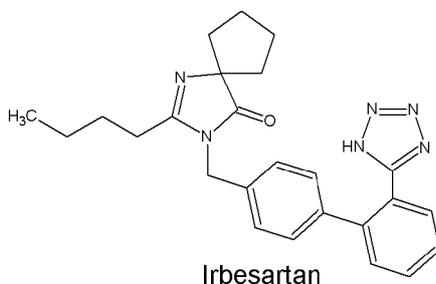
(iii) reacting N-(1-cyanocyclopentyl)pentanamide (V) obtained in step (ii) with hydrochloric acid and acetic acid to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I)



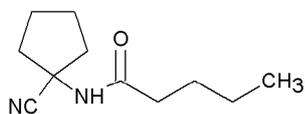
(I)

[Claim 5]

5. A process of preparation of Irbesartan

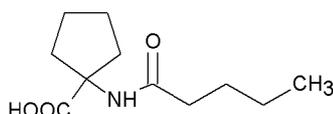


comprising a step of reacting N-(1-cyanocyclopentyl)pentanamide (V)



(V)

with hydrochloric acid and acetic acid to give 1-(pentanoylamino)cyclopentanecarboxylic acid (I)



(I)