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(74) Agents: **MAJUMDAR, Subhatosh** et al.; S. Majumdar & Co. 5, Harish, Mukherjee Road, Kolkata 700 025 (IN).

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(71) Applicant (for all designated States except US): **SANDOZ AG** [CH/IN]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LUTHRA, Parven, Kumar** [IN/IN]; Development Centre, MIDC, Plot No.8-A/2, 8-B TTC Industrial Area, Kalwe Block, Village Dighe, Navi Mumbai 400 708 (IN). **KHAN, Rashid** [IN/IN]; Development Centre, MIDC, Plot No.8-A/2, 8-B TTC Industrial Area, Kalwe Block, Village Dighe, Navi Mumbai 400 708 (IN). **SALUNKHE, Dadasaheb** [IN/IN]; Development Centre, MIDC, Plot No.8-A/2, 8-B TTC Industrial Area, Kalwe Block, Village Dighe, Navi Mumbai 400 708 (IN). **NASIR ALI, Shafakat, Ali** [IN/IN]; Development Centre, MIDC, Plot No.8-A/2, 8-B TTC Industrial

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(57) Abstract: The present invention relates to process of preparation of 2-(3-cyano-4- isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat). The present invention in particular relates to an efficient and easily to operate scalable process of manufacturing of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat) of Formula I and its crystalline polymorphic Form C.

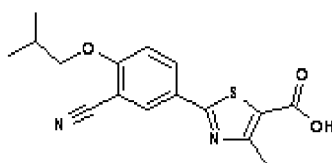


WO 2012/131590 A1

**AN IMPROVED PROCESS FOR PREPARATION OF FEBUXOSTAT AND ITS
POLYMORPHIC CRYSTALLINE FORM C THEREOF**

FIELD OF INVENTION

5 The present invention relates to a process of preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat). The present invention in particular relates to an efficient and easily to operate scalable process of manufacturing of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid
10 (Febuxostat) of Formula I and its polymorphic crystalline form C thereof.



Formula I

15 **BACKGROUND OF INVENTION**

Prior art literature:

Febuxostat is the compound of formula (I) chemically known as 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid, which is disclosed in EP 0 513
20 379.

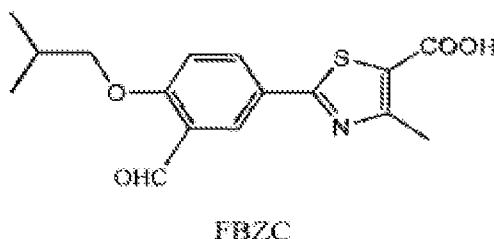
The synthesis of Febuxostat disclosed in EP 0 513 379 involves condensation of 4-hydroxy-3-nitrobenzaldehyde with hydroxylamine hydrochloride in the presence of sodium formate to give 4-hydroxy-3-nitrobenzonitrile. Conversion of the cyano group
25 into a thioamide and subsequent reaction with ethyl 2-chloroacetoacetate provides ethyl 2-(4-hydroxy-3-nitrophenyl)-4-methyl-5-thiazolecarboxylate. Alkylation of the 4-hydroxyl group with isobutyl bromide, and catalytic hydrogenation of the 3-nitro moiety provides ethyl-2-(3-amino-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate. Finally, reaction of the latter with sodium nitrite and subsequent hydrolysis of the ethyl
30 carboxylate gives Febuxostat.

JP1998045733 (JP10045733) describes formylation of 2-(4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester which on alkylation gives 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester which is converted into
5 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester. Finally, the resultant compound is hydrolyzed to give Febuxostat. Alternatively 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester can be treated with formic acid, sodium formate and hydroxylamine hydrochloride to provide to 2-(3-cyano-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, which is then alkylated to
10 give the 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester. The said manufacturing process involves isolation of intermediate product at the end of all the steps, which is not commercially suitable since many operations are required to carry out and results in lower overall yield. Recrystallization of intermediates is required to meet quality standards resulting in material losses and large amount of solvent
15 consumption. Excessive use of halogenated hydrocarbon such as dichloromethane and isobutyl bromide damages environment.

An article "A Facile One-pot synthesis of 4-alkoxy-1, 3-Benzendicarbonitrile" by Masaichi Hasegawa of Teijin Institute for Bio-Medical Research Heterocycles, Vol 47, no 2, 1998 discloses synthesis of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole
20 carboxylic acid by treating alkoxy 1, 3- benzenedicarbonitrile with thioacetamide followed by cyclization with chloroacetoacetate and hydroxylation. Use of toxic reagents/solvents such as potassium cyanide and dimethylsulfoxide during formation of 4-alkoxy-1, 3-Benzendicarbonitrile. Industrially non feasible column chromatography technique is used to get required quality of the intermediates such as 4-alkoxy-1, 3-
25 benzenedicarbonitrile and 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester. Intermediate isolation involves solvent extraction, concentration followed by isolation which consumes high amount of solvents and gives lower yields. Final hydrolysis step yield is very poor ~ 35%, isolation of quality product with such poor yielding step is not an easy task.

30 CN101781270 discloses an intermediate (FBZC) and method of its preparation.

3



It further discloses method of preparation of 2-[3-formyl-4-(2-methylpropyloxy) phenyl]-4-methyl-5-thiazole formic acid (**FBZC**), comprising the step of converting 2-[3-formyl-4-(2-methylpropyloxy) phenyl]-4-methyl-5-thiazole ethyl formate or methyl ester to intermediate FBZC by hydrolysis in the mixed solution of alkali and organic solvent.

EP 1020454 B1 discloses polymorphs, their transitions and process for the preparation of crystal C. Crystal C is produced by solvent-mediated polymorphic transition. The solvent used is mixed solution of methanol and water and the ratio of methanol to water preferably is from 70:30 to 60:40 and requires small amount of crystal C (1 to 2% or less). Heating temperature exerts an influence on the completion time of the conversion into the crystal C.

15 **Drawbacks of the Prior art:**

Reported manufacturing process for Febuxostat requires many process steps which also results in the formation of impurities from starting materials/ intermediates, side reactions, degradation during work-up/ hydrolysis thereby reducing the overall yield of the product. Furthermore the process steps are not environment friendly. Toxic chemicals such as thioacetamide, ethyl 2-chloroacetoacetate and sodium cyanide are used in the processes known in the literature, which are not environment friendly and require stringent reaction conditions.

When the hydrolysis reaction in the process for preparation of Febuxostat is carried out using excess strong base i.e sodium hydroxide as disclosed in **CN101781270**, poor yield of the product is obtained against reported ~43% yield and reaction is non-reproducible indicating degradation of the starting material under the condition disclosed.

The active substance prepared by the processes known until now can be obtained after running through a large number of process steps. The main drawbacks associated with the known synthesis are harsh conditions, the toxic reagents to form the thioamide and the highly toxic cyanides. Therefore the need for an alternative synthesis for the industrial preparation of Febuxostat, which makes use of commercially available, cheaper and non toxic reagents. Hydrolysis with strong bases such as sodium hydroxide, potassium hydroxide gives low yield due to hydrolysis of the cyano functional group and is corrosive in nature. Removal of structurally similar Impurity by crystallization of the final compound is not an easy task and also results in overall cost increase of the product.

Processes known in the prior art result in lower yield of the product obtained after the hydrolysis step; last step governs the overall costs of the process. Hydrolysis of ethyl ester group using strong base also results in side reaction i.e. hydrolysis of cyano group of the compound to give amide impurity. This also lowers the yield of the product. Febuxostat produced using strong base requires additional purification step to get product meeting ICH quality.

Other reported methods for introducing formyl group in phenol derivatives use toxic raw material, or has problems, viz expensive, highly corrosive raw materials, which are not methods of choice for industrial scale.

The crystal form C of Febuxostat disclosed in EP 1020454 B1 is a stable crystal, however, solvent-mediated polymorphic transition into this crystal form usually requires several days and it is difficult to produce the crystal C of Febuxostat in an industrially good reproducible manner.

The processes of the present invention offers several advantages over previous methods of making Febuxostat known in prior literature, and its industrial preparation thereof and also overcome the drawbacks related to the same.

The present inventors have found that the Duff reaction of said improved processes using hexamethylenetetramine and trifluoroacetic acid gives better conversion and commercially feasible process in production point of view than reported ones using

polyphosphoric acid. Trifluoroacetic acid can be recovered and reused in same step, whereas polyphosphoric acid which is used in the prior art cannot be recovered and reused.

- 5 The present inventors have found that carrying out hydrolysis of the ethyl ester group in the process for preparation of Febuxostat using alkali metal carbonate in methanol or ethanol is facile, unique and does not bear any resemblance with the method described in prior art.
- 10 Hydrolysis employing alkali metal carbonate as a mild base is safe to handle, effective and one of the unique feature of the present invention; it reduces hydrolysis of cyano group which is main side reaction. This reaction is very clean as compared to one with stronger base such as sodium hydroxide, potassium hydroxide which gives low yield and is corrosive in nature.
- 15 Alkali metal carbonate such as potassium carbonate, caesium carbonate or sodium carbonate when used in lower alcohol such as methanol or ethanol, the hydrolysis reaction proceeds smoothly resulting in quantitative yield of the product.
- 20 In an embodiments of the present invention, the present inventors have developed an improved process wherein the cyano group is formed at the end of the process and therefore not exposed to hydrolysis, thereby avoiding the hydrolysis of cyano group which is the main side reaction in the preparation of Febuxostat, is one of the unique features of the present invention.
- 25 The present inventors have surprisingly found that hydrolysis of the ester group using alkali metal carbonate such as potassium carbonate, caesium carbonate or sodium carbonate in lower alcohol such as methanol or ethanol yielded hydrolysed product which on further subjecting to functional group transformation (formyl to cyano) by formic acid
- 30 in presence of hydroxyl amine hydrochloride and sodium formate followed by cooling yielded highly pure crystalline Febuxostat, as a polymorphic form C which does not require further purification by crystallization.

The present inventors found that the processes of the present invention results in the formation of substantially pure Febuxostat or polymorphic form C of Febuxostat free from all process impurities. Thus purification of Febuxostat by crystallization to deplete these process impurities is not required, which is not easy and leads to heavy losses thereby increasing cost of the product.

OBJECT OF THE INVENTION

It is an object of the present invention to provide improved, efficient, economic environment friendly, easy to scale-up and commercially useful process for the manufacture of compound of formula I or its crystalline polymorphic form C that is devoid of drawbacks of prior art processes.

It is another object of the present invention to provide an improved process for the preparation of compound of formula I or its crystalline polymorphic form C that does not employ any hazardous reagents and condition is safer to carry out.

It is another object of the present invention to provide an improved process for the preparation of compound of formula I or its crystalline polymorphic form C in high yield.

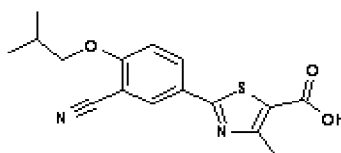
It is yet another object of the present invention to provide an improved process which yields substantially pure compound of formula I or its crystalline polymorphic form C.

It is yet another object of the present invention to provide an improved process for the preparation of compound of formula I or its crystalline polymorphic form C that is easy to commercialize and provide product free from impurities.

It is a further object of the present invention to provide an improved process for the preparation of compound of formula VA. (corresponding to formula V in the provisional application 664/KOL/2011 dated 16/05/2011).

SUMMARY OF THE INVENTION

According to an aspect of the present invention there is provided an improved process for preparing Febuxostat, compound of formula (I).

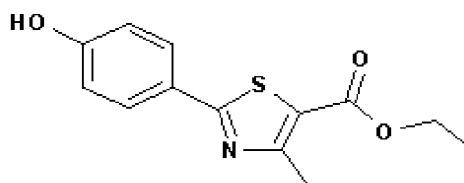


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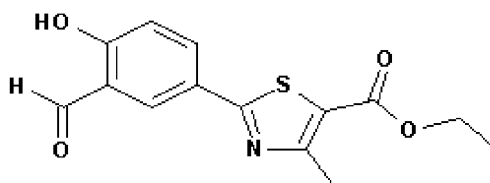
Formula (I)

which comprises the step of:

- 10 i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, compound of Formula II

**Formula II**

- 15 with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula III;

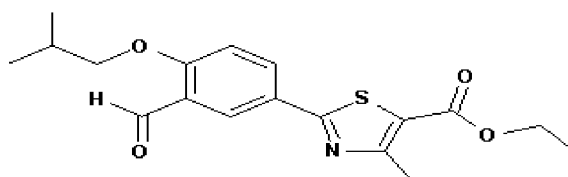


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Formula III

- ii. Alkylating compound of formula III with isobutyl bromide to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of
25 formula IV;

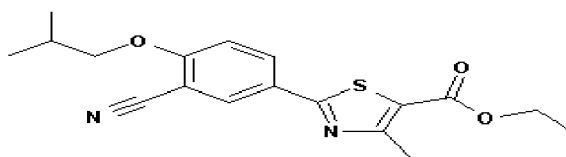
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Formula IV

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- iii. Converting compound of formula IV to 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula V by using hydroxylamine hydrochloride and sodium formate in formic acid;

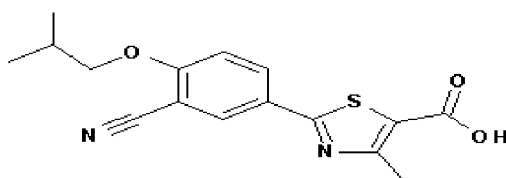


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Formula V

- iv. Hydrolyzing compound of formula V with alkali metal carbonate in the presence of lower alcohol to obtained 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid of formula I.

15



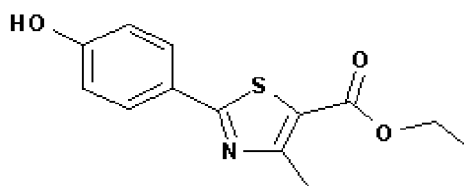
Formula I

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According to another aspect of the present invention there is provided an improved process for preparing Form C of Febuxostat, which comprises the step of:

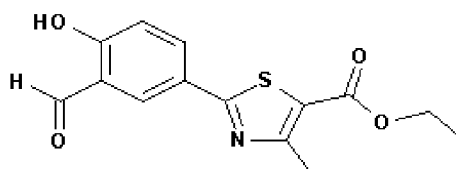
- i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, compound of Formula II.

25



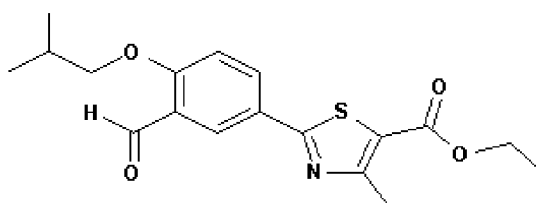
Formula II

with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-
 5 formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester,
 compound of formula III;



Formula III

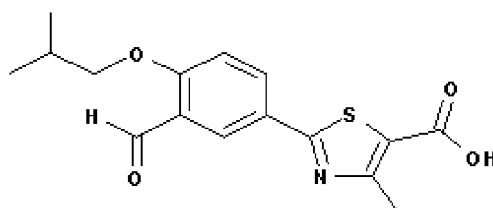
- ii. Alkylating compound of formula III with isobutyl bromide to obtain 2-(3-formyl-
 4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of
 formula IV;



Formula IV

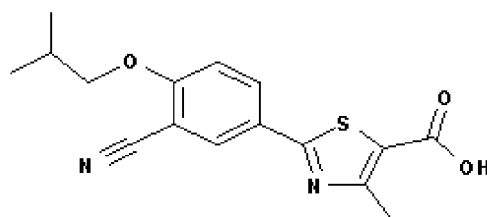
- iii. Hydrolyzing compound of formula IV with alkali metal carbonate in the presence
 20 of lower alcohol to obtained 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-
 carboxylic acid, compound of formula VA or its salt thereof;

10



Formula VA

- iv. Converting compound of formula VA or its salt thereof to 2-(3-cyano-4-
- 5 isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula I by using hydroxylamine hydrochloride and sodium formate in formic acid;



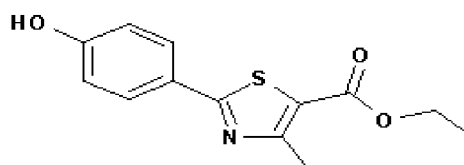
Formula I

- v. Isolation of pure compound of formula I with polymorphic form C from reaction mixture as obtained in step iv by addition of water above 60°C and cooling to room temperature.

According to yet another aspect of the present invention there is provided an improved

15 process for the preparation of the compound of formula VA comprising the steps of:

- i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, compound of Formula II

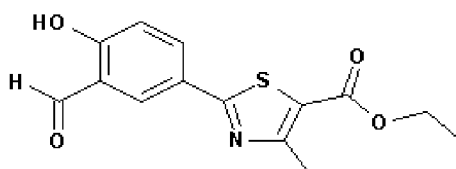


Formula II

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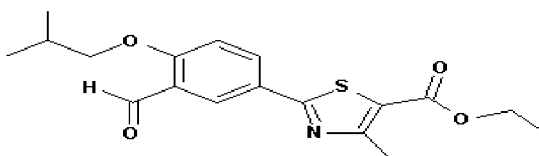
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with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula III;



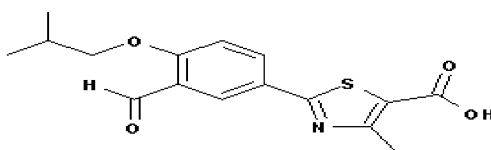
Formula III

- ii. Alkylating compound of formula III with isobutyl bromide to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula IV;



Formula IV

- iii. Hydrolyzing compound of formula IV with alkali metal carbonate in the presence of lower alcohol to obtained 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid, compound of formula VA or its salt thereof.



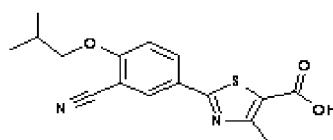
Formula VA

DETAILED DESCRIPTION

The present invention relate to an improved scalable process for the preparation of Febuxostat. Compound of formula I. (Febuxostat) or its crystalline form C that is industrially feasible and commercially viable.

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In an embodiment of the present invention there is provided an improved process for preparing Febuxostat of formula (I).



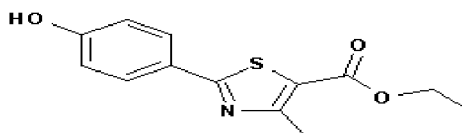
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Formula (I)

which comprises the step of:

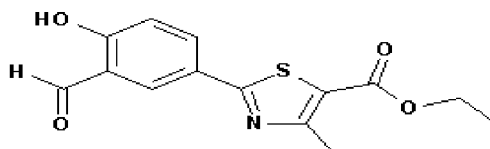
- i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, Compound of Formula II.

15

**Formula II**

- with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula III.

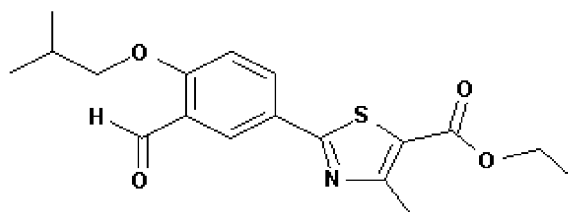
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**Formula III**

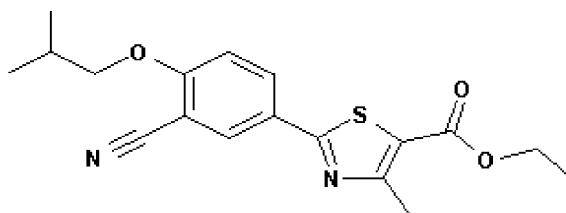
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- ii. Treating the compound of formula III with isobutyl bromide to obtained 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula IV.

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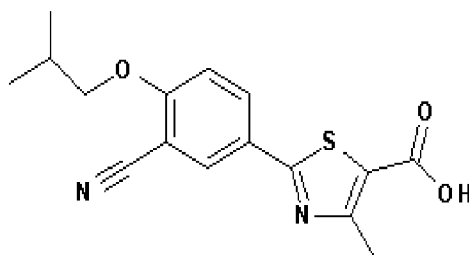
**Formula IV**

- 5 iii. Converting compound of formula IV to 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula V by using hydroxylamine hydrochloride and sodium formate in formic acid.

**Formula V**

10

- vi. Hydrolyzing compound of formula V with alkali metal carbonate in the presence of lower alcohol to obtained 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid of formula I.
- 15

**Formula I**

- 20 Ethyl 2-(4-hydroxyphenyl)-4-methyl thiazole-5-carboxylate is converted to Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate using hexamethylenetetramine and strong acid through well known Duff reaction.

Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl thiazole-5-carboxylate is alkylated with isobutyl bromide using alkali metal carbonate in dimethyl formamide to give Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl thiazole-5-carboxylate.

5 Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl thiazole-5-carboxylate is further converted to ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methyl thiazole-5-carboxylate by using hydroxylamine hydrochloride and sodium formate in formic acid.

10 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid (Febuxostat) is obtained from ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazole carboxylate using milder hydrolysis with alkali metal carbonate such as potassium carbonate, caesium carbonate or sodium carbonate in lower alcohol such as methanol or ethanol in water.

15 Alkali metal carbonate preferably employed in the process of the present invention is potassium carbonate.

The process of the present invention can be represented in scheme I as follows:

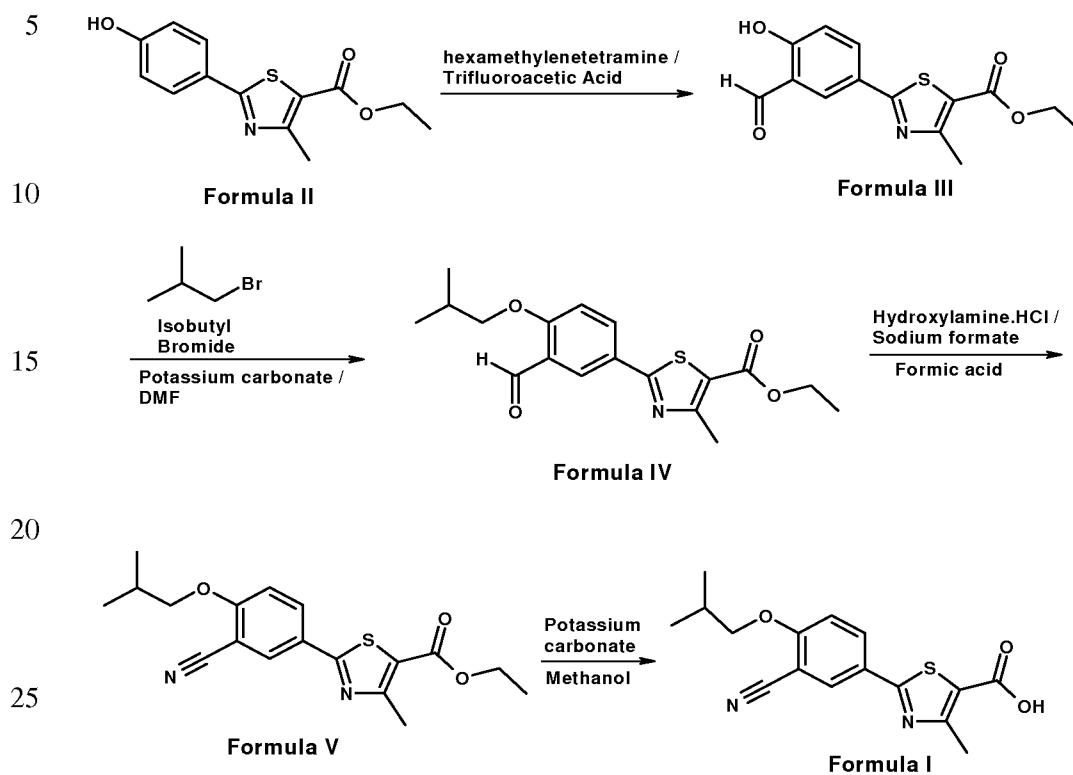
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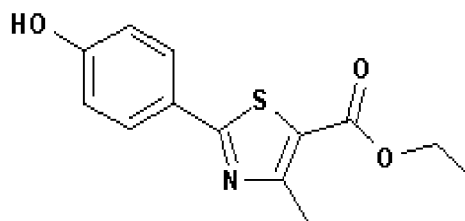
Scheme I:

The present invention also relates to an improved scalable process for the preparation of polymorphic crystalline form C of Febuxostat, compound of Formula I that is industrially feasible, easy to operate and commercially viable.

In other embodiment of the present invention there is provided an improved process for preparing Form C of Febuxostat which comprises the step of:

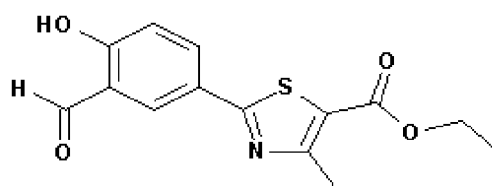
- i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, compound of Formula II.

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Formula II

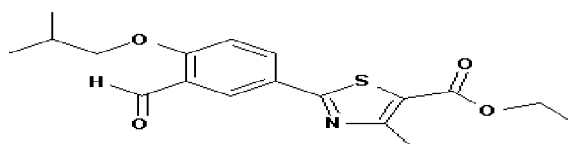
5 with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula III.



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Formula III

ii. Alkylating compound of formula III with isobutyl bromide to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula IV.

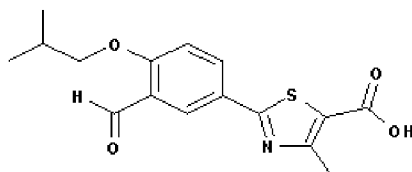


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Formula IV

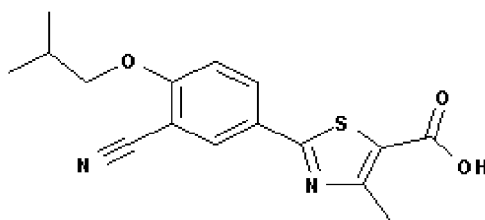
20 iii. Hydrolyzing compound of formula IV with alkali metal carbonate in the presence of lower alcohol to obtained 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-thiazole-5-carboxylic acid, compound of formula VA or its salt thereof.

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Formula VA

- iv. Converting compound of formula VA or its salt thereof to 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula I by using hydroxylamine hydrochloride and sodium formate in formic acid.



Formula I

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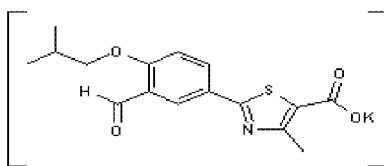
- v. Isolation of pure compound of formula I having polymorphic form C from reaction mixture as obtained in step iv by addition of water above 60°C and cooling to room temperature.
- 15 Ethyl-2-(4-hydroxyphenyl)-4-methyl thiazole-5-carboxylate is converted to Ethyl-2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate using hexamethylenetetramine and strong acid through well known Duff reaction.

20 Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl thiazole-5-carboxylate is alkylated with isobutyl bromide using potassium carbonate in dimethyl formamide to give Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl thiazole-5-carboxylate which on hydrolysis in aqueous lower alcohol with alkali metal carbonate such as potassium carbonate or caesium carbonate or sodium carbonate resulted in the formation of 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid or a alkali metal salt thereof, which

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is further reacted with hydroxylamine hydrochloride in formic acid at reflux to give Febuxostat with impurities well below the ICH limit.

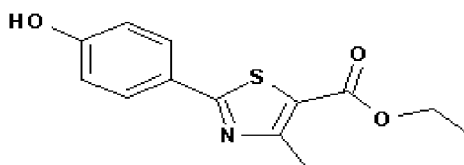
In a preferred embodiment of the present invention Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl thiazole-5-carboxylate (compound of formula IV) is hydrolysis in aqueous lower alcohol with potassium carbonate resulting in the formation of Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid potassium salt, Compound of formula VB (corresponding to formula VA in the provisional application 664/KOL/2011 dated 16/05/2011) which is further reacted with



Formula VB

In another embodiment of the present there is provided an improved process for the preparation of the compound of formula VA comprising the steps of:

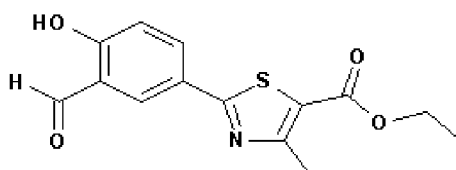
- i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, compound of Formula II



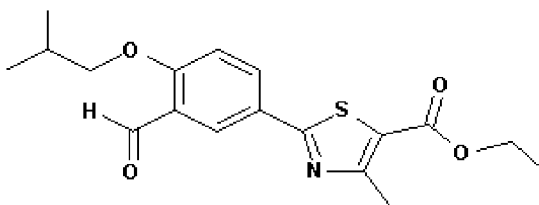
Formula II

with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula III;

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**Formula III**

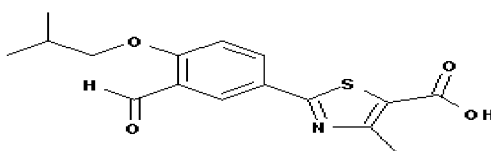
- 5 ii. Alkylating compound of formula III with isobutyl bromide to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula IV;



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Formula IV

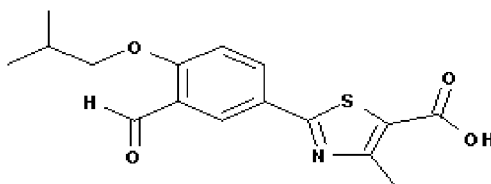
- iii. Hydrolyzing compound of formula IV with alkali metal carbonate in the presence of lower alcohol to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid, compound of formula VA or its salt thereof.



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Formula VA

In yet another embodiment of the present invention there is provided a compound of formula VA prepared according to the process of the present invention.



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Formula VA

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Alkali metal carbonate used in the process of the present invention is selected from potassium carbonate, caesium carbonate or sodium carbonate.

Alkali metal carbonate preferably employed is potassium carbonate.

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Lower alcohol used in the process of the present invention is selected from methanol or ethanol.

The process of the present invention can be represented in scheme II as follows:

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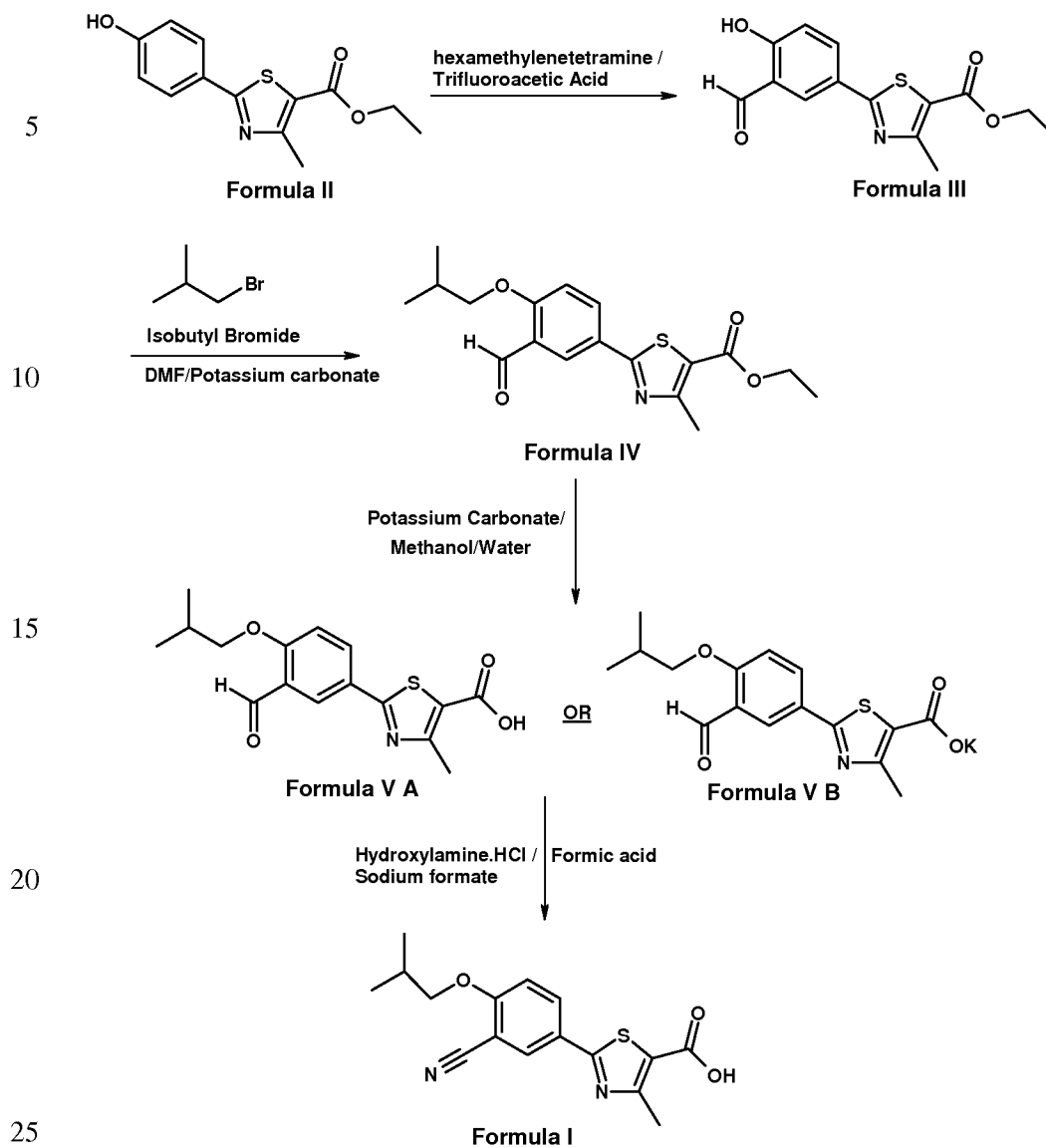
Scheme II:**Comparative data:**

Table 1: Comparison of percentage yield and purity of Febuxostat obtained by the process of the present invention vis-à-vis acknowledge prior art JP1998045733.

Table 1:

Preparation of Febuxostat	% yield	% purity
JP10045733	Not reported	Not reported
Present invention	80.81%	94.31%

5

Table 2: Comparison of percentage yield and purity of compound of formula V obtained by the process of the present invention vis-à-vis acknowledge prior art CN101781270.

Table 2:

10

Preparation of compound of formula V	% yield	% purity
CN101781270	43%	99%
Present invention	88%	97.41%

15 Table 3: Comparison of percentage yield and purity of polymorphic form C obtained by the process of the present invention vis-à-vis acknowledge prior art EP1020454.

Preparation of crystalline polymorphic form C of Febuxostat.	% yield	% purity
EP1020454	Not reported	Not reported
Present invention	88.24%	99.35%

20 The following examples are meant to illustrate the present invention. The examples are presented to exemplify the invention and are not to be considered as limiting the scope of the invention.

EXAMPLES

25 **Example 1**

Preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat) [Compound of formula I].

30 a) Preparation of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate [Compound of formula III].

- 10.0gm of Ethyl 2-(4-hydroxyphenyl)-4-methyl-5-thiazole carboxylate, [Compound of formula II] and 5.86gm of hexamethylenetetramine was added to 100.0ml of trifluoroacetic acid. Reaction mixture was heated to reflux under stirring for 40 hr.
- 5 Trifluoroacetic acid was distilled out at $80 \pm 3^\circ\text{C}$. Residue obtained was cooled to 25°C and slowly added 100 ml of water. Slurry formed was stirred for 2.0hr. Slurry of the product was filtered, washed and dried under vacuum to give 9.6 gm of titled compound.

- b) Preparation of Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate
10 [Compound of formula IV].

- 350.0gm of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate, [Compound of formula III] 332.0gm of potassium carbonate and 330.0gm of isobutyl bromide were added to 1.75ltr of DMF. Reaction mixture was heated to $90 \pm 3^\circ\text{C}$ and
- 15 stirred for 4 hr. Reaction mixture was cooled to 25°C and slowly added 10.50 ltr of water. Slurry of the product formed was stirred for 2.0hr, filtered, washed and dried under vacuum to give 389 gm of titled compound.

Analytical Data-

- 20 • ^1H NMR (CDCl_3 , 400 MHz) : δ 1.079-1.101 (doublet, 6H); δ 1.366-1.413 (triplet, 3H); δ 2.185-2.230 (multiplet, 1H); δ 2.769 (singlet, 3H); δ 3.914-3.935 (doublet, 2H); δ 4.316-4.387 (quartet, 2H); δ 7.045-7.074 (doublet, 1H); δ 8.188-8.225 (doublet of doublet, 1H); δ 8.353-8.361 (doublet, 1H).
- Mass (m/e): 348.3
- 25

- c) Preparation of Ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate
[Compound of formula V].

- 30 350.0gm of Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate, [Compound of formula IV] 123.0gm of sodium formate followed by 84.0gm of hydroxylamine hydrochloride were added to 1.4 ltr of formic acid. Reaction mixture was heated to reflux and stirred for 5hr to complete the reaction. Reaction solution was cooled

to 25°C. Slowly added 2.8 ltr of water at 25°C. Slurry formed was stirred for about 1.0hr, filtered, washed with water and dried under vacuum to give 321.0gm of titled compound.

Analytical Data-

- 5 • ¹HNMR (CDCl₃, 400 MHz) : δ 1.053-1.104 (doublet, 6H); δ 1.368-1.416 (triplet, 3H); δ 2.164-2.253 (multiplet, 1H); δ 2.768 (singlet, 3H); δ 3.890-3.911 (doublet, 2H); δ 4.324-4.395 (quartet, 2H); δ 6.998-7.027 (doublet, 1H); δ 8.075-8.112 (doublet of doublet, 1H); δ 8.175-8.182 (doublet, 1H).
- Mass (m/e) : 345.2

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d) Preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat) [Compound of formula I].

- 250.0gm of Ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate,
15 [Compound of formula V] and then 200.0gm of potassium carbonate were added to the mixture of 7.5ltr of methanol and 250.0ml water. Heated the solution to reflux under stirring for 3hr to complete the reaction. Cooled the clear solution formed and applied vacuum to distill out the solvent to maximum extent below 40°C. To the residue 5.0ltr of water was added and stirred to obtain solution. Added 2.5ltr of ethyl acetate, stirred and
20 layers separated. pH of aqueous solution adjusted to 2.5 ± 0.2 by addition of dil. hydrochloric acid solution at 40°C and stirred for about 1.0hr. Slurry of the product was filtered, washed with water and dried under vacuum to give 215.0gm of Febuxostat.

Analytical Data-

- 25 • ¹HNMR (CDCl₃, 400 MHz): δ 0.992-1.067 (doublet, 6H); δ 2.029-2.117 (multiplet, 1H); δ 2.636 (singlet, 3H); δ 3.963-3.985 (doublet, 2H); δ 7.317-7.347 (doublet, 1H); δ 8.160-8.197 (doublet of doublet, 1H); δ 8.238-8.245 (doublet, 1H); δ 13.397 (Broad singlet, 1H).
- Mass (m/e) : 317.1

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Example 2

Preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat) [Compound of formula I].

5 1.0gm of Ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate, [Compound of formula V] and 1.9gm of caesium carbonate were added to the mixture of 30.0ml of methanol and 1.0ml water. Raised the temperature of reaction mixture to reflux under stirring and refluxed for 3hr to complete the reaction. Clear solution formed was cooled to 40°C and applied vacuum to distill out the solvent to the maximum extent at
10 40°C. Residue obtained was dissolved in 20.0ml of water and added 10.0ml of ethyl acetate. Stirred and separated the aqueous phase. pH of aqueous phase adjusted to 2.5 ± 0.2 by dilute hydrochloric acid solution at 40°C and stirred for 1.0hr. Slurry of the product formed was filtered, washed with water and dried under vacuum to give 0.85gm of Febuxostat.

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Example 3.

1.0gm of Ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate, [Compound of formula V] and 0.6gm of sodium carbonate were added to the mixture of 30.0ml methanol and 1.0ml of water. Temperature of mixture raised to reflux and stirred
20 at reflux for 36 hr. Clear solution formed was cooled to 40°C and applied vacuum to distill out the solvent to the maximum extent maintaining temperature below 40°C. Residue obtained after distillation was dissolved in 20.0ml of water and 10.0ml of ethyl acetate. Stirred and aqueous phase separated. pH of the aqueous phase was adjusted to 2.5 ± 0.2 by dil. hydrochloric acid at 40°C and stirred for 1.0hr. Slurry of the product formed
25 was filtered and washed with water and dried under vacuum to give 0.59 gm of Febuxostat.

Example 4

30 Preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat) [Compound of formula I].

a) Preparation of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate [Compound of formula III].

10.0gm of Ethyl 2-(4-hydroxyphenyl)-4-methyl-5-thiazole carboxylate, [compound of
5 formula II] and 5.32gm of hexamethylenetetramine was added to 100.0ml of trifluoroacetic acid. Reaction mixture was heated to reflux under stirring for 40 hr. Trifluoroacetic acid was distilled out. Residue obtained was cooled to 25°C and slowly added 200 ml of water. Slurry formed was stirred for 4.0hr. Slurry of the product was filtered, washed and dried under vacuum to give 7.67 gm of title compound.

10

b) Preparation of 2-(3-formyl-4-isobutoxyphenyl)-4-methyl- 5- thiazolecarboxylic acid [Compound of formula VA].

Process A:

15 25.0gm of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate, 24.0gm of potassium carbonate and 24.0gm of isobutyl bromide were added to 125 ml of DMF. Reaction mixture was heated to $90 \pm 3^\circ\text{C}$ and stirred for 4 hr. Reaction mixture was cooled to 25°C and slowly added 3.0ltr of water. Slurry of the product formed was stirred for 1.0hr, filtered, washed and unloaded to give 64.5 gm of wet Ethyl 2-(3-formyl-4-
20 isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate.

61.0gm of above wet compound and 24.0gm of potassium carbonate were added to the mixture of 0.750ltr of methanol and 25.0ml water. Solution heated to reflux under stirring for 3hr and methanol distilled out under vacuum below 40°C. Residue cooled to 40°C and 0.5ltr of water was added. Stirred for 15.0mins. pH of aqueous solution adjusted to $5.5 \pm$
25 0.2 by addition of dil. hydrochloric acid solution at 40°C. Stirred for about 2.0hr. Slurry of the product was filtered, washed with water and dried under vacuum to give 22.32gm of 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid

Process B:

30 3.0gm of Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate and 5.63gm of caesium carbonate were added to the mixture of 30.0ml of methanol and 3.0ml water. Reaction mixture was heated to reflux under stirring and stirred for 4hr. Slurry was

cooled to 25°C and added 60.0ml of water at 25°C. pH of aqueous solution adjusted to 3.0 ± 0.2 by addition of dil. hydrochloric acid at 25°C. Slurry stirred for about 1.0hr. Filtered, washed with water and dried under vacuum to give 2.29gm of 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid.

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Analytical Data-

¹HNMR (DMSO-d₆, 400 MHz): δ 1.026-1.045 (doublet, 6H);

δ 2.093-2.159 (multiplet, 1H); δ 2.664 (singlet, 3H); δ 3.989-4.005 (doublet, 2H); δ 7.340-7.362 (doublet, 1H); δ 8.176-8.182 (doublet, 1H); δ 8.197-8.219 (doublet of

10 doublet, 1H); δ 10.409 (singlet, 1H); δ 13.389 (broad singlet, 1H).

Mass (m/e): 320.2

Process C:

50.0gm of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate, 47.44gm

15 of potassium carbonate and 47.04gm of isobutyl bromide were added to 200 ml of DMF. Reaction mixture was heated to 90 ± 3°C and stirred for 3 hr. Reaction mixture was cooled to 25°C and slowly added 1.50ltr of water. Slurry of the product formed was stirred for 1.0hr, filtered, washed and unloaded to give 119.06 gm of wet Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate.

20 Charged above wet compound and 47.44gm of potassium carbonate were added to the mixture of 0.50ltr of methanol and 0.050ltr water. Solution heated to reflux under stirring for 4hr and methanol distilled out under vacuum below 40°C. Residue cooled to 25°C and 2.0ltr of water was added. Stirred for 15.0mins. pH of aqueous solution adjusted to 3.0 ± 0.2 by addition of dil. hydrochloric acid solution at 40°C. Stirred for about 30.0mins.

25 Slurry of the product was filtered, washed with water and dried under vacuum to give 46.38gm of 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid

d) Preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat) [Compound of formula I] as a crystal form C.

30

20.0gm of Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-thiazole-5-carboxylic acid, 8.52gm of sodium formate followed by 4.57gm of hydroxylamine hydrochloride were

added to 200.0ml of formic acid. Reaction mixture was heated to reflux and stirred for 5hr to complete the reaction. Reaction solution was cooled gradually to 25°C. Slurry formed was stirred for about 2.0hr, filtered, washed with water and dried under vacuum to give 12.8 gm of Febuxostat as a crystal form C.

5

Analytical Data-

¹HNMR (DMSO-d₆, 400 MHz): δ 1.014-1.030 (doublet, 6H); δ 2.059-2.126 (multiplet, 1H); δ 2.657 (singlet, 3H); δ 3.990-4.006 (doublet, 2H); δ 7.346-7.369 (doublet, 1H); δ 8.191-8.219 (doublet of doublet, 1H); δ 8.266-8.271 (doublet, 1H); δ 13.410 (broad singlet, 1H).

10

Mass (m/e): 317.2

Crystal C Data-

15

IR (KBr): 1702.1, 1217.6 cm⁻¹

XRD Pattern (2θ) – 6.80°, 11.03°, 13.57°, 15.76°, 16.98°, 17.62°, 18.26°, 18.93°, 20.38°, 20.64°, 22.12°, 23.73°, 24.74°, 25.37°, 34.29°, 36.83°, 38.25°

20

e) Preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat) [Compound of formula I] as a crystal form C.

25.0gm of Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-thiazole-5-carboxylic acid, 10.65.0gm of sodium formate followed by 5.98gm of hydroxylamine hydrochloride were added to 250.0ml of formic acid. Reaction mixture was heated to reflux and stirred for 5hr to complete the reaction. Slowly added 25.0ml of water to the reaction mixture at reflux. Reaction solution was cooled to 25°C. Slurry formed was stirred for about 1.0hr, filtered, suck dried and washed with water. Dried under vacuum to give 19.68gm of titled compound as Febuxostat as a crystal C.

30

Crystal C Data-

IR (KBr): 1702.1, 1217.6 cm⁻¹

XRD Pattern (2θ) – 6.83°, 11.05°, 13.59°, 15.77°, 17.03°, 18.30°, 18.97°, 20.14°, 20.69°, 22.15°, 23.77°, 24.77°, 25.05°, 34.34°, 36.86°, 38.30°.

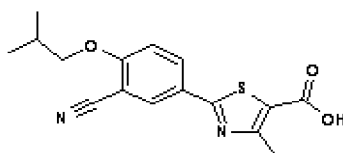
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f) Preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (Febuxostat) [Compound of formula I].

- 5 5.0gm of Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate and 4.0gm of potassium carbonate were added to the mixture of 50.0ml of methanol and 5.0ml water. Reaction mixture was heated to reflux under stirring for 4hr to complete the reaction. Solvent distilled out under vacuum below 40°C. Residue obtained was cooled to 25°C and added 1.76gm of sodium formate followed by 1.20gm of hydroxylamine
- 10 hydrochloride and 50.0ml of formic acid. Reaction mixture was heated to reflux and stirred for 5hr. Reaction solution was cooled gradually to 25°C and added 50.0ml of water dropwise at 25°C. Slurry formed was stirred for about 1.0hr, filtered, washed with water and dried under vacuum to give 3.76gm of Febuxostat.

CLAIMS

1. An improved process for preparing Febuxostat, compound of formula (I).

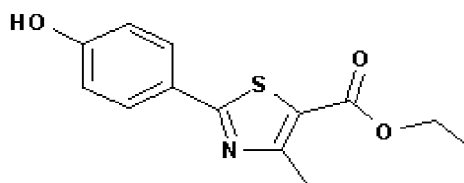


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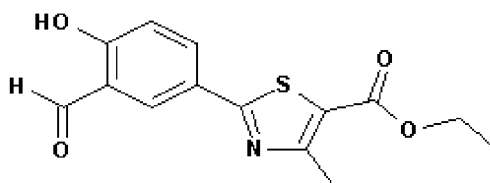
Formula (I)

which comprises the step of:

- 10 i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, compound of Formula II

**Formula II**

- 15 with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula III;

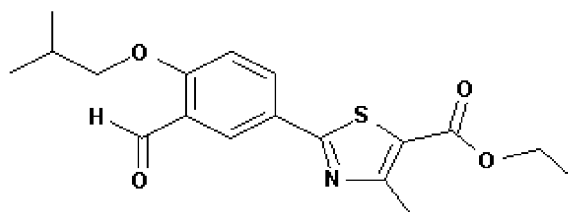


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Formula III

- 25 ii. Alkylating compound of formula III with isobutyl bromide to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula IV;

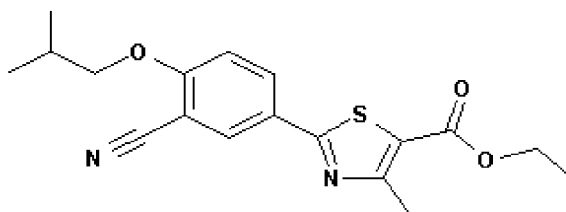
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Formula IV

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- iii. Converting compound of formula IV to 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula V by using hydroxylamine hydrochloride and sodium formate in formic acid;

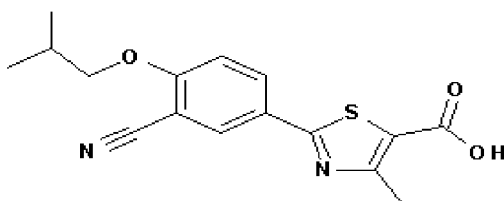


10

Formula V

- iv. Hydrolyzing compound of formula V with alkali metal carbonate in the presence of lower alcohol to obtained 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid of formula I.

15



Formula I

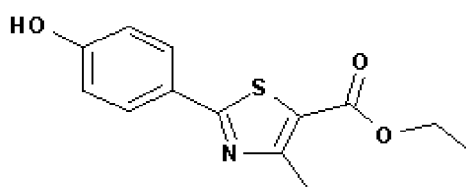
20

2. The process for preparing Febuxostat according to claim 1 wherein the alkali metal carbonate used in step iv is selected from potassium carbonate, caesium carbonate or sodium carbonate.

3. The process for preparing Febuxostat according to claim 1 wherein the lower alcohol used in step iv is selected from methanol or ethanol.

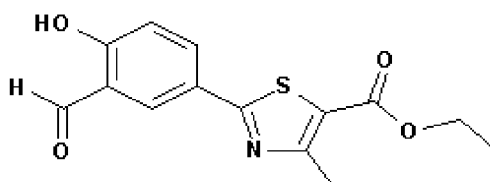
5 4. An improved process for preparing polymorphic Form C of Febuxostat which comprises the step of:

i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, compound of Formula II



10 **Formula II**

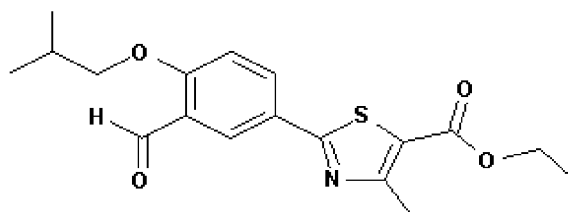
with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula III;



20 **Formula III**

ii. Alkylating compound of formula III with isobutyl bromide to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula IV;

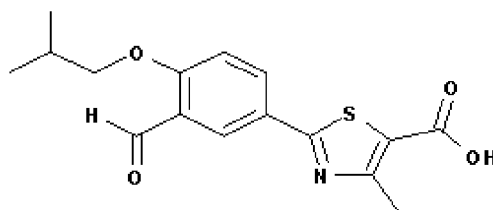
33



Formula IV

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- iii. Hydrolyzing compound of formula IV with alkali metal carbonate in the presence of lower alcohol to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid, compound of formula VA or its salt thereof;

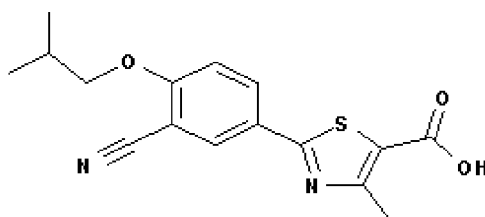


10

Formula VA

- iv. Converting compound of formula VA or its salt thereof to 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula I by using hydroxylamine hydrochloride and sodium formate in formic acid;

15



Formula I

- v. Isolation of pure compound of formula I with polymorphic form C from reaction mixture as obtained in step iv by addition of water above 60°C and cooling to room temperature.

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5. The process for preparing polymorphic Form C of Febuxostat according to claim 4 wherein the alkali metal carbonate used in step iii is selected from potassium carbonate, caesium carbonate or sodium carbonate.

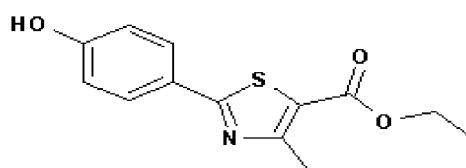
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6. The process for preparing polymorphic Form C of Febuxostat according to claim 4 wherein the lower alcohol use in step iii is selected from methanol or ethanol.

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7. A process for the preparation of the compound of formula VA comprising the steps of:

- i. Reacting 2-(4-hydroxyphenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester, compound of Formula II

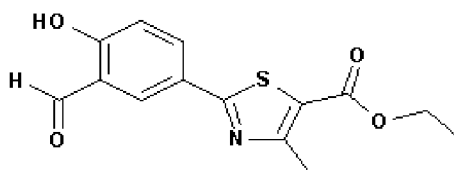


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Formula II

with hexamethylenetetramine in the presence of trifluoroacetic acid to obtain 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula III;

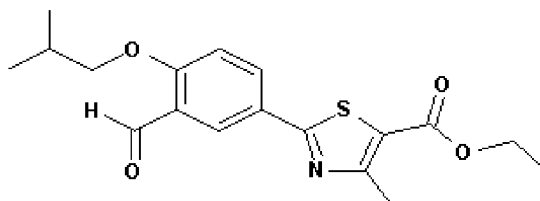
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**Formula III**

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- ii. Alkylating compound of formula III with isobutyl bromide to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid ethyl ester, compound of formula IV;

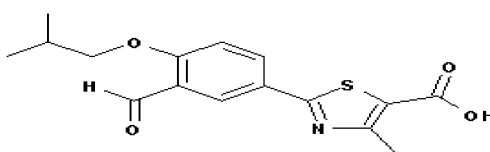
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Formula IV

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- iii. Hydrolyzing compound of formula IV with alkali metal carbonate in the presence of lower alcohol to obtain 2-(3-formyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid, compound of formula VA or its salt thereof.



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Formula VA

8. The process for preparing compound of formula VA according to claim 7 wherein the alkali metal carbonate used in step (iii) is selected from potassium carbonate, caesium carbonate or sodium carbonate.

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9. The process for preparing compound of formula VA according to claim 7 wherein the lower alcohol used in step (iii) is selected from methanol or ethanol.

10. The compound of Formula (VA) prepared by the process according to claim 7.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051475

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D277/56
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2011/141933 A2 (MSN LAB LTD [IN]; SATYANARAYANA REDDY MANNE [IN]; VENKATA PANAKALA RAO) 17 November 2011 (2011-11-17)	10
Y,P	Claim 1, step (c): alkali metal carbonates in a suitable solvent; page 12, lines 10-12: suitable solvent; page 40, scheme II; page 47, example 12.	1-3,7-9
Y	----- JP 6 329647 A (TEIJIN LTD) 29 November 1994 (1994-11-29)	1-3,7-9
A	the whole document	4-6
Y	----- JP 10 045733 A (TEIJIN LTD) 17 February 1998 (1998-02-17)	1-3,7-9
A	cited in the application the whole document	4-6
	----- -/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

* 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

31 May 2012

Date of mailing of the international search report

26/06/2012

Name and mailing address of the ISA/

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

Authorized officer

Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2012/051475

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 101 781 270 A (CHONGQING PHARMACEUTICAL RES I) 21 July 2010 (2010-07-21) cited in the application	10
Y	the whole document	7-9
X,P	-& US 2011/282069 A1 (ZHOU XINGGUO [CN] ET AL) 17 November 2011 (2011-11-17)	10
Y,P	Paragraphs [0004], [0005], [0009]; page 5, example 3.	7-9
A	----- EP 1 020 454 B1 (TEIJIN LTD [JP] TEIJIN PHARMA LTD [JP]) 25 November 2009 (2009-11-25) cited in the application Paragraphs 0013, 0019, 0027, 0048, 0061.	1-10
Y	----- "Interconversion of Nitriles, Carboxylic Acids and Derivatives: Esters to Carboxylic Acids"; "Chapter 9.17" In: Larock: "Comprehensive Organic Transformations - A Guide to Functional Group Preparations, 2nd ed.", 1999, Wiley-VCH, New York, XP002676948, ISBN: 0471190314 pages 1959-1968, Page 1965, lines 12-13: M2C03, MeOH, H2O, reference to TL 32 327 (1991). Cited as common general knowledge.	1-3,7-9
Y	----- KAESTLE ET AL.: "CLEAVAGE OF ESTERS USING CARBONATES AND BICARBONATES OF ALKALI METALS: SYNTHESIS OF THYMOPENTIN", TETRAHEDRON LETT., vol. 32, no. 3, 1991, pages 327-330, XP55028570, The whole document. Cited as common general knowledge.	1-3,7-9
Y	----- YAMAGATA ET AL.: "Studies on Heterocyclic Enaminonitriles, XII. Reactions of 4,5-Dihydro-2-morpholino- (and -2-pyrrolidino)-3-furancarbonitriles with Dichlorocarbene", LIEBIGS ANNALEN DER CHEMIE, no. 11, 1 January 1992 (1992-01-01), pages 1109-1112, XP55028573, DOI: 10.1002/jlac.1992199201183 Page 1110, scheme 2: conversion of 7 to 9; page 1112, left column: preparation of 9.	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/051475

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011141933	A2	17-11-2011	NONE
JP 6329647	A	29-11-1994	JP 2834971 B2 14-12-1998 JP 6329647 A 29-11-1994
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/051475

Patent document cited in search report	Publication date	Patent family member(s)	Publication date

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/051475

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.:
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:

see additional sheet

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 an 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3

a process for preparing febuxostat I.

2. claims: 4-6

a process for preparing polymorphic form C of febuxostat I.

3. claims: 7-9

a process for preparing compound VA.
